NELSON MANDELA UNIVERSITY

THE SYNTHESIS OF ANASTRAZOLE INTERMEDIATES USING CONTINUOUS FLOW SYSTEMS

By

Sam Tanyi Tambi

Submitted in fulfilment of the requirements for the degree of

MASTER OF SCIENCE: CHEMISTRY

in the

FACULTY OF SCIENCE

at the

NELSON MANDELA UNIVERSITY

Department of Chemistry

Supervisor: Prof P Watts

July 2021

Abstract

In this study, the continuous flow synthesis of anastrazole intermediates were investigated using mesitylene as starting material. Anastrazole is an important drug used for the treatment of breast cancer. In the first step, mesitylene was brominated using *N*-bromosuccinimide to obtain 3,5-bis(bromomethyl)toluene. Selectivity became an issue due to the formation of two by-products; namely 1,3,5-tris(bromomethyl)benzene (the tribrominated by-product) and 1-(bromomethyl)-3,5-dimethylbenzene (the monobrominated by-product). Since the reaction parameters can be more precisely controlled in flow chemistry systems, we were able to optimize the formation the desired product 3,5-bis(bromomethyl)toluene. The reaction was initially optimized in a 15 μL Chemtrix glass micro reactor resulting in 100% conversion with 95% selectivity towards the desired product 3,5-bis(bromomethyl)toluene in 15 seconds, with a throughput of 0.006 g/h. The reaction was then scaled up in a 1.7 mL LTF reactor, equally yielding 100% conversion with 95% selectivity in 4 minutes, with a throughput of 2.01 g/h. The bromination of mesitylene was also attempted in a homemade photochemical reactor consisting of a 3.02 mL polytetrafluoroethylene coil reactor and BLE-6T365 UV lamp. In this photochemical reactor, although 100% conversion was again obtained only 75% selectivity was achieved in 20 minutes, with a throughput of 0.025 g/h. This drop in selectivity was attributed to poorer mixing in the larger polytetrafluoroethylene coil reactor and possibly insufficient light penetration.

The next step, involving the cyanation of 3,5-bis(bromomethyl)toluene to obtain 2,2'-(5-methyl-1,3-phenylene)diacetonitrile gave 100% conversion in 1 minute at 190 °C in a 1.7 mL LTF reactor, with a throughput of 5.2 g/h. The subsequent methylation of 3,5-bis(cyanomethyl)toluene to obtain 3,5-bis(1-cyano-1-methylethyl)toluene was investigated using a 1 mL polytetrafluoroethylene coil reactor, ultimately achieving 99% conversion at 40 °C in 8 minutes, with a throughput of 0.045 g/h. Next, the bromination of 3,5-bis(1-cyano-1-methylethyl)toluene using *N*-bromosuccinimide to yield 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) gave 100% conversion at 120 °C in 4 minutes, with a throughput of 0.35 g/h. Lastly, the multistep synthesis of 3,5-bis(cyanomethyl)toluene was done in two integrated 1.7 mL LTF reactors, using the predetermined optimum conditions to achieve 94% conversion towards 3,5-bis(cyanomethyl)toluene with a total residence time of 5 minutes.

Research output

- Sam Tanyi and Paul Watts, The synthesis of anastrazole intermediates in continuous flow systems (in preparation).

Dedication

To my parents Agnes Tanyi and Prof. Emmanuel Tanyi.

Acknowledgements

Firstly, l would like to express my deep and sincere gratitude to my research supervisor and mentor, Prof. Paul Watts, for his patience, enormous support and for giving me the opportunity to work under his mentorship. His vision, guidance, feedback and dedication to excellence have encouraged me to always strive to do better.

I would also like to thank the NRF for making this research possible. Many thanks to the flow chemistry research group for the support and good times we shared.

My immense gratitude goes to my family, especially my parents, for always believing in me and supporting my dreams.

Last but not the least, I would like to thank God for life, breath and everything.

Declaration

I **Sam Tambi Tanyi** hereby declare that this thesis is my own work and has not been previously submitted for assessment in any other Institution. It is now being submitted for the degree of Master of Science (Chemistry) at the Nelson Mandela University, Gqeberha.

Sam Tambi Tanyi

July 2021

Table of contents

Abbreviations

ACN	Acetonitrile
AI	Aromatase Inhibitor
AIDS	Acquired immunodeficiency syndrome
API	Active Pharmaceutical Ingredient
BPO	Benzoyl peroxide
BPR	Back pressure regulator
BRCA1	Breast cancer gene one
BRCA2	Breast cancer gene two
$CDCl_3$	Deuterated chloroform
DIBAL	Diisobutylaluminium hydride
D_2O	Deuterium oxide
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
dt	Doublet of triplets
ER+	Estrogens receptor positive
FDA	Food and drug administration
FT-IR	Fourier transform infrared
GC	Gas chromatography

HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
ICI	Imperial chemical industries
IR	Infrared radioscopy
2-Me-THF	2-Methyltetrahydrofuran
MS	Mass Spectroscopy
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
PFA	Perfluoroalkoxy polymer
PR+	Progesterone receptor positive
PTC	Phase transfer catalyst
PTFE	Polytetrafluoroethylene
TBAB	Tetrabutylammonium bromide
TLC	Thin layer chromatography
TFAA	Trifluoroacetic anhydride
WHO	World Health Organisation

Chapter 1- Introduction

1.1 Introduction to cancer

Cancer is a major public health problem worldwide, being the second leading cause of death after cardiovascular diseases.[1] It causes more deaths every year than malaria, tuberculosis and AIDS combined. In 2018, an estimated 18.1 million new cancer cases were diagnosed worldwide, with more than 9 million cancer deaths in the same year.[2] The number of cancer cases worldwide is expected to increase, due to an increase in the global population and aging. The World Health Organisation (WHO) predicts that by 2040 there will be about 29 million cancer cases worldwide.[2] This increase will significantly affect economies, especially in developing countries, due to the high cost of cancer drugs and in some cases, the loss of the young productive population.[2,3] The rate of incidence of cancer is higher in developed countries than in less developed countries. Despite the lower incidence rate in the less developed countries, the mortality rate is much higher, with slightly over two-thirds of the patients eventually dying.[2] This higher mortality rate is mainly due to inaccessibility to life-saving drugs, late detection, inaccessibility to new treatment methods and shortage of necessary medical equipment.[3,]

Cancer is a disease that develops when normal body cells begin to divide uncontrollably and invade surrounding tissue.[4] The aetiology of cancer usually begins with a genetic mutation, followed by the abnormal proliferation and survival of the cells containing the mutated genes resulting in the formation of tumours and eventually the invasion of other tissue, a process known as metastasis. Genetics and environmental factors play a major role in the development of cancer. In addition to these, some other factors, often referred to as risk factors, increase the probability of developing cancer. Such risk factors include smoking, obesity, lack of exercise, poor diet and ageing.[1,5] There are many different forms of cancer. In males worldwide, lung, liver and gastric cancers are the leading cause of cancer-related deaths. In females, the leading causes of cancer deaths are breast cancer, lung cancer and colorectal cancer.[1]

There are different types of cancer treatments, which can be classified into systemic and local therapy. Surgery and radiation therapy are referred to as local treatments because they can only affect targeted tumour cells at a specific location in the body *e.g.* a mastectomy to remove cancerous breast tissue. The rest of the treatment methods are classified under systemic therapy because they can reach tumour cells almost anywhere in the body. These include chemotherapy, hormone therapy, immunotherapy and targeted drugs.[5,6,7]

The rising number of cancer cases and its high mortality rate has led to a lot of research, aimed at finding different treatment methods and drugs for the disease.[1] As a result, significant progress has been made over the past decades towards understanding the disease, increasing early detection, improving patient care *etc*. The diagnosis and staging of the disease have also improved, due to better imaging techniques and equipment.[8,9] Many new treatment methods have also been introduced in recent years *e.g.* the use of nanotechnology to target tumour cells.[10] New life-saving cancer drugs have also been discovered *e.g.* imatinib, trastuzumab and rituximab.[11]

1.2 Breast cancer

Breast cancer is the most frequently diagnosed form of cancer in sub-Saharan Africa and the world. Breast cancer is also the leading cause of cancer deaths in women worldwide.[12] It impacts about 2.1 million people globally each year and in 2018, about 627,000 people worldwide died from the disease. This form of cancer is very rare amongst men, but it does occur in mostly older men.[13]

1.2.1 Causes of breast cancer

Between 5-10% of all breast cancer cases are believed to be hereditary, as a result of mutated genes inherited from parents. Two genes have been associated with hereditary breast cancer, the BRCA1 and BRCA2 genes.[13] BRCA1 and BRCA2 are genes that code for the synthesis of tumour repressor proteins.[14] Women born with BRCA mutations are more likely to develop breast cancer during their lifetime and usually at a younger age than women born without any of these mutations. Mutations in other genes that result in breast cancer are rare cases of hereditary breast cancer. Most breast cancer cases, about 90 to 95% of all cases, are non-hereditary. The causes of non-hereditary breast cancer are not yet fully understood, but are believed to be most likely due to alterations in genetic material. These alterations often being related to life choices or lifestyle, which exposes us to cancer causing agents known as carcinogens.[12,13] Carcinogens are believed to cause mutations that culminate in the development of cancer. These carcinogens are often classified into three classes namely: chemical carcinogens, physical carcinogens and oncogenic viruses.[15,16]

1.2.2 Treatment methods of breast cancer

Originally, the only way to treat breast cancer was by surgically removing the affected area, with the first radical mastectomy done by William Halsted in 1882.[5] Due to the mutilating nature of the surgery, physicians researched other ways of treating the disease. Research done over the decades

led to improved treatment strategies, better radiation therapy and new drug discoveries used for chemotherapy, targeted therapy, immunotherapy and hormone therapy.[5,17,18] Typical therapy guidelines tailor therapy to the specific features of the tumours, like the cancer detection stage, type of breast cancer, means of proliferation, sensitivity of the tumour cells to certain hormones like progesterone and HER2 *etc*. A combination of different therapies is usually needed to completely eradicate the tumour cells where possible *e.g*. mastectomies are often followed by radiotherapy and chemotherapy treatments to completely eradicate cancerous cells.[17,19,20]

1.2.3 Hormone therapy

This form of treatment is often given after surgery or radiation therapy to ensure that the cancer does not return. Most cases of breast cancer are hormone-receptor positive, which means that their proliferation will be affected by the presence of certain hormones. There are two types of hormone-receptor positive breast cancers; the ER-positive (Estrogen-receptor-positive) breast cancer (constitutes most of the cancer cases) and the PR-positive (Progesterone-receptor-positive) breast cancer, which is very rare. Some cases are both ER-positive and PR-positive.[21] ER-positive tumours need estrogens to grow, while PR-positive tumours need progesterone to grow. Hormone therapy drugs stop the effects of these hormones, either by lowering the levels of the hormones in circulation or preventing them from acting on breast cancer cells. One major class of hormone therapy drugs are the aromatase inhibitors *e.g.* anastrazole.[21,22]

1.3 Cancer in sub-Saharan Africa.

A recent estimate shows that there are almost 850,000 new cancer cases diagnosed in Africa each year, with more than 600,000 deaths.[23,24] These numbers are expected to increase as the population increases. Even though the region sees a substantial increase in the number of cancer cases each year, the treatment necessary to respond to the demand is lacking. As a result, the region has one of the lowest cancer survival rates in the world.[25,26] In addition to limited medical resources like radiation therapy machines and fewer well-trained specialists, another major drawback faced in sub-Saharan Africa is the difficulty in accessing lifesaving cancer drugs. The region has a low socioeconomic status, with most of the population being in the low income and middle-income range. This makes lifesaving cancer drugs unaffordable for most within the region.[24,26]

1.3.1 Availability of cancer medication in sub-Saharan Africa

Governments in SSA are attempting to improve cancer care, but the cost of cancer medication remains a huge obstacle. Most cancer drugs and active pharmaceutical ingredients used in the region are imported, thus making them expensive and even unaffordable for most.[28,29]

It is important to note that the cost of many cancer drugs in Africa decreased significantly since the start of the millennium. This was due to the inter-governmental discussions at the 4th ministerial conference of the World Trade Organisation (WTO) in Doha, to increase flexibility on the Trade Related Aspects of Intellectual Property (TRIPS). This came as a result of rising pressure from the global community to increase access to lifesaving drugs, especially with the rise of the HIV and tuberculosis co-epidemics, which eventually culminated in the Doha declaration of 2001.[27] The purpose of the Doha declaration of November 2001, is to ensure that the TRIPS is interpreted in a way that protects public health by making existing medication available to all and encouraging the introduction of new medications. This declaration guarantees some flexibilities in patent laws, like the compulsory granting of licenses to member countries, allowing them to use a patented invention to make generics of these lifesaving drugs. This was an important declaration, as the previous agreement guaranteed monopoly over patent use by the patent holders for the full validity period of the patent, a period of 15 years. This previous narrow interpretation of the TRIPS resulted in unfavourable public health outcomes by reducing access to most drugs in sub-Saharan Africa and other developing countries. The Doha declaration was adopted in South Africa in April 2004. Countries like Brazil, China and India have implemented and benefited from the Doha declaration more than SSA, as they have been able to make some drugs and APIs. In addition to this, some effective cancer drugs have recently come off patent protection, making even more options available for manufacturers.[27,28]

In SSA however, most countries lack the necessary capital, infrastructure and adequately trained personnel to manufacture their own drugs. These factors make the manufacture of drugs in the area more tedious and have discouraged most countries. Very few countries in SSA have some primary drug manufacturing ability and can manufacture some APIs, like South Africa. Paragraph 6 of the Doha declaration also allows importation of generics made using the issued compulsory licenses by countries that cannot manufacture their own drugs, like most of sub-Saharan Africa.[27] Most of the drugs used in SSA are imported and this weighs heavily on the economies of these countries.

Most of the APIs in SSA are imported from China and India, and this affects the cost of the drugs in the region; every drug consists of the API and excipients. Excipients are substances that enable the API to be delivered appropriately to the target cells and have the desired effects.[29]

It is also worth noting that many donor funds exist to make cancer drugs more available in SSA. Different types of donor programs exist. Some of programs are financial donations for various healthcare projects like purchasing pharmaceuticals from outside sub-Saharan Africa and making them available for free within the region, purchasing necessary equipment to be used within the region *etc.* Other donations are direct drug donations from big pharmaceutical companies to the impacted nations.[33] Yet other donations aim to improve local production of drugs in the region by supplying both financial and technical support, *e.g.* collaboration between Brazil and Mozambique.[31] However, SSA cannot depend long-term on donations as a sustainable solution for many reasons. One reason is that financial donations aimed at improving local production drugs, without the necessary infrastructural and human resources could result in drugs that do not meet the WHO and DHA approval.[31] Also, the global economic crisis that started in 2008 also significantly decreased donations for cancer drugs in sub-Saharan Africa, further showing that donor funds are not a sustainable solution to the problem of lack of drugs in SSA.[30]

Recently in 2015, the WHO added 16 cancer medicines to its List of Essential Medicines for low and middle-income countries.[30] For the first time, amongst the drugs added were costly medicines such as imatinib, trastuzumab and rituximab due to the very positive results these medicines had on patients. There was an expectation that by adding these drugs to the list the prices will be forced down, as had been done for HIV drugs at the beginning of the millennium after the Doha declaration. However, these drugs remain unaffordable for most in SSA. Generics of some of these medicines with similar effects and safety have been made available at lower prices, but even these generics are too costly for most people in the region.[30]

It is also important to note that measures have been taken to ensure that the cost of cancer drugs are cheaper in developing countries, like those in SSA, than it is in developed countries like the USA. However, comparing the GDPs of these regions, it is obvious that these drugs are more affordable for people in the USA despite the higher prices, especially since many within SSA can also not afford full cover medical aid.[20,32]

Despite all the measures taken to lower the prices of these drugs in SSA, they are still unaffordable for most of the predominantly middle and low income SSA. One way to solve this problem is to find new, cost effective ways to synthesize APIs locally. South Africa, when compared to other African countries, has made significant progress in providing healthcare for its people. Many essential medicines are available in public hospitals across the nation. But there is still a huge need for investment into drug development, as well as API manufacture for SSA and the rest of Africa.

Statistics obtained from the United Nations COMTRADE database, shows that South Africa spends billions of US Dollars on active pharmaceutical ingredients each year. In 2019 for example, South Africa spent about US $ 2.4 billion dollars on pharmaceutical importation and over US $18 billion on pharmaceutical imports in the past decade.[33] The weight of these import costs is felt even more severely when the Rand falls, like in March of 2020, when the Rand fell drastically due to the Coronavirus pandemic and the national lockdown. Local production could increase jobs, better the economy and increase standards of living for many. Also, local production of APIs which are the most expensive components of drugs, will lower the costs of the drugs and shield the economy from the negative effects of Rand fluctuations on the import costs of APIs. This further highlights the need for investing in new, cost-effective ways of developing these APIs locally. The pharmaceutical importation data for South Africa between 2011 and 2019 is shown in Figure 1 .

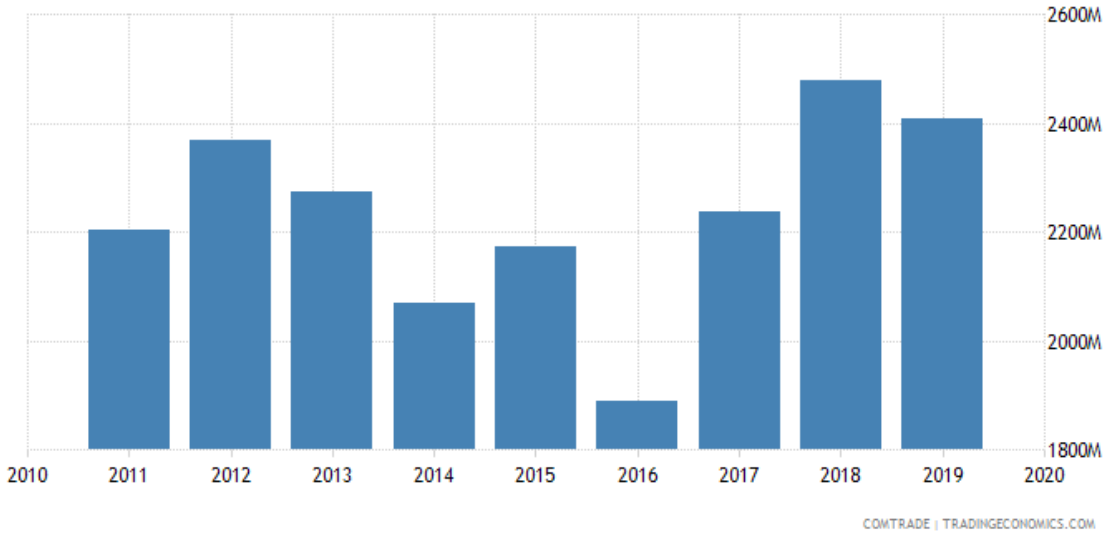


Figure 1: *Showing the pharmaceutical importation data for South Africa from 2011to 2019.*[34]

1.4 Flow chemistry

Flow chemistry, also referred to as continuous flow processing or micro reaction technology is a relatively new technology that makes use of micro and macro flow reactors to enable chemical reactions to be carried out continuously.[35] It involves pumping reagents through reactor inlets into channels in the temperature-controlled reactors, where the reaction occurs. There are two main types of reactors; micro and macro flow reactors.[35] Micro reactors are flat devices consisting of channels with sizes in the micrometre range. These devices are mainly used for small scale reactions, as the internal volume of their channels range from nanolitres to microlitres.[35] Figure 2 shows one of these micro reactors manufactured by Chemtrix BV®.

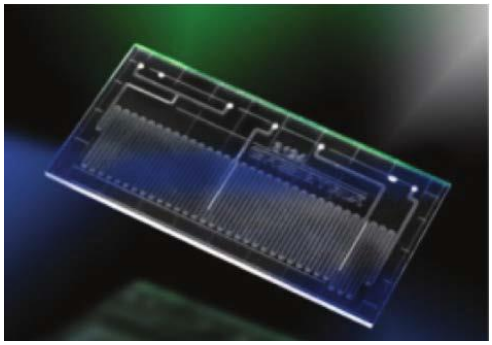


Figure 2: *Showing a Chemtrix micro reactor*.[36]

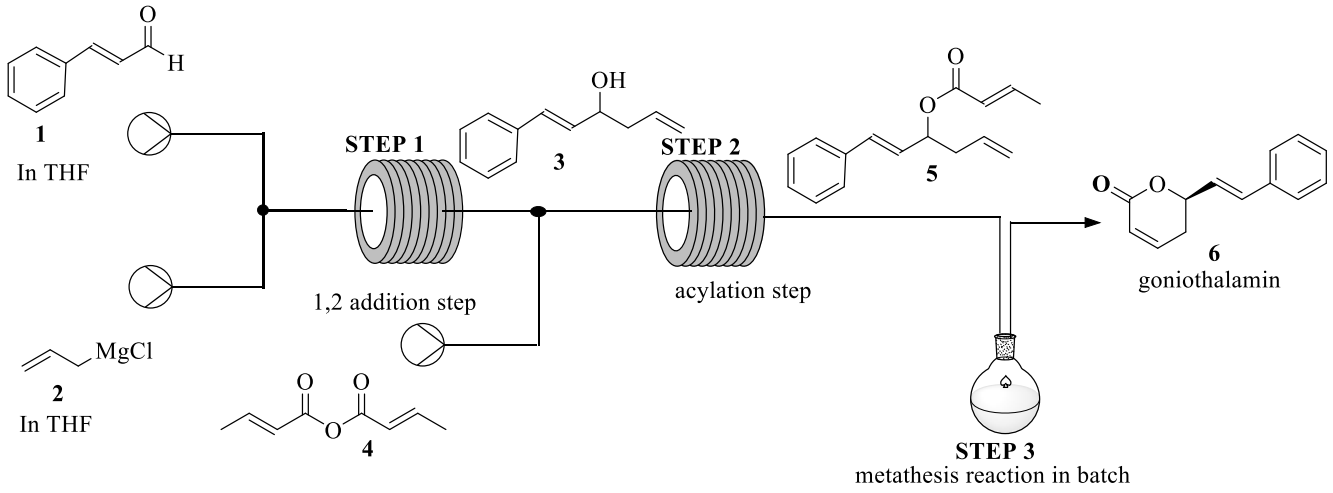
Macro reactors (also called meso flow reactors) are larger than micro reactors, having channels with sizes over 300 μm and into the millimetre range. The size of the reactors, together with the type of material used to make them determines the properties of the reactors. The reactors used in continuous flow chemistry are often made from silicon, metal, glass, polymer or quartz.[35,37] Reactors made from different materials are suitable for different types of reactions. Selection of a suitable reactor will therefore take into consideration different aspects of the reaction's chemistry, especially the method of activation of the reaction. Reactions may be activated by heating, ultrasonication, ultraviolet rays, microwaves, radiowaves *etc*. The reactor selected must be compatible with the mode of activation.

It is worth highlighting that flow chemistry has been amply utilized in the petrochemical industry, but not so much in the fine chemical and pharmaceutical industry for organic synthesis.[35] In recent

years, the use of flow chemistry technology in organic synthetic chemistry has been surging due to the advantages it has over the conventional batch chemistry.

1.4.1 Comparing flow chemistry and batch chemistry for organic synthesis

Batch chemistry and flow chemistry both have advantages and disadvantages. Flow chemistry does not seek to completely replace the conventional batch chemistry for all organic synthetic processes. Rather, flow chemistry can be used in cases where it is preferable to the corresponding batch method. In some cases, flow chemistry and batch chemistry can be used in combination with each other, to give an overall improved process with better results than would have been achieved by the individual flow or batch method *e.g.*, Ley *et al.* combined batch and flow chemistry in their synthesis of goniothalamin **6**. The first two steps of the three-step synthesis were done in flow reactors and the final step was done in batch, giving an overall improved process. The first step involved the 1,2-addition of the Grignard reagent to trans-cinnamaldehyde **1** in a PFA (perfluoro alkoxy polymer) reactor coil to obtain the allylic alcohol **3**. The resulting allylic alcohol **3** was then acylated in a second PFA reactor coil using crotonic anhydride **4** as the acylating agent to form the ester **5**. The last step involved the ring closing metathesis of the ester **5** which was cyclised in batch, to obtain goniothalamin **6**. The setup was arranged as shown in Scheme 1 below, giving a good overall yield of 96%.[38]



Scheme 1: *Combination of batch and flow towards the synthesis of goniothalamin* ***6****.*

Batch chemistry is the long-established method used for organic synthesis of APIs. At small scale, batch synthetic methods can be suitable due to its low cost of production and flexibility. However,

batch methods often become unfavourable when it comes to scaling up. During scaling-up, occurrences like heat transfer, mass transfer and problems associated with poor mixing, which are negligible in small scale batch synthesis become significant. In contrast to batch methods, continuous flow methods are suitable for both small scale and large-scale organic synthesis due to the very efficient mass and heat transfer in flow systems, as well as better mixing.[39]

Other significant advantages of using continuous flow methods for synthesis of APIs include much shorter reaction times, lower cost of production of APIs and shorter development cycles, which lead to quicker scale-up processes from the academic or laboratory scale to the industrial scale.[40] Furthermore, using continuous flow chemistry systems results in less waste production making continuous flow methods a more viable and sustainable option for pharmaceutical industries.[41,42] Perhaps the most important advantage of using continuous flow technology is that it provides a considerably higher selectivity towards the desired product, which often results in higher yields. Cost of production is also reduced, as solvent and energy waste can be cut down by up to 90% in some instances.[35,43,44] The field of continuous flow chemistry is relatively new and is frequently being ameliorated. This relatively new technology has been used recently in the production of new drugs, like anti-cancer drug imatinib.[45,46]

1.4.2 Flow chemistry characteristics

Using continuous flow chemistry for organic synthesis has many significant advantages over the conventional batch methods. In this section, these advantageous characteristics of flow chemistry are discussed.

1.4.2.1 Mixing

Mixing is a very important process in both batch and flow synthetic processes. The aim of mixing is to achieve an even distribution of all the components of the reaction mixture. There are two different types of mixing: laminar mixing and turbulent mixing.[47] In micro reactors, mixing can be achieved either by laminar flow or turbulent flow, depending on the flow rates and the internal structure of the reactors.

During laminar mixing, liquid-liquid streams or liquid-gas streams flow in parallel and mix only by diffusion. The small dimensions and short diffusion distances in micro reactors ensure efficient mixing even in laminar flow. Turbulent flow offers even better mixing than laminar flow and is

more effective at uniformizing the reaction mixture than laminar mixing. Turbulent mixing in contrast to laminar mixing, is an agitated or irregular type of mixing. In flow systems, turbulent mixing can be achieved by pumping the fluids at higher flow rates into the reactors, using reactors with rough segmented channels or using devices known as mixers to combine the components of the reaction, before they are streamed through the reactor. Turbulent mixing is often necessary when scaling-up to larger reactors, containing larger diameter channels.[45,46]

By using the Reynold's number, R_e, we can establish whether the flow will be laminar or turbulent. The formula from which R_e is derived is shown below (Equation 1):

$$Re = {}^{\upsilon\rho L}/_{\eta} \quad \text{.....(1)}$$

where υ is the velocity, ρ is the density of the fluid, L is the diameter of the micro reactor channel and η represents viscosity. From the formula we see that R_e is directly proportional to the velocity of flow, the density of the fluid and the diameter of the reactor. R_e is also inversely proportional to the viscosity of the fluid. When *Re* is less than approximately 2000 the flow will be laminar and when the number is greater than 2000 the flow will be turbulent.[49,50] Turbulent flow ensures efficient mixing.[51] Turbulent mixing is more effective than laminar mixing.[49] The high surface area to volume ratio, an intrinsic property of micro reactors, results in short diffusion distances. This allows for very efficient mixing, avoiding concentration hotspots within the reactor and achieving good mixing, even when the mixing is achieved by laminar flow.[47,48,51,52] A very low R_e will imply very laminar flow. This will result in poor mixing, with the fluids mostly streaming side by side of each other, as a result of the viscous forces between molecules being stronger than the inertial forces.[51] Some reactors have internal structures and geometries than enhance rigorous, turbulent mixing. In addition, flow reactors can be used with other devices like sonicators, ensuring turbulent mixing.[49]

1.4.2.2 High surface area to volume ratio in micro reactors

The small dimension of micro reactors ensures high surface area to volume ratio in micro reactors; this is larger in micro reactors than in batch reactors. This makes mixing more effective due to short diffusion distances.[46,53] Most significantly, it also enables quick and efficient heat and mass transfer. This improves temperature homogenizing within the system and ensures proper

mixing,[37,54] thus resulting in a reduction in the cost of production due to an increase in the overall efficiency of the system. The small dimensions in micro reactors also make it possible for small amounts of solvents and reactants to be used, making the process safer in handling dangerous intermediates.[54]

1.4.2.3 Temperature

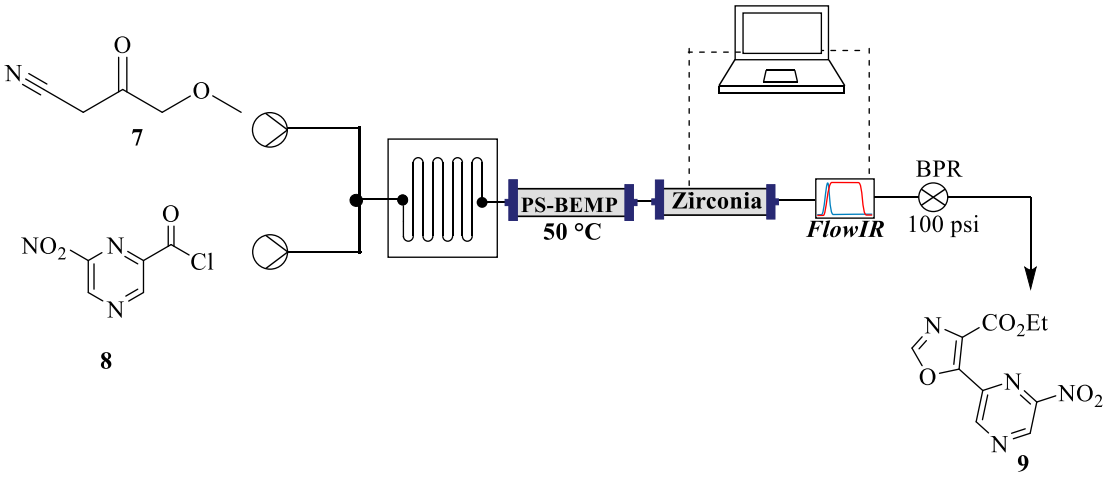
The temperature of a reaction mixture is one of the most important factors in reaction kinetics. Occurrences like fluctuations in the temperature of the reactions often seen in exothermic processes, where the uneven temperature distribution creates temperature hotspots. These temperature hotspots can decrease product selectivity, reducing the yield of the desired product.[55] The issue of temperature control is also an issue of safety, as some reactions are highly exothermic and could even lead to laboratory explosions in batch reactors.[43,46,55] Heat transfer efficiency is very good in flow chemistry reactors due to their high surface area to volume ratio. The high heat transfer efficiency in micro reactors also ensures the quick dissipation of heat released during exothermic reactions. The temperature in micro reactors can therefore be more accurately controlled in contrast to batch reactors, in which temperature gradients often develop.[46,55]

Two very important factors that sometimes affect the equilibrium and rate of a chemical reaction are the temperature and pressure. Flow chemistry reactors can be pressurized using back pressure regulators. This pressure module also allows for reactions to be carried out above the boiling points of the solvents or reactants involved, which often results in shorter reaction times and higher yields.[43,46,55,56]

1.4.2.4 Real-time reaction monitoring

Flow reactor technology makes it possible for the product being formed to be analyzed and monitored as the reaction progresses, using analytical technologies like IR, GC, NMR and MS.[43,57] This enables reactions to be controlled and optimized more accurately and in real time. A major advantage of using real-time reaction monitoring technology is that it not only shows the formation of product, but also the formation of unwanted byproducts.[57] The reaction can then be stopped if the wrong products are being formed, reducing waste of reactants, catalysts, solvents and precious experimental time. Also, real-time reaction monitoring eliminates dead-time observed with offline monitoring methods, between the sampling of the product and analysis.[58,59] This is a significant

advantage, as some product samples could undergo changes in composition during this period. Real time monitoring also reduces the risk of sample contamination. A very commonly used technique for in-line reaction monitoring in continuous flow systems is FTIR spectroscopy. An experiment done by Ley *et al.* demonstrated the advantages of real time monitoring in the flow synthesis of the oxazole ethyl 5-(3-nitrophenyl) oxazole-4-carboxylate **9** from the isocyanide **7** and the corresponding acid chloride **8**. The research group was able to monitor the formation of the product oxazole in real-time, making the optimization of the reaction much quicker and easier. The setup included a raspberry® pi computer connected to a flow IR cell, as shown in Scheme 2 below, achieving a high yield of 94%.[57]

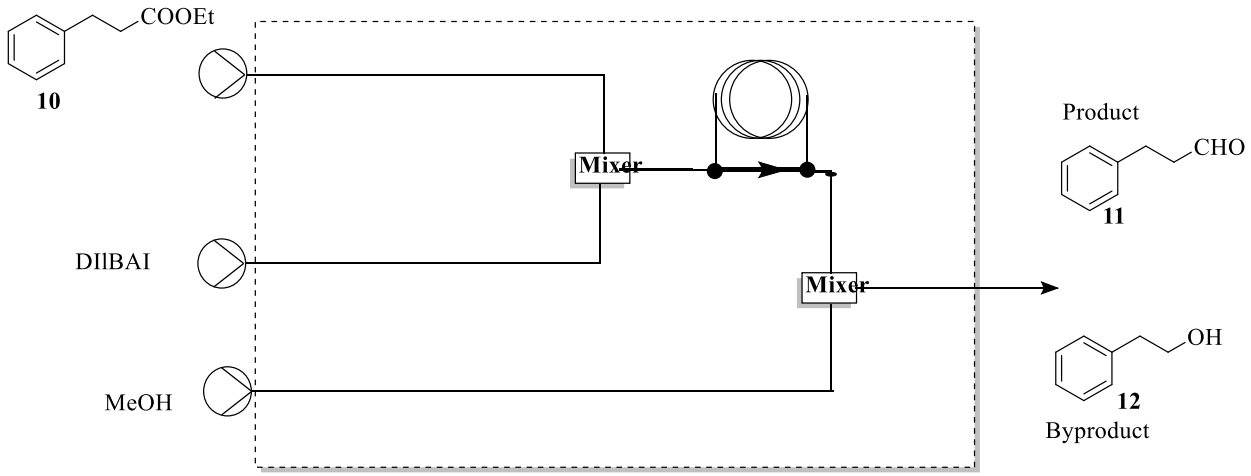


Scheme 2: *Flow set up for the automated machine assisted synthesis of ethyl 5-(3-nitrophenyl) oxazole-4-carboxylate* ***9****.*

1.4.2.5 Increased rates of reaction, yields and selectivity

The yield, rates of reaction and selectivity of many batch reactions is significantly increased when transferred to continuous flow systems. This is because of the much better mixing and heat transfer inherent to flow reactors.[56,60,61] This improved selectivity was demonstrated by Jamison *et al.* in the synthesis of 3-phenyl propanal through the diisobutylaluminium hydride (DIBAL) reduction of ethyl hydrocinnamate **10** to yield 3-phenylpropanal **11**. The setup consisted of two microtube reactors as shown in Scheme 3. The reaction was initially studied at -78 °C. Surprisingly, it was observed that shorter residence times selectively favoured the formation of the desired product 3-phenyl propanal **11**, due to the highly effective turbulent mixing occurring at the high flow rates

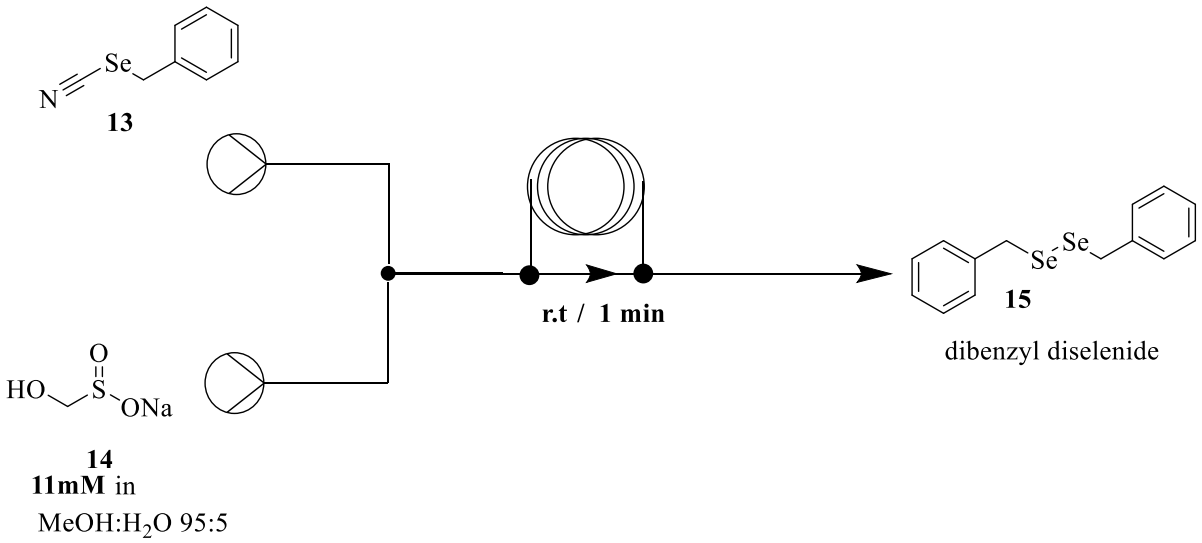
employed. The reaction was quenched with methanol, to ensure that the reaction does not progress beyond the desired residence times. Higher residence times selectively favoured the formation of the by-product 2-phenylethan-1-ol **12**, ultimately achieving full conversion and selectivity at residence time below 0.38 seconds.[62]



Scheme 3: *Schematic setup for the selective flow synthesis of 3-phenyl propanal* ***11***.

1.4.2.6 Small scale optimization reactions

Optimization of reactions using micro reactors allow for only very small amounts of chemicals to be used. This is especially advantageous when dealing with complex and multistep synthesis which require a lot of optimization studies. Using small amounts of material will make the optimization process cheaper, faster, safer and also reduce the amount of waste produced.[63] Heredia *et al* demonstrated the benefits of small scale optimizations in their synthesis of many selenides, one of which was dibenzyl diselenide **15**. The synthesis was done in a perfluoroalkoxy polymer (PFA) reactor coil, as shown in Scheme 4.[64] In their study, optimization reactions were done using micromolar concentrations of starting material, resulting in very small amounts of material being used to completely optimize the reactions. In their synthesis and optimization of dibenzyl diselenide for example, only 20 mM and 11 mM of the starting material benzyl selenocyanate **13** and Rongalite **14** were used respectively for optimization studies, eventually yielding 100% conversion of the diselenide in 1 minute.[64]



Scheme 4: *Flow setup for the synthesis of dibenzyl diselenide* ***15****.*

1.4.2.7 Improved safety

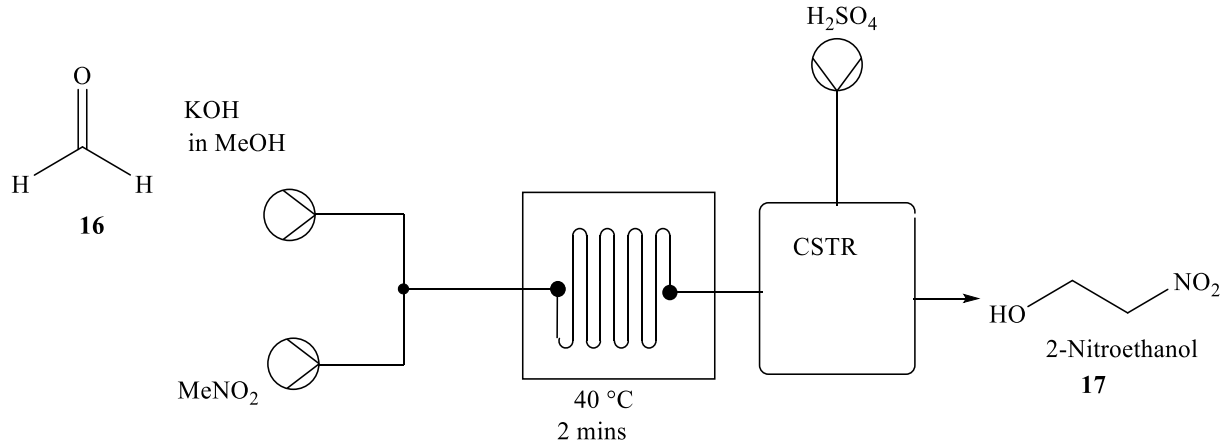
A significant advantage of using micro reactor technology is that there is an overall improvement in the safety of the synthetic process. Only small quantities of starting material are used at any time, ensuring that only small amounts of reactants are in contact with each other, thus improving process safety. The high heat and mass transfer efficiency allows for the quick dissipation of heat produced when dealing with dangerously exothermic reactions, thus improving the safety of these reactions.[39]

Another safety advantage of using continuous flow reactors is that the system can be pressurized, allowing reactions to occur at temperatures higher than the boiling point of the solvents used. This gives a wider range of options with regards to the solvents used. The more toxic, solvents can be therefore be easily replaced with less dangerous ones.[65,66]

In addition, toxic intermediates can be synthesized *in situ* in the closed micro reactor system and converted to a non-toxic product in the subsequent reaction. This means that toxic intermediates can be handled more safely, with no need for contact with the outside environment.[65,67]

Roberge *et al.* demonstrated the safety advantages of flow chemistry in the synthesis of 2-nitroethanol **17** in continuous flow systems. 2-Nitroethanol **17** is an important starting material in the synthesis of the API aliskiren, a drug used to treat high blood pressure. The high risk of explosion of nitroalkanes posed a major problem in the batch synthesis of 2-nitroethanol. Roberge

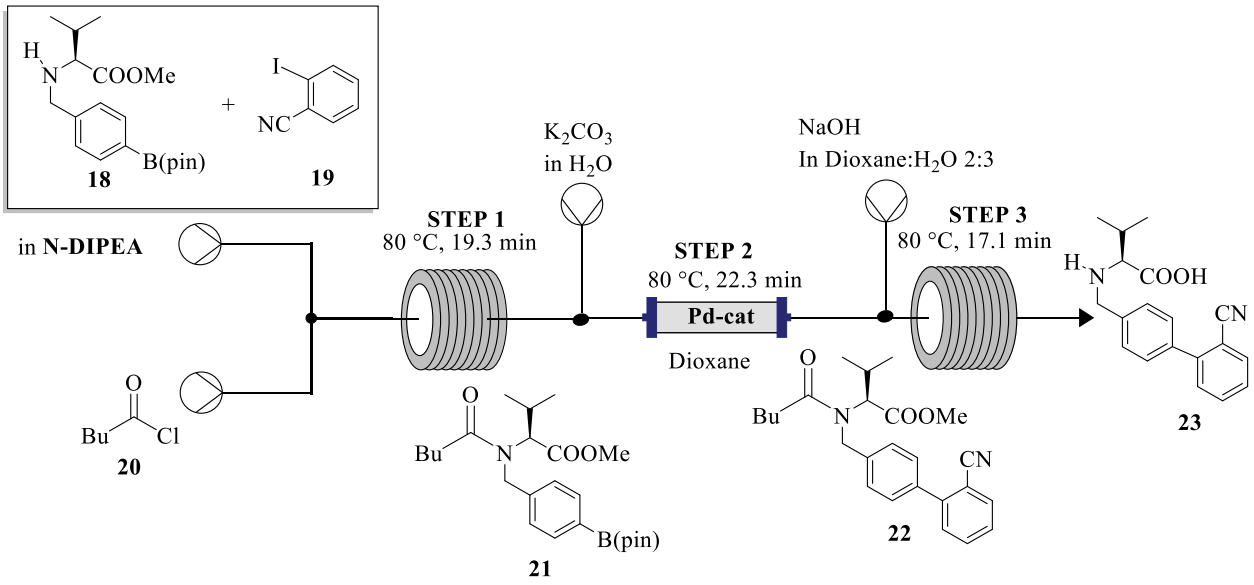
et al. exploited the safety benefits inherent to continuous flow chemistry, designed a flow setup for the synthesis, consisting of a micro reactor and a continuous stirred tank reactor (CSTR) as shown in Scheme 5. 2-Nitroethanol was safely produced with 100% conversion and a high isolated yield of 95%.[68]



Scheme 5: *Showing the continuous flow synthesis of 2-nitroethanol **17**.*

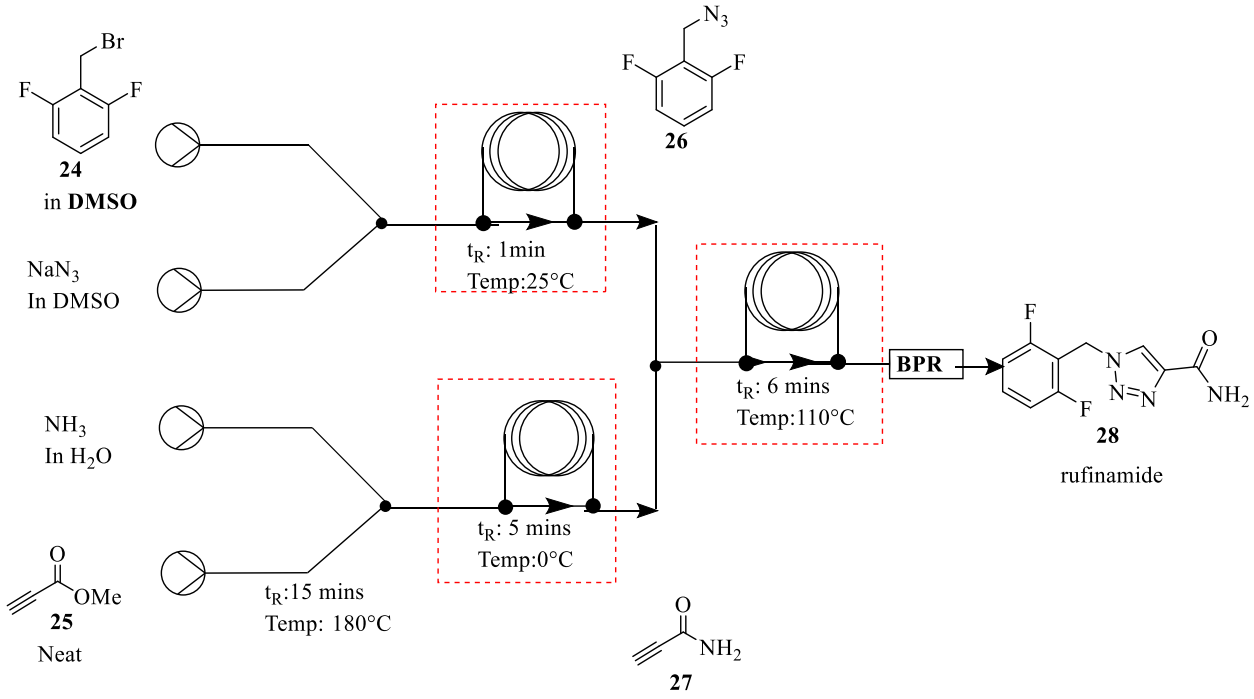
1.4.3 Flow chemistry in use

Continuous flow reactors have been used in the synthesis of some drugs and fine chemicals. Hielber *et al.* described the synthesis of a valsartan precursor. Valsartan is a nonpeptide angiotensin II receptor blocker, which is used to lower blood pressure in hypertensive patients. The first step of the synthesis in flow involved the *N*-acylation of the boronic acid pinacol ester **18** with valeryl chloride **20** with dioxane as solvent in a coil reactor to yield the intermediate **21**. The intermediate **21** then undergoes cross coupling with the 2-halobenzonitrile **19** in a packed bed reactor equipped with a fixed-bed of heterogeneous Pd-catalyst ($Ce_{0.20}Sn_{0.7}9Pd_{0.01}O_2$-δ) to yield the methyl ester **22**. Thirdly the methyl ester is then hydrolysed using NaOH in a long PTFE coil reactor to yield the valsartan precursor **23**. The synthesis of the valsartan precursor was adapted to flow chemistry reactors as shown in Scheme 6. The desired valsartan precursor was obtained with 100% conversion and 96% overall yield, in contrast to only 28% yield obtained for the corresponding batch synthesis on the desired valsartan precursor.[69]



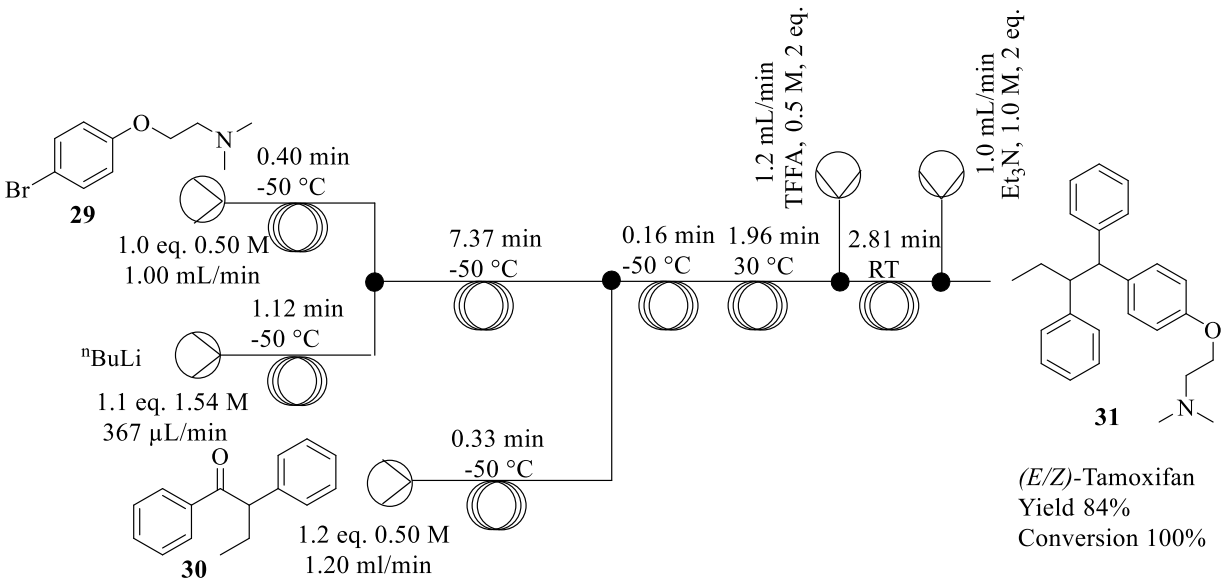
Scheme 6: *Flow setup for the synthesis of a valsartan precursor **23**.*

Jamison *et al.* described the multistep continuous flow synthesis of rufinamide. The process also included the safe synthesis and handling of a hazardous organic azide. In the first step, the benzyl azide **26** was synthesized by reacting the aryl bromide **24** with sodium nitrite in DMSO at room temperature with a residence time of 1min in a 40 μL copper coil reactor. In another 57 μL copper coil reactor connected in parallel, a propiolamide **27** was synthesized by reacting methyl propiolate **25** with aqueous ammonia at 0 ℃ and a residence time of 5 minutes, giving a 95% yield of the desired propionamide. The highly hazardous azide **26** and the unstable amide **27** were immediately mixed and streamed into a 431 μL copper tubing reactor for an azide-alkyne cycloaddition, ensuring the safe handling of these compounds. The reaction was done at 110 ℃ and 100 psi with a residence time of 6 minutes, after which rufinamide **28** was obtained with 100% conversion and a high overall yield of 92% (Scheme 7).[65]



Scheme 7: *Flow setup for the synthesis of rufinamide **28**.*

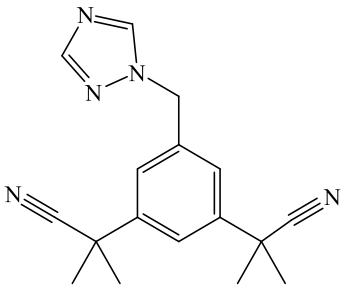
Another good example of continuous flow chemistry is in the synthesis of tamoxifen, a drug used to treat estrogen-receptor-positive (ER+) breast cancer, by the Ley group.[70] In the first step, *n*-butyllithium and the aryl bromide **29** were each passed through two reagent precooling PFA loops at -50 °C connected in parallel, before being streamed through a 10 mL PFA reactor. The reaction was then combined with the ketone **30** emerging from a precooling PFA loop at -50 °C before being streamed through a quenching PFA coil at -50 °C, followed by a reactor PFA coil at 30 °C. Next, a piston pump pumped trifluoroacetic anhydride (TFAA), into the reaction mixture which was then streamed in a PFA reaction coil at ambient temperature, followed by another piston pump pumping a solution of triethylamine to yield the *E* and *Z* isomers of tamoxifen (Scheme 8) The group was able to achieve a good yield of 84% of (*E/Z*)-tamoxifen **31** (*E/Z* ratio 25:75).[67] In contrast to the batch procedure, the product was achieved much quicker, with 13 g being formed in just 80 mins, enough treatment for a single patient for about two and a half years. Also, Ley *et al.* were able to achieve rapid temperature changes in the continuous flow setup. For example, a change in temperature from -50 °C in one reactor coil to 30 °C in the next coil. These rather drastic temperature changes would be difficult to replicate in a batch setup.[67]



Scheme 8: *Flow setup for the synthesis of E/Z Tamoxifen **31**.*

1.5 Anastrazole

Anastrazole **32**, chemical name 1,3-benzenediacetonitrile, a,a,a',a'-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl), is a potent third generation, non-steroidal aromatase inhibitor(AI) used to treat ER-positive breast cancer. The drug is often used after a mastectomy, to prevent the cancer from relapsing.[19,55,71] Anastrazole belongs to the chemical class of molecules known as azoles. Azoles are five-membered heterocyclic compounds that include a nitrogen atom and at least one other non-carbon atom, which could be oxygen, nitrogen or sulphur. Anastrazole is further classified under a subgroup of azoles known as triazoles. Triazoles are azoles that contain 3 nitrogen atoms and 2 carbon atoms in a 5-membered heterocyclic ring.[72,73]



32

Figure 3: *Showing the chemical structure of anastrazole.*

Clinical trials conducted with anastrazole involving post-menopausal women, at the early stages of hormone receptor-positive breast cancer, show that the drug is well tolerated and is a very potent third generation AI. Other generations of AIs are shown in Figure 4 below.

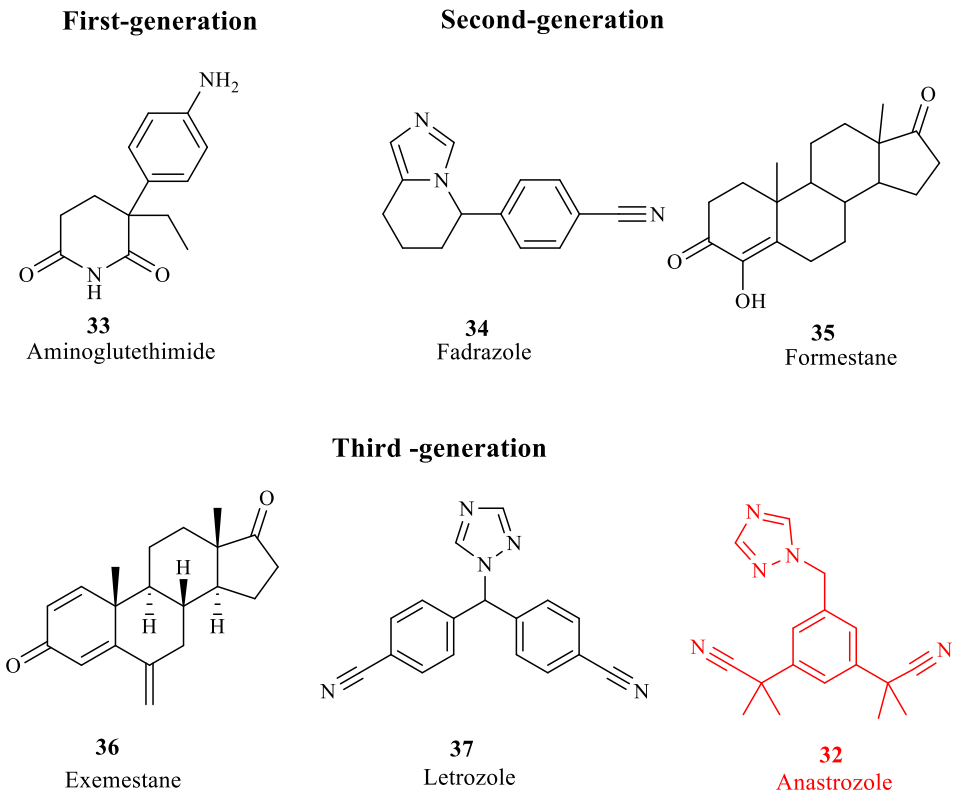


Figure 4: *The three generations of aromatase inhibitors.*

AIs inhibit the action of the enzyme aromatase, also called estrogen synthase and CYP19A1, part of the CYP-450 family of hormones. The enzyme aromatase catalyses an important step in the conversion of androgens to estrogens and these estrogens promote tumour growth in ER-positive breast cancer.[73] Therefore, by blocking the action of the enzyme aromatase, the drug prevents the proliferation of cancerous cells in ER+ breast cancer. However, the drug is only used for postmenopausal patients. This is because in premenopausal women, the ovaries are the primary production site for estrogens and AI's cannot stop the ovaries from making estrogens.[13,21,72,73]

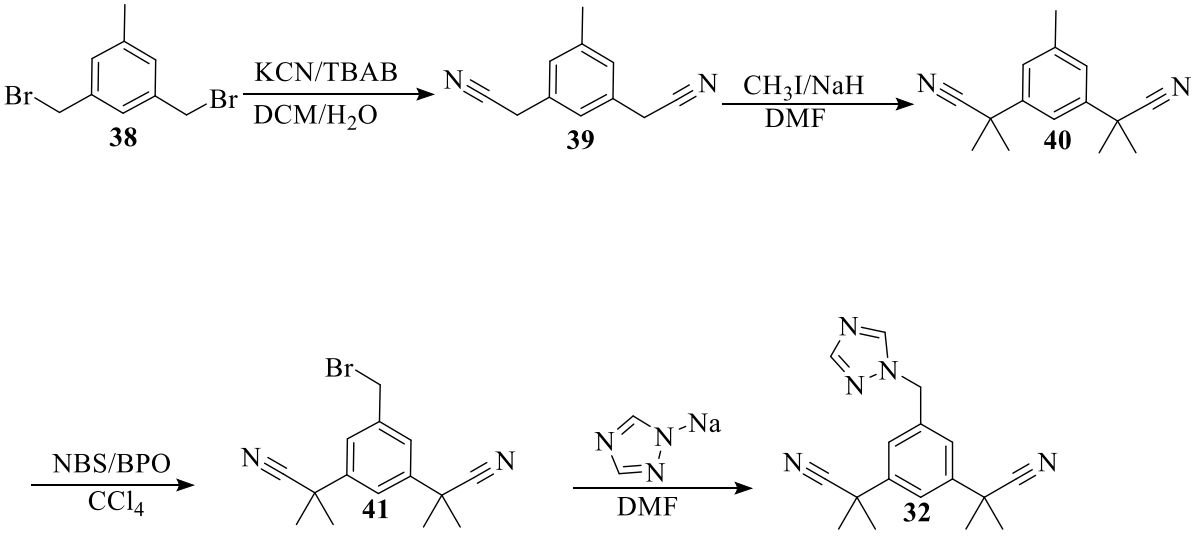
Anastrazole has been approved by the Food and Drug Administration (FDA) in the United States and in many other countries including the developing world. The drug is sold under the trade name Arimidex®.[73] The dosage of the drug is kept between 1-10 mg a day, the low dosage being due to

the drug's long plasma elimination half-life of about 30 hours. The drug is generally better tolerated than previous generations of AI's. Anastrazole can also be used in combination with other drugs. For example, anastrazole is often combined with tamoxifen in a tablet to treat early stages of breast cancer in post-menopausal women.[57,58,59]

1.5.1 Reported methods for synthesizing anastrazole

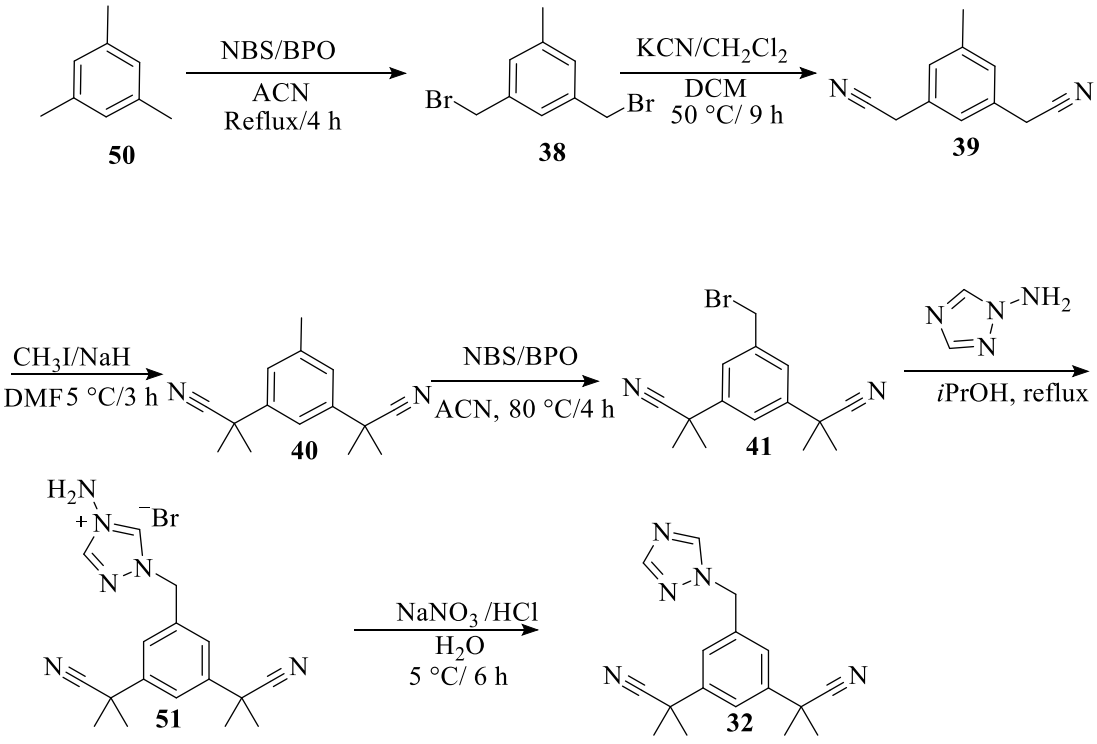
Many synthetic routes have been reported for the synthesis of anastrazole. The problems faced during scaling up for each of these synthetic routes have also been outlined. Some of these problems include low yields, high cost of production, slow product formation due to many steps in the synthetic route, formation of an unwanted anastrazole isomer, expensive starting materials and reagents *etc*.

The first synthetic route for the drug was disclosed by Edwards *and Large* of Imperial Chemical Industries (ICI) in 1987, as part of a patent that describes the synthesis of many important substituted heterocyclic compounds. The synthetic route comprised of 4 steps. In the first step 3,5-bis(bromomethyl)toluene **38** was reacted with potassium cyanide (KCN) in the presence of tetrabutylammonium bromide to give 3,5-bis(cyanomethyl)toluene **39**, which was then permethylated using iodomethane and sodium hydride as base to give 2,2'-(5-methyl-1,3-phenylene)bis(2-methylpropiononitrile) **40**. This product was then reacted with *N*-bromosuccinimide (NBS) with benzoyl peroxide as catalyst to yield the product 2,2'-(5-(bromomethyl)-1,3-phenylene)di-(2-methylpropiononitrile) **41**, which was then reacted with sodium 1,2,4 triazole to give anastrazole (Scheme 9). The overall yield for all the steps was not reported in this patent. The major problem encountered with this route is that an unwanted regioisomer is formed, during the conversion of **41** to anastrazole **32**. The quantity of this regioisomer formed was between 10-20%.[75]



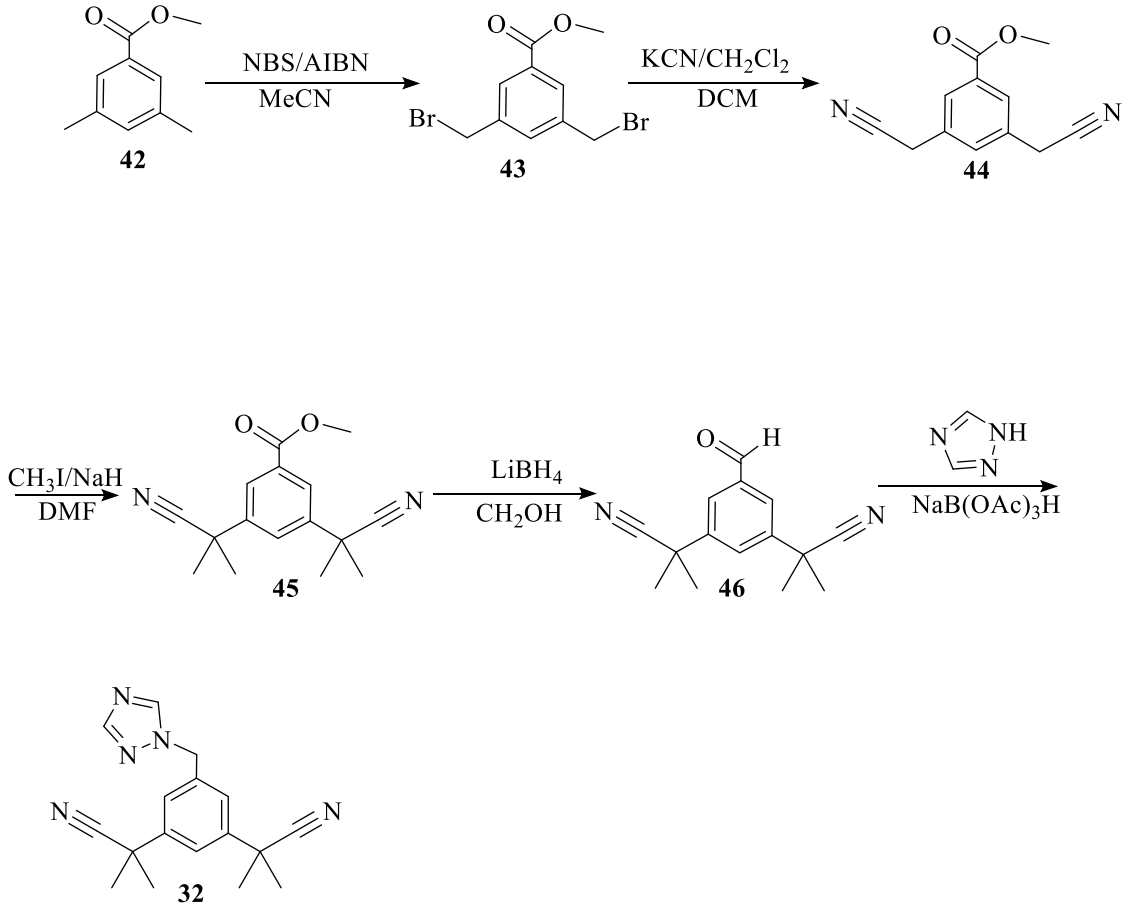
Scheme 9: *Alternative route for anastrazole* ***32*** *synthesis.*

Khile *et al.* revised the synthetic route proposed by Edward *and* Large came up with an overall improved synthetic route, with higher yield and shorter reaction times. In our opinion, this synthetic route is without a doubt the most practical and advantageous. This six-step synthetic route resulted in a 13% overall yield. In addition, the desired product was obtained from much cheaper starting material, making the process more sustainable, especially for large scale pharmaceutical production. In the first step, the starting material, mesitylene **50** was brominated using *N*-bromosuccinimide, in the presence of benzoyl peroxide as catalyst, forming **38**. The product **38** was then reacted with sodium cyanide and tetrabutylammonium bromide to yield the dinitrile **39**. Methylation using iodomethane and sodium hydride yielded **40**. Bromination of **40** using NBS yielded **41**, which was then reacted with 1*H*-1,2,4-triazol-1-amine in the presence of isopropyl alcohol forming the triazolium **51**. The triazolium **51** was then deaminated by reacting it with sodium nitrate in the presence of hydrochloric acid and water, forming anastrazole **32** (Scheme 10).[76]



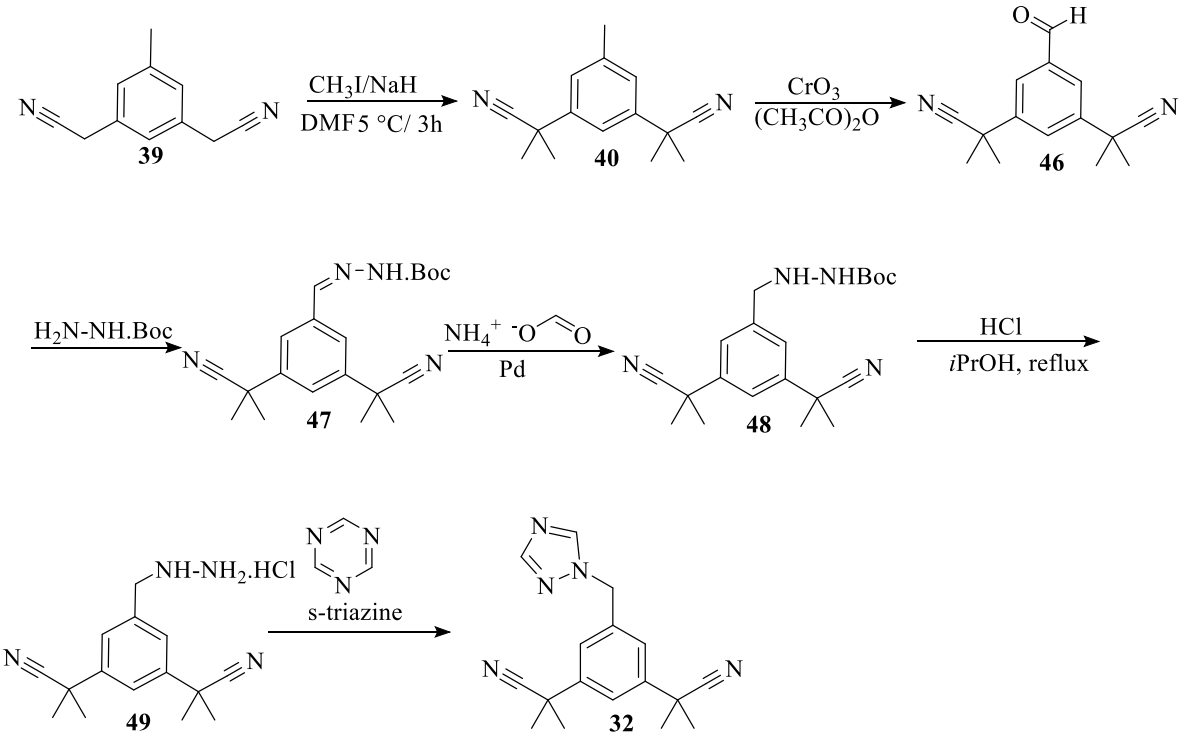
***Scheme 10**: Alternative synthetic route for Anastrazole **32**.*

Hailong *et al.* proposed another route starting from the dimethyl benzoate **42**, which was brominated using NBS to yield the di(bromomethyl)benzoate **43**. The reaction of **43** with KCN yielded **44**, which was then methylated using methyl iodide to produce the intermediate **45**. The intermediate **45** was then reacted with lithium borohydride to yield the benzaldehyde **46**. Reductive amination of the aldehyde **46** using triacetoxy sodium borohydride produced anastrazole **32** (Scheme 11). An overall yield of 52% was reported for this synthetic route. The main drawback with this synthetic route is the very expensive starting material and reagents, which makes the process less sustainable, especially for large scale pharmaceutical production.[77]



***Scheme 11**: Alternative synthetic route for Anastrazole by* Hailong *et al.*

Gaitonde *et al.* proposed another route for synthesizing anastrazole. In this synthetic route, the starting material **39** was methylated using iodomethane and sodium hydride to produce the nitrile **40**, which was then oxidized using chromium trioxide in the presence of acetic anhydride and sulfuric acid to obtain the aldehyde **46**. The aldehyde **46** was then reacted with H_2N-NHBoc to yield the hydrazone **47**, which is in turn hydrogenated using ammonium formate in the presence of palladium as catalyst to produce the hydrazine **48**. The hydrazine **48** was then treated with hydrochloric acid to obtain **49**, which was subsequently reacted with *s*-triazine to yield anastrazole **32** (Scheme 12). An overall yield of 14.5% was obtained, but the intermediate used as started material is very expensive, making the process very costly and less sustainable, especially for large scale production.[78]



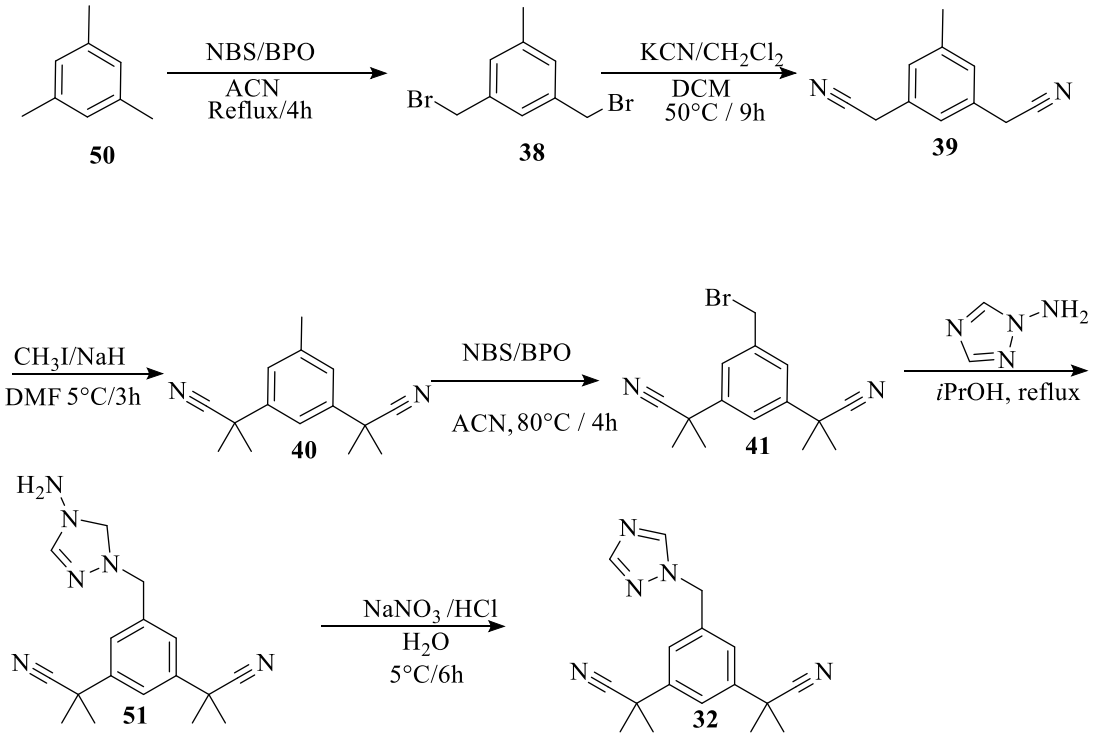
***Scheme 12**: Alternative synthetic route for Anastrazole.*

1.5.2 Proposed synthetic route towards anastrazole

In this study, anastrazole intermediates, will be synthesized using the synthetic route disclosed in the patent by Khile *et al,* with some small modifications. This synthetic route is the most practical and advantageous, due to the affordability of the starting Materials and reagents. Though some of the other synthetic routes towards anastrazole resulted in higher overall yield, the very expensive starting materials and reagents utilized make them less advantageous and unsustainable, especially for large scale pharmaceutical synthesis. Khile et al. revised the synthetic route proposed by Edward and Large of ICI and came up with an overall improved synthetic route, with higher yield and shorter reaction times. The six-step synthetic route resulted in a 13% overall yield. Also, the desired product was obtained from much cheaper starting material, making the process more sustainable, especially for large scale pharmaceutical production.

In the first step, the starting material **50** will be brominated using *N*-bromosuccinimide (NBS), in the presence of benzoyl peroxide as catalyst forming **38**. The product **38** will then be reacted with sodium cyanide and tetrabutylammonium bromide to yield the nitrile **39**. Methylation of the nitrile **39** using iodomethane and sodium hydride will potentially yield the propanenitrile **40**. Bromination

of **40** using *N*-bromosuccinimide will then hopefully yield the propanenitrile **41**, which will then be reacted with 1*H*-1,2,4-triazol-1-amine in the presence of isopropyl alcohol to form the triazolium **51**. The product **51** will then de-aminated by reacting it with sodium nitrate in the presence of hydrochloric acid and water, forming anastrazole **32**(Scheme 13).[76]



Scheme 13: *Proposed synthetic route towards anastrazole.*

1.6 Problem statement

Cancer is the second leading cause of death worldwide, with about 18.1 million cancer deaths in 2018. The annual number of cancer related deaths worldwide is predicted to rise to over 20 million deaths by 2030 and most of these cancer-related deaths are expected to occur in middle-income and low-income countries.[12,49] Most of the cancer deaths already occur in the predominantly low and middle income countries. In 2012, for example, more than 60% of the global cancer fatalities occurred in middle and low income countries and this is predicted to rise to more than 70% by 2030.[79]The African continent largely depends on importation of APIs and drugs to satisfy the ever-growing number of cancer cases. Importation places a very heavy financial strain on the governments and people of these low- and middle-income countries.

Most of the APIs and generics of drugs used in SSA are imported from China and India. The non-generic drugs are imported from countries like Germany, France, Italy and the United Kingdom. The weight of this import cost is significantly felt on the economy of these nations. In addition to this, despite efforts by Governments and other private organisation to make drugs more affordable, most of these life-saving drugs and generics are still too costly, due the low GDP per capita of these countries.[80] There is therefore a need to invest in alternative methods of synthesizing these life-saving APIs and drugs locally.

A relatively new technology which can be used to synthesize APIs and drugs locally to satisfy the growing African market is continuous flow reactor technology. Using simple and cheaper starting material, many drugs can be synthesized using flow chemistry reactors achieving high yields in shorter time. Anastrazole is one of these important drugs, being on the WHO list of essential medicines. The synthesis of intermediates of anastrazole, which is an important anti-cancer drug can potentially be telescoped into a multistep continuous flow system starting from mesitylene, to give a high yield and purity of the desired intermediates of anastrazole.

1.7 Research Questions

i. Can anastrazole intermediates be effectively synthesized in continuous-flow reactors?
ii. What is the effect of temperature, mole ratios, residence time, flow rate and catalyst on the conversion of starting material to the desired product for each step?
iii. What is the effective solvent system to use for the multistep telescoped synthesis of the intermediates?

1.8 Research Aims and Objectives

The overall objective of the project is to develop and demonstrate a continuous flow reactor system that can be used in the production of anastrazole intermediates. The project involves the development and optimization of a multistep continuous-flow chemical reactor system capable of producing an intermediate of anastrazole from the simpler starting material mesitylene.

The specific objectives of the study are as follows:

i. To synthesise anastrazole intermediates using known batch chemistry methods and obtain synthetic standards for each of the steps in the synthesis.

ii. These intermediates will be characterised by NMR spectroscopy, FTIR spectroscopy and HPLC.

iii. To design and construct a small continuous reactor system to produce anastrazole intermediates.

iv. To study the effect of reaction conditions which are temperature, flow rate, residence time and reactants composition on the conversion, yield and selectivity for each step in the synthesis of the intermediates.

Chapter 2 - Experimental details

2.1 Reagents and chemicals

All the reagents used in this research are tabulated below (Table 1), including the suppliers and their respective purities. Chemicals were used as received without further purification.

***Table 1**: Chemicals used with their grades, suppliers and purity.*

Chemical	**Formula**	**Purity**	**Source**
Mesitylene	C_9H_{12}	98%	Industrial Analytical
N-Bromosuccinimide	$C_4H_4BrNO_2$	99%	Industrial Analytical
Carbon tetrachloride	CCl_4	99%	Merck
Sodium cyanide	NaCN	99.9%	Sigma-Aldrich
Dichloromethane	CH_2Cl_2	99.8%	Sigma-Aldrich
Chloroform	$CHCl_3$	99.9%	Industrial Analytical
2-Methyltetrahydrofuran	$C_5H_{10}O$	99.9%	Merck
Acetonitrile	C_2H_3N	99%	Sigma-Aldrich
Methyl iodide	CH_3I	99.5%	Sigma-Aldrich
Sodium hydride	NaH	90%	Sigma-Aldrich
Dimethyl formamide	C_3H_7NO	99.8%	Industrial Analytical
Methanol	CH_3OH	99%	Sigma-Aldrich

2.2 Instrumentation

2.2.1 Nuclear magnetic resonance (NMR) spectroscopy

The NMR spectra of the samples were obtained using deuterated chloroform ($CDCl_3$) as the solvent. The spectra were recorded on a Bruker Ultra shield Plus spectrometer, which was operated at 400 MHz and the chemical shifts were recorded in parts per million (ppm). Samples were characterized using both ^{1}H-NMR and ^{13}C-NMR spectroscopy.

2.2.2 High performance liquid chromatography (HPLC)

The following HPLC methods were used. The sample analysis was done using an Agilent 1220 infinity LC, which was fitted with a PerkinElmer analytical C18 column and a diode array detector. The organic phase used was HPLC grade acetonitrile obtained from Sigma-Aldrich while the aqueous phase was degassed deionised water. The HPLC method parameters, like the run time, ratio of stationary phase to the mobile phase and flow rate were all tailored to suit the compound being analysed and these are detailed in Table 2 below. The column temperature was kept constant at 30 °C.

***Table 2**: HPLC parameters for analysis.*

Compound	**Solvent ratio**	**Flow rate**	**Run time**	**Optimum detection wavelength**
3,5-Bis(bromomethyl)toluene **38**	Acetonitrile: water (66:34)	1 mL/min	7 mins	265 nm
1,3,5-Tris(bromomethyl)benzene **53**	Acetonitrile: water (66:34)	1 mL/min	7 mins	265 nm
1-(Bromomethyl)-3,5-dimethylbenzene **54**	Acetonitrile: water (66:34)	1 mL/min	7 mins	265 nm
2,2'-(5-Methyl-1,3-phenylene)diacetonitrile 39	Acetonitrile: water (70:30)	1 mL/min	5 mins	254 nm
3,5-Bis(1-cyano-1-methylethyl) toluene **40**	Acetonitrile: water (70:30)	1.5 mL/min	5 mins	254 nm
2,2'-(5-Bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41**	Acetonitrile: water (70:30)	1.5 mL/min	5 mins	265 nm

2.2.3 Fourier transform infrared (FTIR) spectroscopy

Samples were analysed using FTIR to identify the functional groups present. A Bruker Platinum Tensor 27 spectrophotometer fitted with an Attenuated Total Reflectance (ATR) cell was used to analyse the samples, recording wavenumbers in the range of 4000-600 cm^{-1} and with the corresponding response variable in transmittance. All samples were analysed without modification.

2.2.4 Thin layer chromatography (TLC)

Thin layer chromatography (TLC) was done using a Mecherey-Nagel Alugram® aluminum backed TLC as the stationary phase and the mobile phase consisted of mixtures of solvents of different polarities. The spots on the TLC plates were visualized upon florescent exposure to short wavelength UV light (λ: 254 nm) in a Camag UV cabinet.

2.2.5 Column chromatography

Column chromatography was done using Fluka Chemie silica gel 60 as the stationary phase and varying polarities of a hexane and ethyl acetate mixtures as the mobile phase. Samples were collected and spotted on TLC for visualisation using fluorescence on exposure to short wave ultraviolet light (λ 254 nm) in a Camag UV cabinet.

2.2.6 Melting point determination

The melting points of the samples were determined using the Stuart SMP10 digital apparatus. Each sample was placed in a capillary tube made of soda glass and the capillary tube containing the sample was then placed in the Stuart SMP10's heating chamber. The instrument was programmed to go up to a temperature of 240 °C, with the temperature increasing by 5 °C every minute. The samples were observed using a magnifying glass and the temperature at which each sample melted was recorded.

2.3 General batch experimental procedures

2.3.1 Batch synthesis of 3,5-bis(bromomethyl)toluene

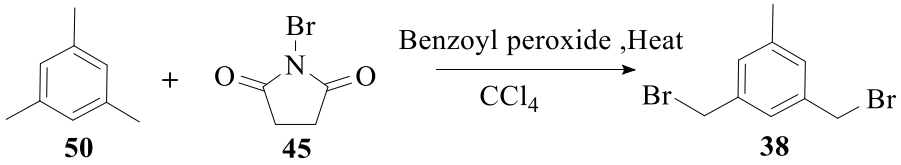


Figure 5: *Benzylic bromination of mesitylene **50** to yield 3,5-bis(bromomethyl)toluene **38**.*

A round-bottom flask containing a solution of 1,3,5-trimethylbenzene **50** (5.00 g, 41.6 mmol) and benzoyl peroxide (0.54 g, 2.2 mmol) in carbon tetrachloride (50 ml) was heated gently to 65 °C. NBS **45** (14.8 g, 83.2 mmol) was added to the mixture in small portions over a period of 1 hour. The solution was further refluxed for 3 hours and monitored using TLC (*n*-hexane: ethyl acetate 9.2:0.8). Upon completion of the reaction, the reaction mixture was filtered. The filtrate was

washed with a solution of sodium sulfite (5% in water, 2 × 10 mL), followed by a solution of sodium carbonate (5% in water, 2 × 10 mL) and finally sodium chloride (5% in water, 2 x 10 mL). The organic layer was concentrated to dryness under reduced pressure using a rotary evaporator, resulting in a yellowish oily residue. The residue obtained was dissolved in methanol at 60 °C, cooled gently to 15 °C in ice water and stirred for 2 hours. After 2 hours the solution was further cooled to 5 °C in ice and stirred for another 2 hours yielding the product 3,5-bis(bromomethyl)toluene **38** as a white solid. (6.9 g, 60% yield) melting point 63-64 °C (lit value: 64-67 °C).[76] ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H NMR: δ 2.27 (3H, s), 4.47 (4H, s), 7.07 (2H, s), 7.15 (1H, s). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*:20.97, 32.87, 126.68, 129.77, 137.97 and 139.55. FT-IR (cm^{-1}) υ: 2913, 1780, 1608, 1455, 1377, 1301, 1205, 1162, 1112, 955, 872, 854, 701, 616, 597 and 538.

2.3.2 Batch synthesis of 1,3,5-tris(bromomethyl)toluene

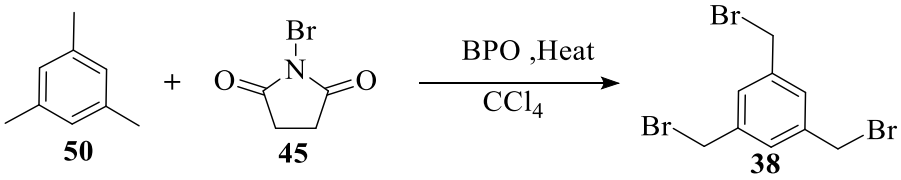


Figure 6: *Benzylic bromination of mesitylene **50** to yield 3,5-tris(bromomethyl)benzene **38**.*

Carbon tetrachloride (40 mL) was added to mesitylene (3.0 g, 25 mmol) in a round bottom flask, and the solution was heated to 70 °C. To the solution, NBS (15.6 g, 87.5 mmol) and benzoyl peroxide (0.121 g, 0.500 mmol) were added in small amounts over a period of one hour. After the final addition, the mixture was refluxed for an additional 18 hours and monitored using TLC (*n*-hexane: ethyl acetate 9.2:0.8). Upon completion of the reaction as determined by TLC, the reaction mixture was cooled and filtered. The filtrate was washed with a solution of sodium sulfite (5% in water, 2 × 10 mL), followed by a solution of sodium carbonate (5% in water, 2 × 10 mL) and finally with a sodium chloride solution (5% in water, 2 × 10 mL). The organic layer was concentrated to dryness under reduced pressure using a rotary evaporator giving a yellowish oily residue. The residue was dissolved in methanol at 60 °C and cooled gently to 15 °C using ice water. The solution was stirred for 2 hours, before being further cooled to 5 °C in ice and stirred for

another 2 hours yielding a white precipitate. This residue was purified through column chromatography by using silica gel column and ethyl acetate-hexane (225 mL: 25 mL) and the solution collected was concentrated to dryness under reduced pressure to yield 1,3,5-tris(bromomethyl)benzene **54** (2.68 g, 30% yield); melting point 94-97 °C (lit value: 94-99 °C).[73] ^{1}H NMR: δ 4.49 (6H, s) and 7.38 (3H, s). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*: 32.26, 129.47 and 139.18. FT-IR (cm^{-1}) υ: 3075, 1770, 1682, 1371, 1291, 1238, 1182, 1002, 935, 817, 636, 556 and 417.

2.3.3 Batch synthesis of 1-(bromomethyl)-3,5-dimethylbenzene

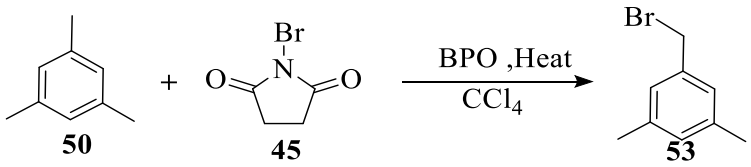


Figure 7*: Benzylic bromination of mesitylene* ***50*** *to yield 1-(bromomethyl)-3,5-dimethylbenzene* ***53****.*

To a round bottom flask containing mesitylene (3 g, 25 mmol), carbon tetrachloride (40 mL) was added and the solution was heated to 70 °C. To the heated solution, NBS (5.2 g, 29.1 mmol) and benzoyl peroxide (0.121 g, 0.5 mmol) were added in small amounts over a period of one hour. After the final addition, the mixture was refluxed for 2 hours and monitored using TLC (*n*-hexane: ethyl acetate 9.2:0.8). Upon completion of the reaction, the reaction mixture was cooled and filtered. The filtrate was washed with a solution of sodium sulfite (5% in water, 2 × 10 mL), followed by a solution of sodium carbonate (5% in water, 2 × 10 mL) and finally with a sodium chloride solution (5% in water, 2 × 10 mL). The organic layer was concentrated to dryness under reduced pressure using a rotary evaporator and the residue was dissolved in methanol at 60 °C and cooled gently to 15 °C using ice water. The solution was stirred for 2 hours, before being further cooled to 5 °C in ice and stirred for another 2 hours yielding a white precipitate. This precipitate was purified through column chromatography by using silica gel column and ethyl acetate-hexane (225 mL: 25 mL) and the solution collected was concentrated to dryness under reduced pressure to yield 1-(bromomethyl)-3,5-dimethylbenzene **53** (2.6 g, 50% yield); melting point 36-38 °C (lit value: 36-40 ^{o} C).[72] ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H NMR: δ 2.30 (6H, s), 4.35 (2H, s), 7.15-7.25 (3H, m). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*:21.28, 32.87, 126.68, 129.47, 137.97 and 139.86. FT-IR

(cm^{-1}) υ: 297, 1605, 1455, 1435, 1208, 1166, 1119, 979, 892, 856, 702, 661, 633, 578, 550 and 529.

2.3.4 Batch synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile

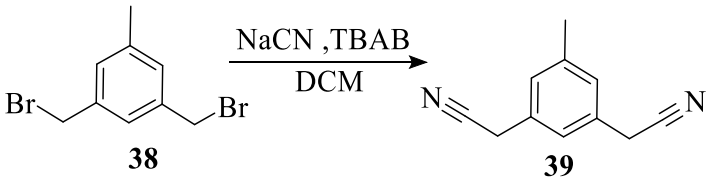


Figure 8: *Synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**.*

To a round bottom flask containing a solution of 3,5-(bromomethyl)toluene **38** (20 g, 72 mmol), tetrabutylammonium bromide (0.7 g, 2.1 mmol) and sodium cyanide (8.8 g, 180 mmol) in dichloromethane (40 mL) and water (20 mL) was added. The resulting mixture was refluxed for 9 hours and the reaction was monitored until completion using TLC (*n*-hexane: EtOAc 7.5: 2.5). Upon completion of the reaction as determined by TLC, the reaction mixture was cooled and the reaction mixture was extracted with dichloromethane (2 × 20 mL). The resulting organic mixture was then washed with water (10 mL), then with a solution of sodium chloride (5% solution, 10 mL). The organic layer was concentrated under reduced pressure at 40 °C. The product was recrystalised using a carbon tetrachloride solution and the solids obtained were dried using a rotary evaporator to obtain 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** as a light brown precipitate**.** (14.5 g , 91% yield); melting point 127-128 °C (lit value: 127-130 °C).[72] ^{1}H NMR: δ 2.31 (3H, s), 3.65 (4H, s), 7.06, (1H, s), 7.19 (2H, s). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*:20.97, 32.87, 116.57,126.68, 129.77, 137.97 and 139.55. FT-IR (cm^{-1}) υ: 2915, 2248, 1604, 1462, 1413, 1398, 1041, 934, 914, 891, 832, 707 and 676.

2.3.5 Batch synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene

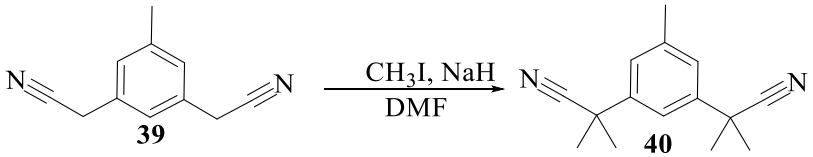


Figure 9: *Synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40*** .

To 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** (8.01 g, 31.0 mmol) in a round-bottom flask, methyl iodide (18 g, 126 mmol) was added, followed by dimethyl formamide (20 mL). The mixture was cooled to 0 ℃ and sodium hydride (60%) dispersion in oil (5.952 g, 248 mmol) was added in portions over a period of 1.5 hours hour. The mixture was then stirred for 4.5 hours while monitoring the reaction using TLC (*n*-hexane: EtOAc-7.5:2.5) until completion. The reaction mixture was poured into ice in a beaker and the solid obtained was filtered. The solid was dissolved in ethyl acetate (20 mL). As for the filtrate, it was also extracted using ethyl acetate (2 ×10 mL). The ethyl acetate solution was combined with the other ethyl acetate solution in which the solid was dissolved, and washed twice with water (2 × 20 mL). The ethyl acetate layer was separated and concentrated to dryness using a rotary evaporator to give a light brown residue. The residue obtained was crystallized from ethyl acetate-hexane (20 mL:10 mL) to obtain 3,5-bis(1-cyano-1-methylethyl)toluene **40** (7.1 g, yield 67%). Melting point 127-128 °C (lit value: 127-130 °C).[73] ^{1}H NMR: δ 1.72 (12H, s), 2.43 (3H, s), 7.27 (2H, s), 7.34 (1H, s). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*:21.55, 29.10, 37.06, 118.70, 124.33, 125.37, 139.39 and 142.44. FT-IR (cm^{-1}) υ: 2984, 2237, 1601, 1456, 1370, 1204, 1138, 867 and 706.

2.3.6 Batch synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile)

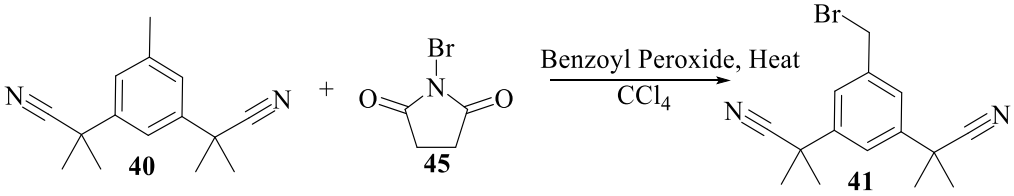


Figure 10: *Synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile)* ***41***.

To a round-bottom flask containing 3,5-bis(1-cyano-1-methylethyl)toluene **40** (4 g, 17.6 mmol) in carbon tetrachloride (40 mL), benzoyl peroxide (0.40 g, 1.70 mmol) and *N*-bromosuccinimide (3.3 g, 18 mmol) were added, and the mixture was refluxed for 3 hours. The reaction mixture was then cooled and filtered. The filtrate was concentrated to dryness at 40 °C and the residue obtained was dissolved in 2-propanol (20 mL) at 75 °C. The mixture was cooled to 15 °C and stirred for an hour, before being further cooled to 0 °C in ice and stirred for another 2 hours yielding a white solid. The solid was filtered and washed with chilled 2-propanol and then washed with *n*-hexane. The solid was then dried under vacuum at 45 °C to obtain 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41** (3.86 g, 72% yield). Melting point 98-99 °C (lit value: 98-100 °C).[76] ^{1}H NMR: δ 1.78 (12H, s), 2.42 (2H, s), 7.27, (2H, s), 7.34 (1H, s). ^{13}C-NMR (100 Hz, $CDCl_3$): *δ*:21.57, 28.50, 37.24, 118.85, 121.63, 125.71, 139.86 and 142.64. FT-IR (cm^{-1}) υ: 2984, 2238, 1602, 1456, 1371, 1204, 1139, 867 and 706.

2.4 Continuous flow systems

2.4.1 Chemtrix Labtrix system

In the synthesis and optimization of anastrazole intermediates, all reactions were optimized using continuous flow systems, to evaluate if the benefits inherent of flow chemistry would result in an overall improved process with shorter reaction times and higher yields and selectivities. The Chemtrix Labtrix system (Figure 11) was used to optimize the benzylic bromination of mesitylene **50** in a 15 µL 3224 Chemtrix reactor (Figure 12). The Chemtrix system was also used for the initial optimization reactions for the second step, the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**. The Chemtrix system reduces the amounts of reagents wasted during the optimizing process, since the system requires only very small amounts of starting material to carry out the reaction, making it ideal for laboratory work and reaction optimization.[81] The system can be used to investigate the effect of temperature between -20 °C to 195 °C and withstand pressures up to 20 bars with the use of a back pressure regulator.[82]

The system used consisted of a temperature controlled Labtrix unit connected to a controller where the temperature can be regulated. It also consisted of syringe pumps and syringes for pumping the different reactants into the micro reactor, connectors between the different components of the Labtrix system, glass reactor where the reaction occurs, pipes to transport material from the

syringes to the reactors and to transport post-reaction material from the micro reactors. The Chemtrix system used is shown in Figure 11.

Figure 11: *Chemtrix Labtrix start unit used in this study.*

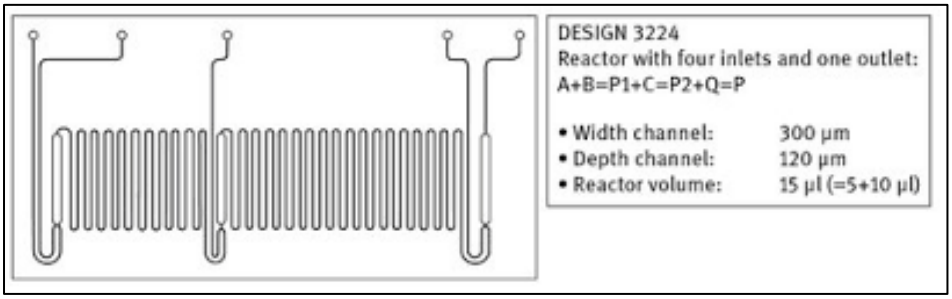


Figure 12: *Diagram showing the 3224 Chemtrix reactor used in this study.*

2.4.2 Little Things Factory reactor

The second step, the synthesis of 3,5-bis(cyanomethyl)toluene **39,** was optimized using both the Chemtrix system and the Little Things Factory reactors (LTF-MS reactor, volume 0.2 mL, channel size 1 mm and LTF-VS reactor, volume 1.7 mL, channel size 1 mm). The LTF reactor was also used to optimize the fourth step (synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41**) and to scale up the first step (synthesis of 3,5-bis(bromomethyl)toluene **38**). A schematic for the LTF reactor used in this study is shown in Figure 13 below.

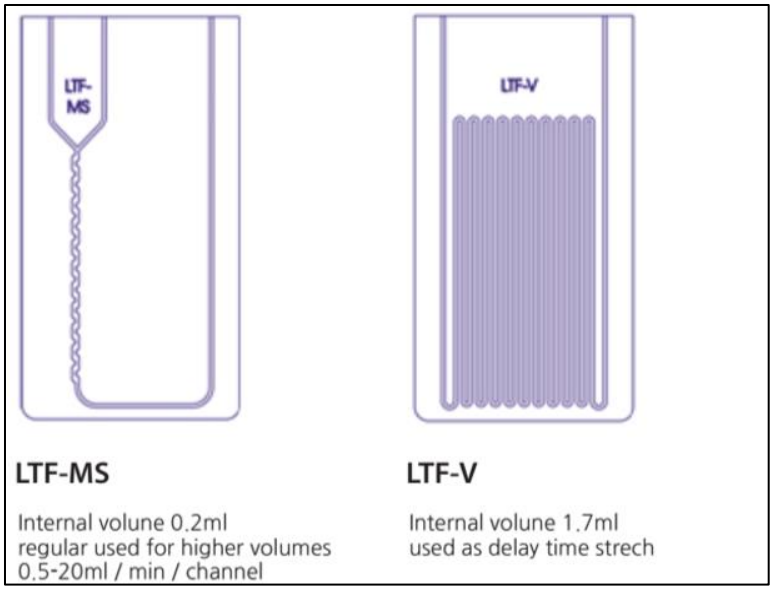


Figure 13: *Little Things Factory reactors used in this study.*

2.4.3 Polytetrafluoroethylene (PTFE) coil reactor

The synthesis of 2,2'-(5-methyl-1,3-phenylene)-di(2-methylpropiononitrile) **40** was done using polytetrafluoroethylene (PTFE) coil reactor (volume 1 mL, 1 mm channel size). An example of this PTFE tubing is shown in Figure 14 below.

Figure 14: *Showing an example of a PTFE coil reactor.*

2.4.4 T-mixer

A T-Mixer (Figure 15) was included in the setup used in the synthesis and optimization of 3,5-bis(1-cyano-1-methylethyl)toluene **40** and the telescoped synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile. Mixers are used to combine reactant components before they are streamed through the reactor. The T junction mixer improves mixing by allowing reactants to

combine with each other lineally and coming from opposite directions, ensuring a more turbulent flow.

Figure 15: *Showing a T junction unilateral mixer.*

2.4.5 Idex ultra-low volume back pressure regulator

The optimizations done in Chemtrix Labtrix start unit involved reactions with temperatures higher than the boiling point of the solvent used. It was therefore necessary to use back pressure regulators. The Idex ultra-low volume back pressure regulator (Figure 16) was used with the Chemtrix system, due to the very small volumes of materials being used. These back pressure regulators are fitted with tubes made of polyether ethyl ketone. While some Idex ultra-low volume back pressure regulators can be calibrated up to a pressure value 500 psi, the one used in this study had a maximum value of 100 psi.

Figure 16: *Idex ultra-low volume back pressure regulator.*[83]

2.4.6 Zaiput back pressure regulator

For optimization reactions done using Little Things Factory reactors, the Zaiput back pressure regulators (Figure 17) were used. These back pressure regulators can be calibrated up to a

maximum value of 290 psi, allowing flow chemists to investigate reaction at temperatures well above the boiling points of the fluids. The pressure set is based on the temperature needs of the reaction being investigated.

***Figure 17**: Zaiput back pressure regulator.*[84]

2.4.7 Chemyx fusion pumps

The Chemyx fusion pumps were used to pump solutions through the different reactors for all steps involved in this study. By varying the flow rate on the pumps, one can accurately replicate the residence time of a reaction. This touch screen enabled pump is easy to use. An example of the pumps used is shown in Figure 18 below.

***Figure 18**: Chemyx fusion pumps.*[85]

2.5 Synthesis and optimizations in flow chemistry

2.5.1 Flow synthesis and optimization of 3,5-bis(bromomethyl)toluene in the Chemtrix Labtrix system

The synthesis and optimization of 3,5-bis(bromomethyl)toluene **38** was carried out in the Chemtrix Labtrix start unit shown in Figure 11 using 15 µL Chemtrix glass reactor shown in Figure 12 above. The setup also included an Idex ultra-low volume back pressure regulator shown in Figure 16 making it possible to investigate temperatures higher than the boiling point of the solvent. The components of the system were connected as shown in Figure 19 below.

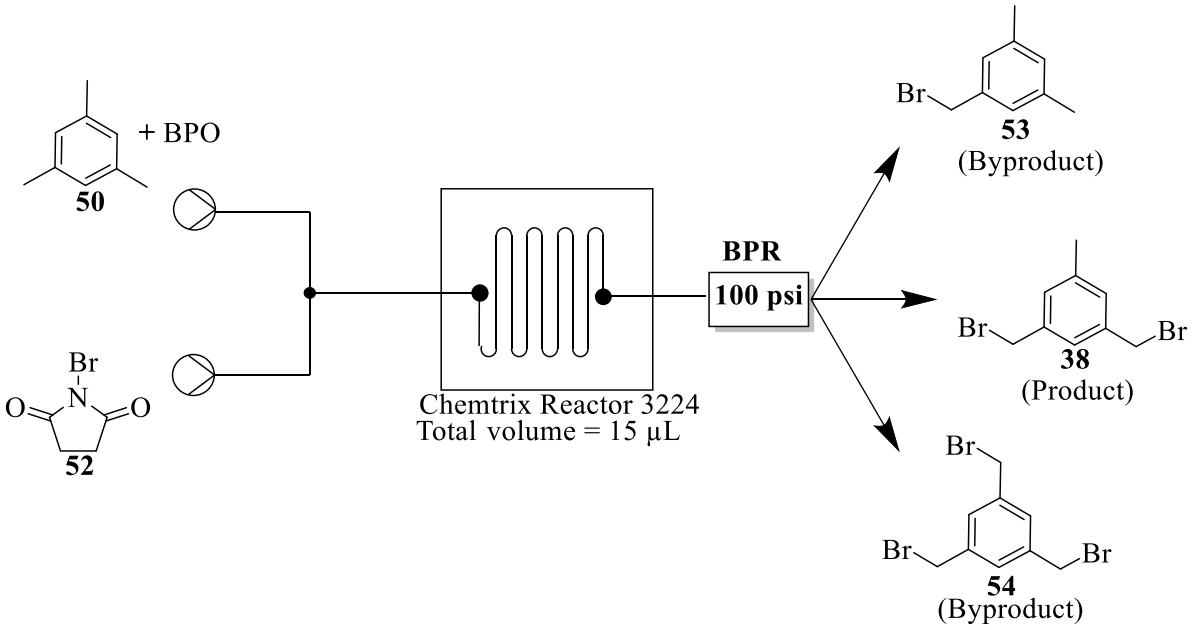


Figure 19: *Flow setup for the optimization of 3,5-bis(bromomethyl)toluene **38** in the Chemtrix Labtrix system (selectivity of other products studied).*

Mesitylene **50** and *N*-bromosuccinimide **45** were separately dissolved in the appropriate solvents to prepare specific concentration solutions which were pumped through the 15 µL Chemtrix micro reactor, at different flow rates, depending on the residence time being investigated. An Idex ultra-low volume back pressure regulator connected in series with the system allowed the reaction to be carried out at temperatures higher than the boiling points of the solvents screened. The products from the optimization reactions in flow were collected into vials containing acetonitrile for HPLC

analysis. Mesitylene **50** and the product 3,5-bis(bromomethyl)toluene **38** eluted at 7.1 min and 5.1 min respectively. The monobrominated byproduct **53** and tribrominated byproduct **54** eluted at 4.3 min and 5.9 min respectively. HPLC analysis was performed using the method reported earlier (Table 2, section 2.2.2).

2.5.2 Scale up synthesis of 3,5-bis(bromomethyl)toluene in an LTF reactor

The synthesis of 3,5-bis(bromomethyl)toluene **38** was also done in a 1.7 mL LTF reactor. The setup included an LTF mixer, the LTF reactor, connecting pipes, Chemyx fusion pumps and a 5 bar Zaiput back pressure regulator. The system was connected as shown in Figure 20 below.

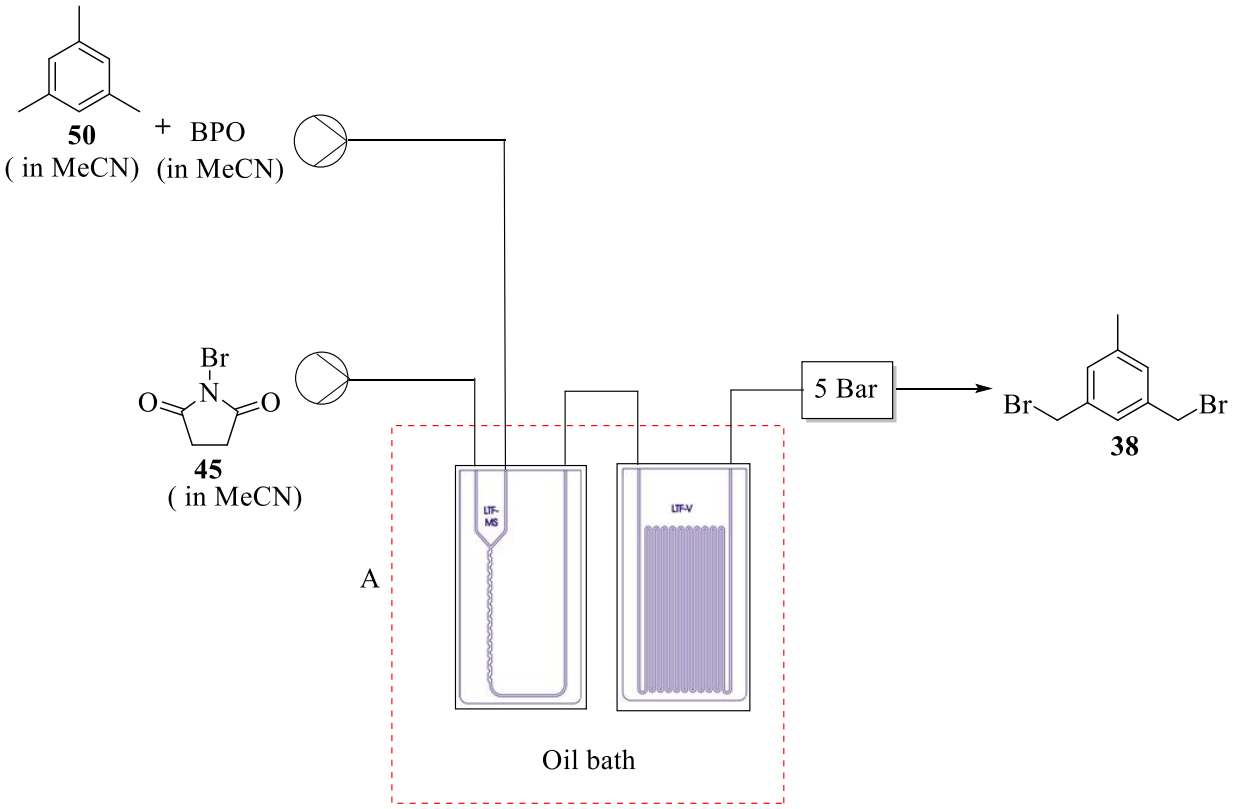


***Figure 20**: Schematic setup for synthesis of 3,5-bis(bromomethyl)toluene **38** in Little Things Factory reactors.*

Sample collection and HPLC analysis was done in the same way as in section 2.4 above.

2.5.3 Synthesis and optimization of 3,5-bis(bromomethyl)toluene in a photochemical reactor

The continuous flow synthesis of 3,5-bis(bromomethyl)toluene **38** was also attempted in a homemade photochemical reactor using UV light as a radical initiator. This homemade

photochemical reactor consisted of a BLE-6T365 UV lamp and 3 mL volume PTFE coil reactor, connected to a Chemyx fusion pump and a T-mixer as shown in Figure 21 below.

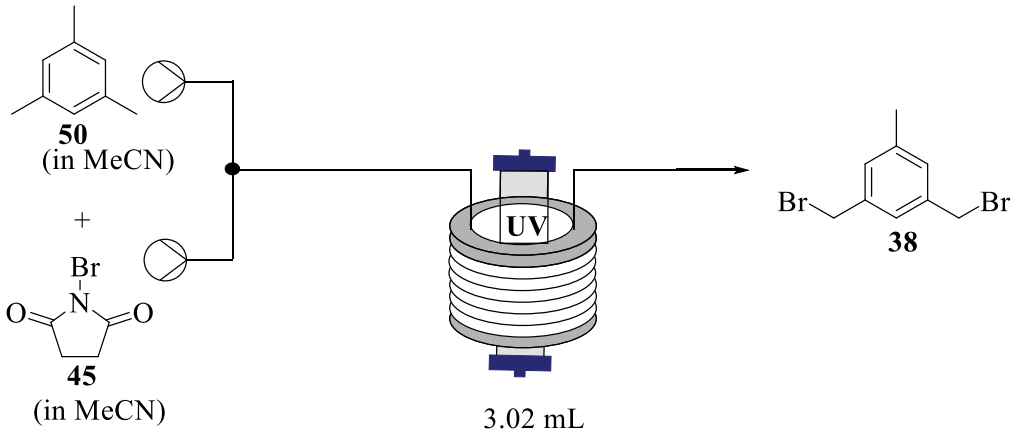


Figure 21: *Setup for the synthesis of 3,5-bis(bromomethyl)toluene* ***38*** *in a photochemical reactor.*

Sample collection and HPLC analysis was done in the same way as in section 2.4 above.

2.5.4 Flow synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile in the Chemtrix Labtrix System

The synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** was carried out in the Chemtrix Labtrix system and LTF reactors. The Chemtrix start unit consisting of a 15 µL Chemtrix glass reactor shown in Figure 12, connected to the Idex ultra-low volume back pressure regulator shown in Figure 16 previously. The schematic for the Chemtrix setup used is shown in Figure 22 .

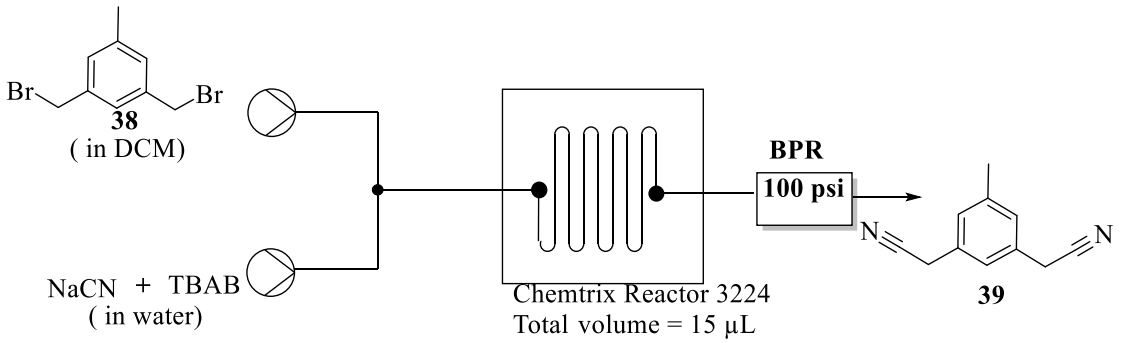


Figure 22: *Setup Schematic for the optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile* ***39*** *in the Chemtrix Labtrix Start unit.*

Due to the Chemtrix Labtrix start unit malfunctioning, we finalised the optimization of the reaction using a Little Things Factory reactor. The solutions were pumped through the 1.7mL LTF-Vs micro reactor. The reactor was fitted with a Zaiput back pressure regulator calibrated to 5 bar. The flow rate was controlled on the Chemyx© fusion pump. The temperature was varied by submerging the reactor in a heated oil bath and the temperature range investigated were between 50 °C and 190 °C. The system was connected and shown in Figure 23 below.

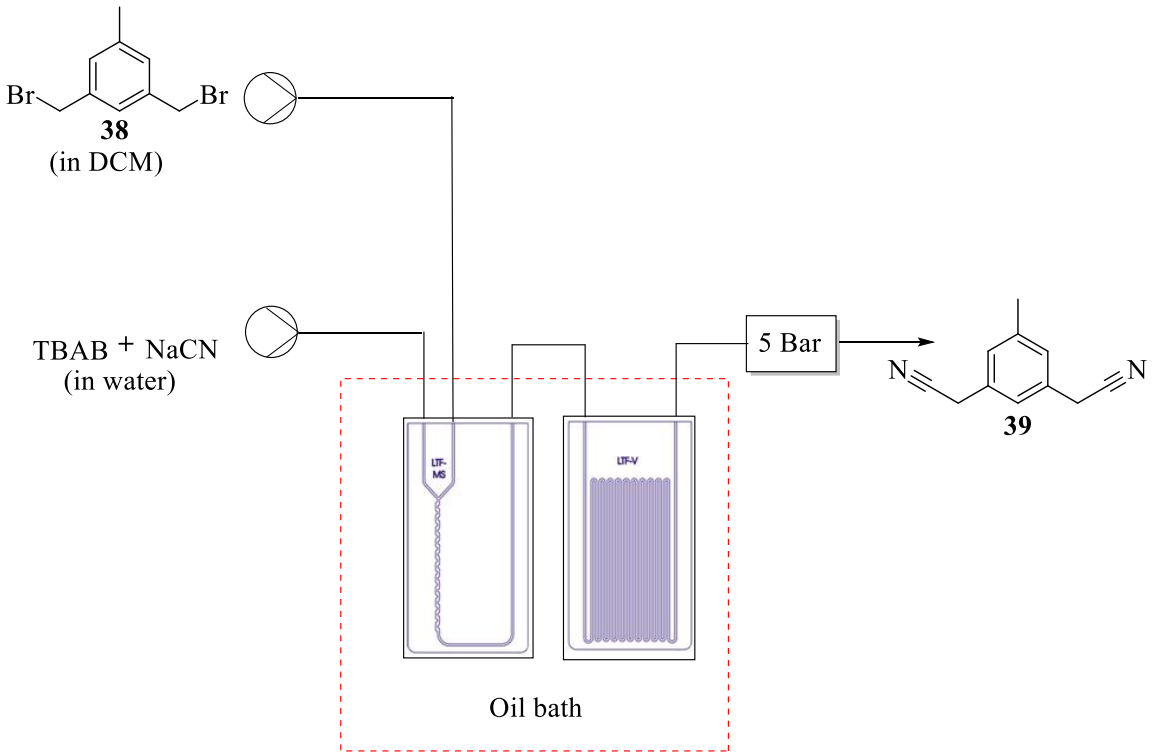


Figure 23: *Setup Schematic for the optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile* ***39*** *using Little Things Factory reactor.*

The samples were quenched with a solution of sodium hypochlorite and analysed *via* HPLC to observe the conversion towards the product 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** in flow from the starting material 3,5-bis(bromomethyl)toluene **38** and sodium cyanide. The 3,5-bis(bromomethyl)toluene **38** eluted at 5.1 min and product 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **39** eluted at 1.9 min. HPLC analysis was done using the method shown in table 2 above (section 2.2.2). The effect of temperature, residence time and reagents mole equivalents, mole equivalents of catalyst and the effect of different solvents on the conversion towards the dinitrile **39** were investigated.

2.5.5 Synthesis and optimization of 3,5-bis(1-cyano-1-methylethyl)toluene in PTFE coil reactor

Optimization reactions 3,5-bis(1-cyano-1-methylethyl)toluene **40** could not be done using the Chemtrix Labtrix system or LTF reactors due to clogging problems experienced with both systems even when using very low concentrations of reactants. It was therefore necessary to use an alternative reactor with larger channels. We therefore moved the optimization reactions to the

PTFE coil reactor, where we did not experience clogging problems, due to the larger channel sizes. The setup was connected as shown in Figure 24 below.

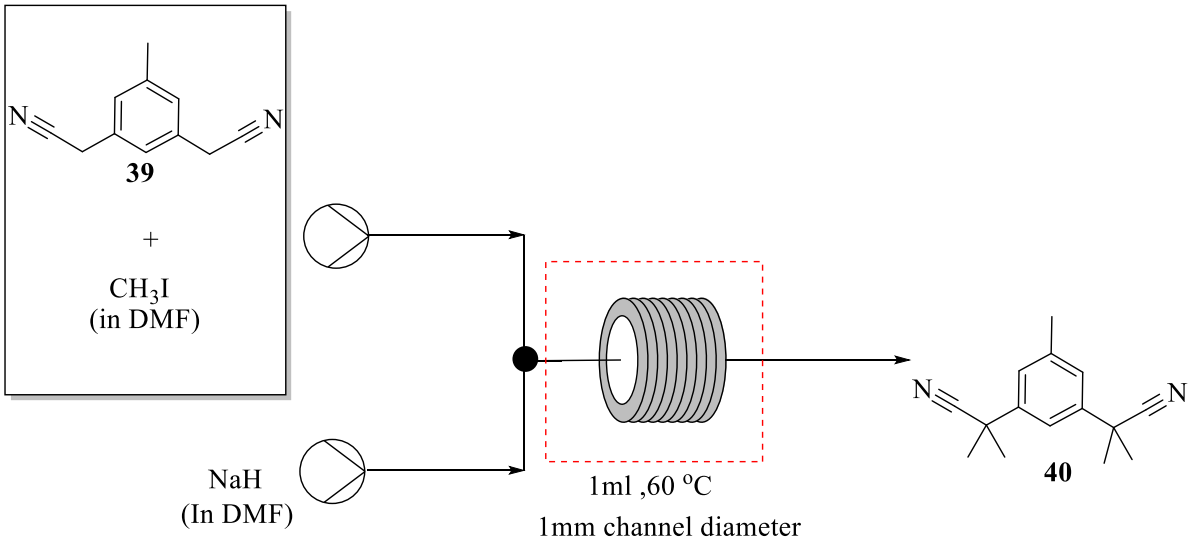


Figure 24: *Setup schematic for the synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40*** *in PTFE coil reactor.*

2,2'-(5-Methyl-1,3-phenylene)diacetonitrile **39** and methyl iodide in one syringe and sodium hydride (NaH) in another syringe were simultaneously streamed through T-mixer then through the 1 mL PTFE coil reactor. The reaction was quenched with water and pH adjusted to 7 using acetic acid upon collection. The quenched samples were taken for analysis using HPLC. 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** and the product 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **40** eluted at 1.9 and 2.8 min respectively, on HPLC analysis. HPLC analysis was the method shown in Table 2 above (section 2.2.2).

2.5.6 Synthesis and optimization of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) in a Little Things Factory reactor

The synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **40** from 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** in flow was done using the LTF reactor. The solutions of the reactants were pumped through a 1.7 mL LTF-Vs micro reactor fitted with a Zaiput back pressure regulator calibrated to 5 bars. The flow rate was controlled on the Chemyx© fusion pump.

The temperature was varied by submerging the reactor in a heated oil bath. The system was connected and shown in Figure 25 below.

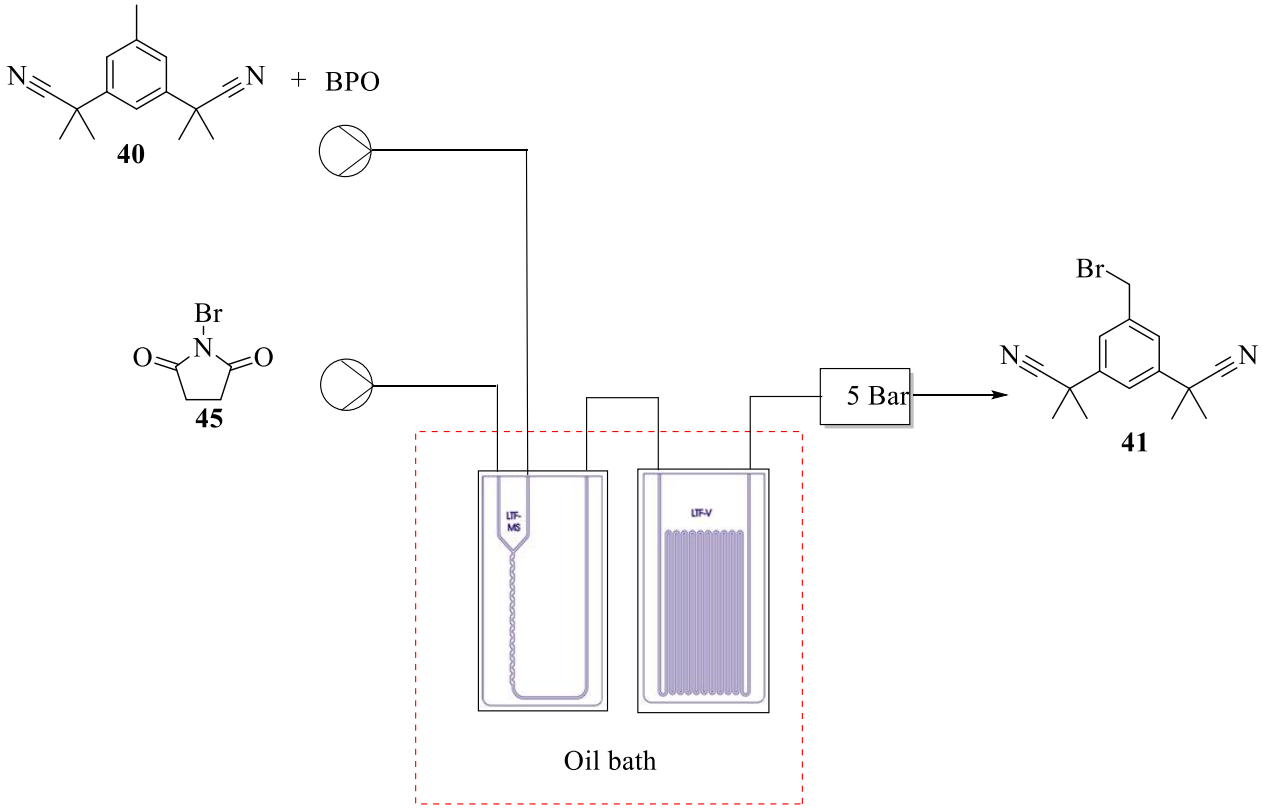


Figure 25: *Setup schematic for the synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile)* ***41*** *in Little Things Factory reactor.*

The solutions were streamed through the 1.7 mL LTF reactor and samples were quenched with a solution of sodium hypochlorite and collected into vials containing acetonitrile for analysis. The 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **40** eluted at 2.8 min and the desired product 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41** eluted at 2.3 min. HPLC analysis was done using the method shown in Table 2 (section 2.2.2).

2.5.7 Continuous flow multistep synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile

The multistep synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** was done using LTF reactors. The setup consisted of three LTF reactors, two T-mixers, three Chemyx fusion pumps and 10 bar back pressure regulator. A solution of mesitylene and BPO in one syringe and another solution of NBS (both in DCM as solvent) were simultaneously pumped through a T- mixer then

through two LTF reactors with a total volume of 3.4 mL. The reaction mixture emerging from the reactors combined with a solution of NaCN and TBAB (in water) in a second T-mixer before being streamed through the third LTF reactor. The reaction was quenched with a solution of sodium hypochlorite and taken for analysis. The system for the telescoped synthesis of **39** was connected as shown in Figure 26 below.

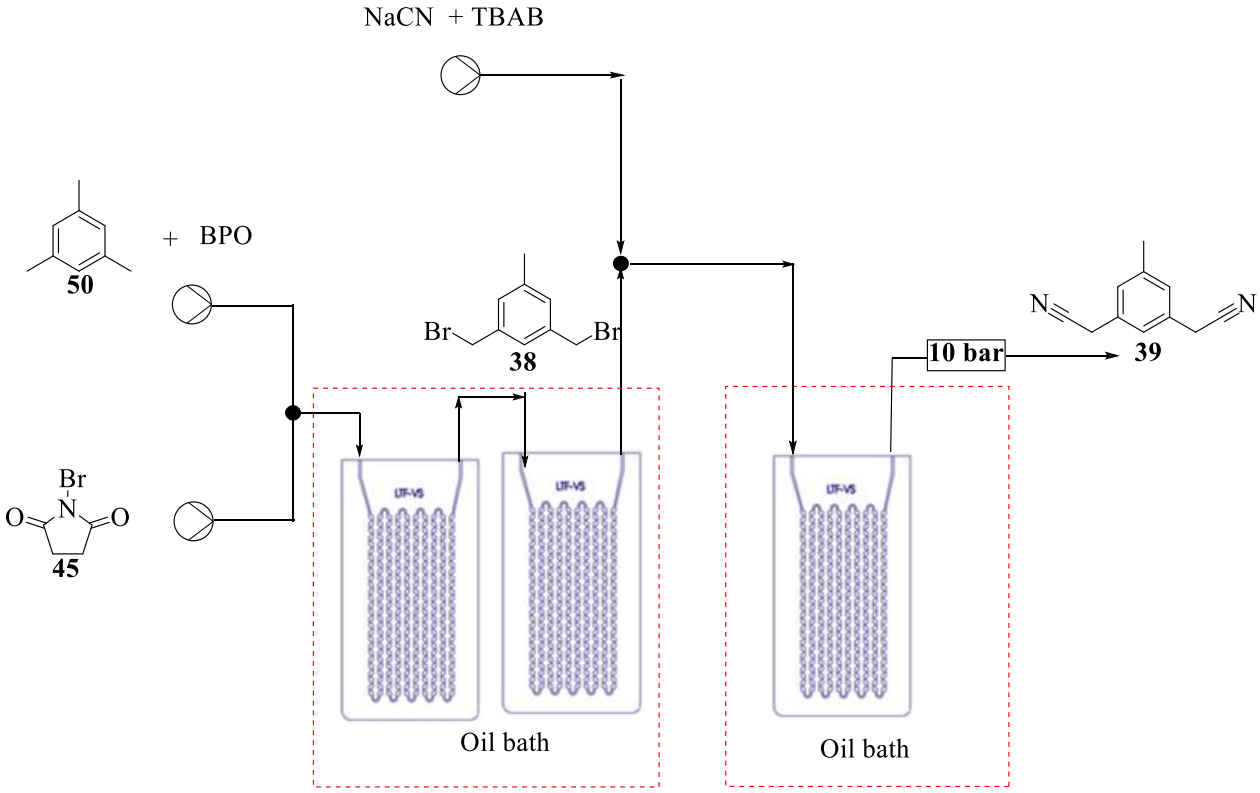


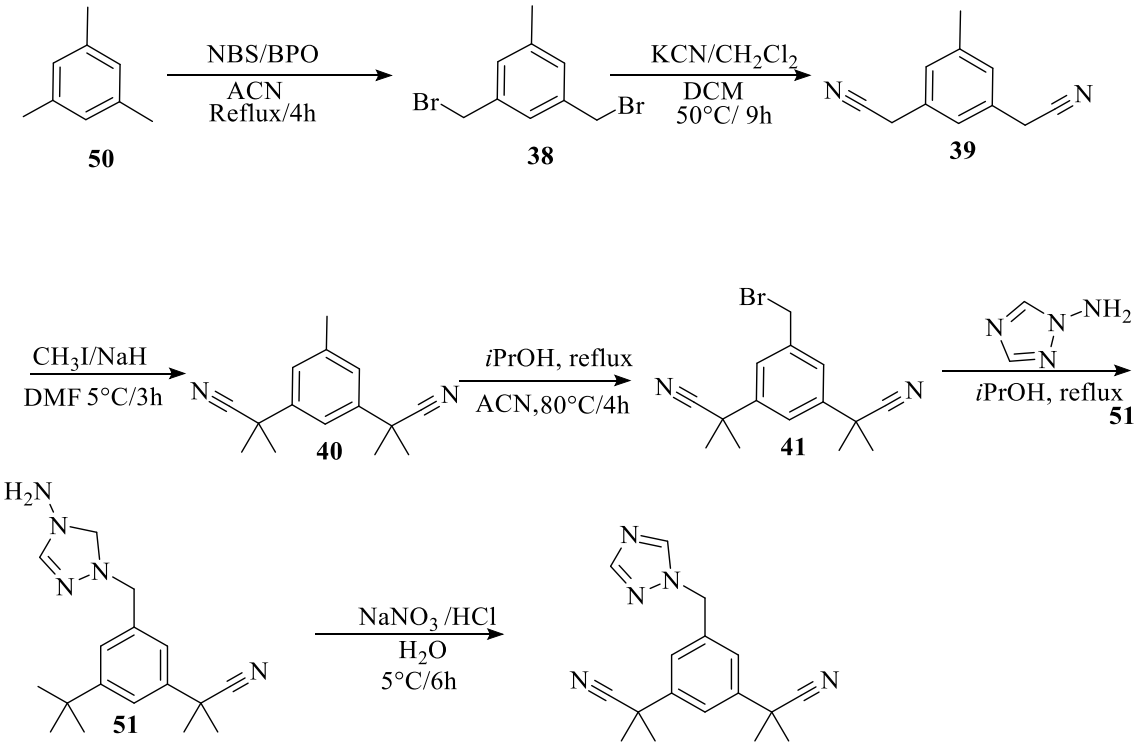
Figure 26: *Setup Schematic for the multistep synthesis of 3,5-bis(cyanomethyl)toluene* ***39****.*

Chapter 3 - Results and discussion

3.1 Introduction

Many synthetic routes have been developed for the synthesis of anastrazole, but most of them culminate in an overall low yield, wasting reagents and solvents. Synthetic routes with higher yields were made from very expensive starting materials.[46,47,48,49] This also increases the cost of production of the API, which translates into higher drug prices. In this chapter we investigate the synthesis of anastrazole intermediates in continuous flow chemistry systems, to evaluate if the benefits inherent to flow chemistry will help achieve the goal of lower production cost.

We sought to adapt the synthetic route shown in Scheme 13 to continuous flow systems. This synthetic route begins with the bromination of starting material **50** using *N*-bromosuccinimide (NBS) **45** in the presence of benzoyl peroxide as catalyst forming the aryl halide **38**. The aryl halide **38** is then reacted with sodium cyanide under phase transfer conditions to yield the diacetonitrile **39**. Then the methylation of the diacetonitrile **39** using iodomethane and sodium hydride to yield the propanenitrile **40** is needed, followed by the bromination of the propionitrile **40** to obtain the intermediate **41**.

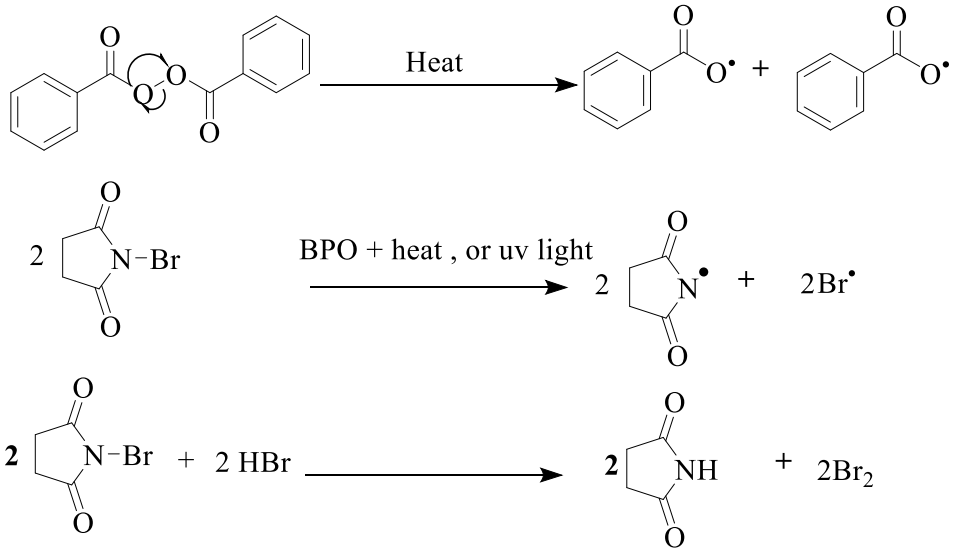


***Scheme 13**: Synthetic route towards anastrazole to be investigated.*

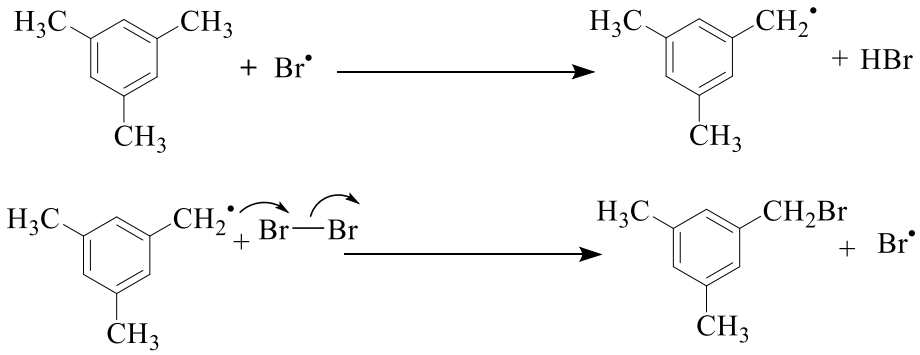
3.1.1 Synthesis and optimization of 3,5-bis(bromomethyl)toluene through the benzylic bromination of mesitylene

In the batch synthesis of 3,5-bis(bromomethyl)toluene **38**, a mixture of mesitylene **50**, *N*-bromosuccinimide (NBS) and benzoyl peroxide, were refluxed in carbon tetrachloride as solvent for 4 hours to give a yield of 60%. The reaction, known as a benzylic bromination reaction, is a free radical reaction. The benzylic position is very reactive due to good resonance stabilization in the transition state, favouring bromination at the benzylic position.[81] A plausible mechanism for the reaction is shown in Figure 27.

Chain initiation :



Chain propagation:



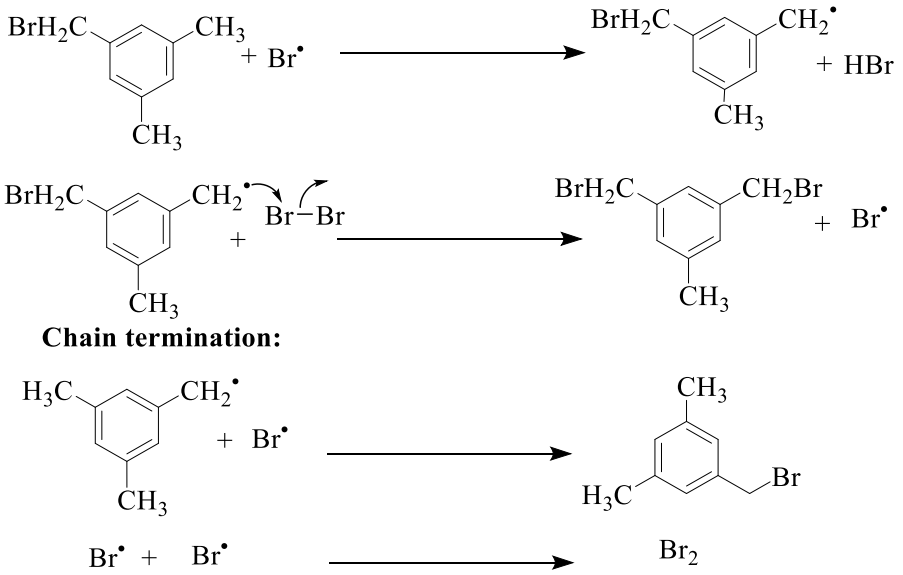


Figure 27: *Plausible reaction mechanism for the bromination of* ***50*** *to yield 3,5-bis(bromomethyl)toluene* ***38****.*

The mechanism for this reaction, can be divided into three stages: free radical initiation, chain propagation and termination.[86] NBS is used as a source of the bromine radicals in very low concentration. Heat and the radical initiator benzoyl peroxide (BPO) are used to induce the release of bromine radicals from NBS during the initiation phase of the mechanism. During the propagation step, the bromine radicals abstract a hydrogen each from two methyl groups on mesitylene **50**, forming the radical mesitylene moiety and releasing HBr. The HBr generated is consumed by NBS in an ionic process, while the mesitylene radical abstracts a bromine atom each from other bromine molecules (Br_2) forming new bromine radicals, which can then repeat the propagation step of the mechanism all over. The termination step of the mechanism involves reaction between the different radicals formed during the initiation and propagation stages to yield either the product 3,5-bis(bromomethyl)toluene **38** or regenerate the bromine molecule.

For the reaction, it is possible to use either molecular bromine (Br_2) directly or NBS as a source of bromine radicals. However, to control the amount of bromine radicals in solution at any given time more accurately, we decided to use NBS. This is because using molecular bromine (Br_2) will result in a high concentration of bromine radicals in solution, which favours polar addition over the radical reaction, resulting in bromine radicals attacking double bonds on the benzene ring and forming of unwanted byproducts.[82,87] The use of NBS guarantees a lower concentration of bromine

radicals in solution and makes aromatic bromination unlikely. For the benzylic bromination reaction, either heat or UV light is required to induce the formation of bromine radicals during the initiation step of the reaction mechanism.[86] We investigated both heat and UV light as radical initiators for the synthesis of 3,5-bis(bromomethyl)toluene **38**. In batch, the maximum temperature attainable was limited to 76 °C, the boiling point of the solvent used which was CCl_4. A major advantage of flow chemistry is that the system can be pressurized so that reactions are carried out at temperatures much higher than the boiling of the solvent being used.[88] Consequently, in flow chemistry reactors, we were able to investigate temperatures ranging between 80 °C to 160 °C. Another very important factor to consider with this reaction is the likely formation of two by-products; 1,3,5-tris(bromomethyl)benzene **54** and 1-bromomesitylene **53**, which reduce the yield of the desired side product **38**. The two most likely by-products are shown in Figure 28 . It was therefore necessary to do selectivity studies to maximize the synthesis of the desired product **38**. To be able to accurately evaluate the selectivity towards **38**, it was necessary to also synthesize both by-products (**53** and **54**) in batch and obtain pure standards, which we then analysed using HPLC. In the batch synthesis of the monobrominated by-product **53**, we obtained 50% yield after 3 hours while the batch synthesis of the tribrominated by-product **54** yielded 30% after 19 hours. A Chemtrix Labtrix system was initially used for the synthesis and optimisation of 3,5-bis(bromomethyl)toluene **38** in flow (Figure 28).

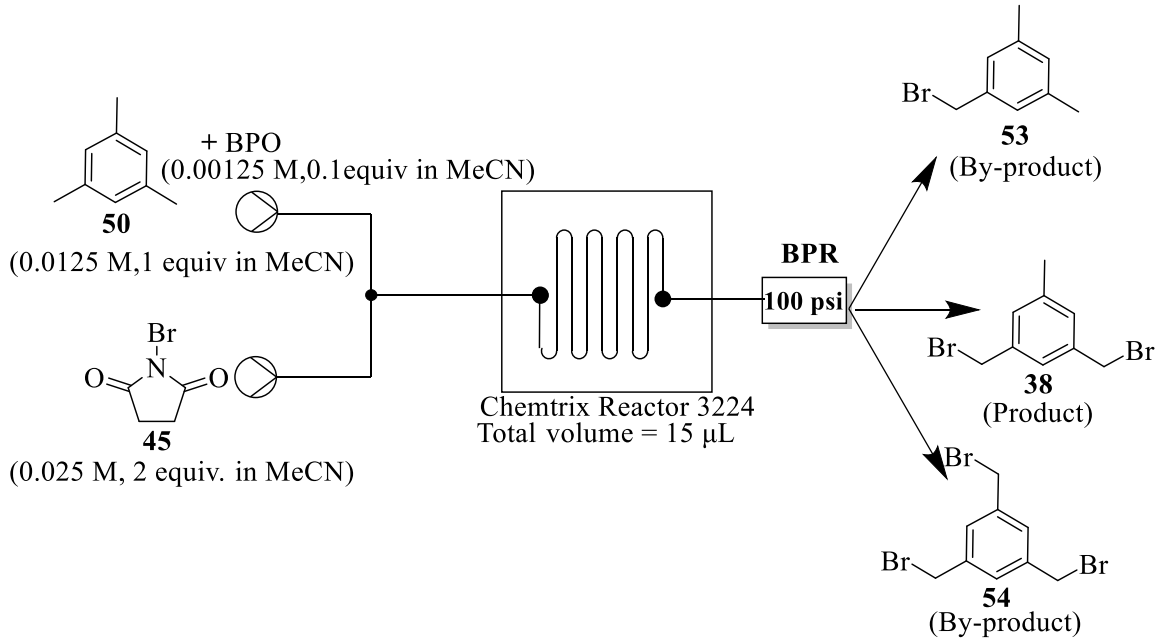


Figure 28: *Chemtrix setup for the synthesis of 3,5-bis(bromomethyl)toluene **38**.*

We were able to optimize the formation of the desired product **38** by investigating different temperatures, molar ratios of reactants, concentrations of the catalyst and residence times. We were unable to use carbon tetrachloride as the solvent for the flow optimization reactions of 3,5-bis(bromomethyl)toluene **38** because it did not dissolve the NBS **45** (or succinimide, the molecule left over after the bromine radical is released from NBS) and will therefore lead to blockages in the system. We were able to identify acetonitrile as a good solvent for the reaction, which also dissolves NBS.[89] We therefore carried out our optimization studies using acetonitrile as the solvent. Acetonitrile, the solvent used in flow, dissolves the succinimide moiety and this would make separating the product **38** from the succinimide difficult in batch.[89]

A preliminary study was done at 80 °C and residence time of 15 seconds. Mesitylene **50** (0.0125 M) and NBS **45** (0.025 M, 2 equiv. w.r.t. **50**) with benzoyl peroxide (0.00125 M, 0.1 equiv. w.r.t. **50**) as catalyst were pumped through the 15 µL Chemtrix glass micro reactor. It was necessary to use these very small concentrations of starting material in the first instance, as we experienced clogging at even slightly higher concentrations due to product precipitation in the very small channel sizes of the Chemtrix micro reactor. In monitoring the disappearance of the starting material (mesitylene **50**) peak on HPLC, we observed 86 % conversion for the preliminary study. Although the conversion was high, HPLC analysis showed that the selectivity towards the desired

product 3,5-bis(bromomethyl)toluene **38** was only 75% (*i.e.* 75% of mesitylene **50** was converted into the desired product **38**). The selectivity towards the tribrominated by-product **54** and the monobrominated by-product **53** were 20% and 5% respectively. We therefore concluded that a selectivity study, to maximise the yield of the desired product **38** was necessary.

3.1.1.1 Selectivity study

The aim of the study was to obtain maximum selectivity for the desired product in the shortest time possible, while using the smallest quantities of reactants necessary. While conversion shows the amount of starting material consumed, selectivity focuses on the formation of a particular desired product. All optimisation reactions were done using the 15 μL Chemtrix glass micro reactor. The effect of temperature, residence time, molar equivalents of the reactants and the concentration of the catalyst on the conversion of **50** and the selectivity towards **38** were all investigated. We began our selectivity study by investigating the effect of different temperatures on the conversion of mesitylene **50** towards the desired product 3,5-bis(bromomethyl)toluene **38**. For this study, mesitylene **50** (0.0125 M in acetonitrile) was reacted with NBS **45** (0.025M, 2 equiv. w.r.t. **50**, in acetonitrile) with benzoyl peroxide (0.00125 M, 0.1 equiv. w.r.t. **50**) as catalyst. The temperature range for the investigation was 80–160 °C. For this study, the residence time was kept constant at 15 seconds. The conversion of mesitylene **50** and the selectivity towards the desired product **38** were both monitored. The results of this study are displayed in Figure 29.

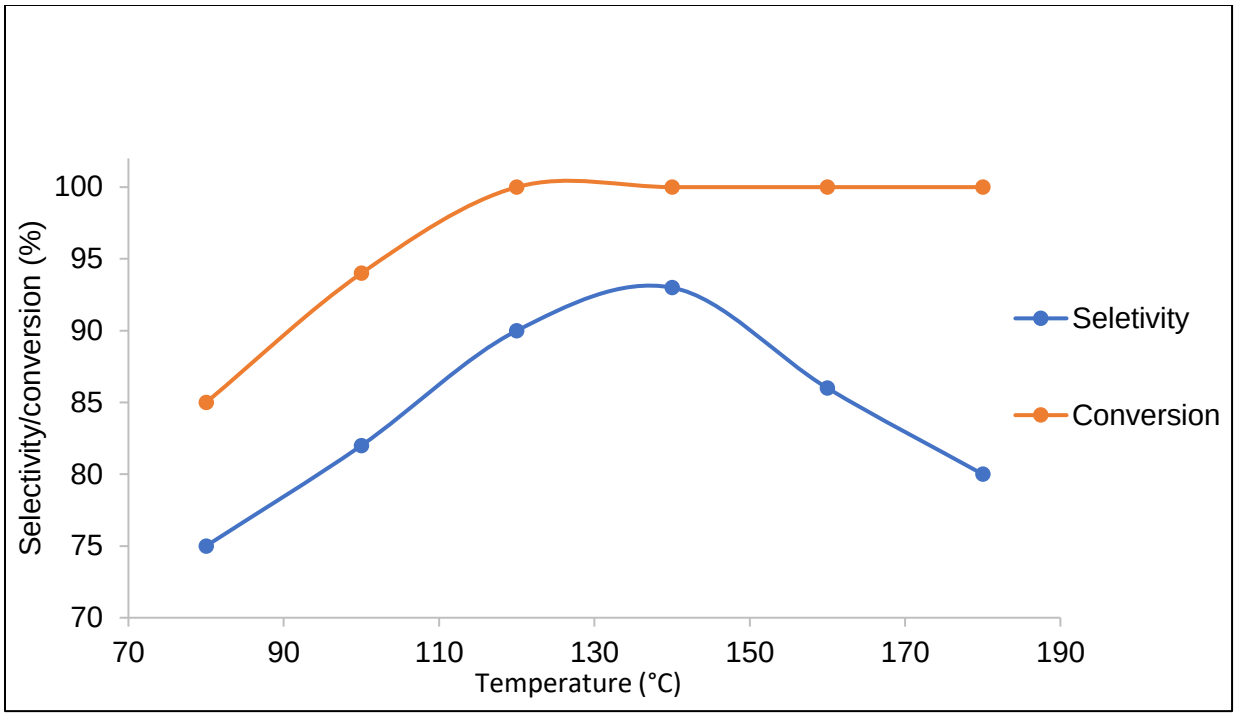


Figure 29: *effect of temperature on the conversion of mesitylene **50** and selectivity towards 3,5-bis(bromomethyl)toluene **38** in Chemtrix Labtrix system.*

The results obtained from the temperature study show that the temperature has a significant effect on both the conversion of mesitylene **50** and selectivity towards 3,5-bis(bromomethyl)toluene **38**. The trend of the curve obtained shows a general increase in the conversion of mesitylene **50**, ultimately achieving a maximum conversion of 100% at 120 °C. The selectivity towards 3,5-bis(bromomethyl)toluene **38** also increased with increase in temperature up to about 140 °C. Beyond 140 °C, an unexpected trend was observed, as the selectivity for **38** began to drop. As the selectivity towards the desired product **38** dropped, we observed that there was a simultaneous increase in the selectivity towards the tribrominated by-product **54**. Noting this trend, we decided to do a more extensive temperature and residence time study to fully investigate the trend observed. In this study, temperature was varied from 80 °C to 160 °C. The residence time was varied from 5 seconds to 60 seconds. In this temperature and residence time study, mesitylene **50** (0.0125 M) was reacted with NBS **45** (0.025 M ,2 equiv. w.r.t. **50**) with benzoyl peroxide (0.00125M, 0.1 equiv. w.r.t. **50**) as catalyst. It is important to note that though mesitylene **50** and NBS **45** were used in the 1:2 molar ratio respectively, this is effectively a 1:1 molar ratio because 2 moles of NBS **45** are needed for each mole of mesitylene **50** to achieve the desired product **38**. The

selectivity towards the desired product, 3,5-bis(bromomethyl)toluene **38** was monitored on HPLC. The results from this study are shown in Figure 30.

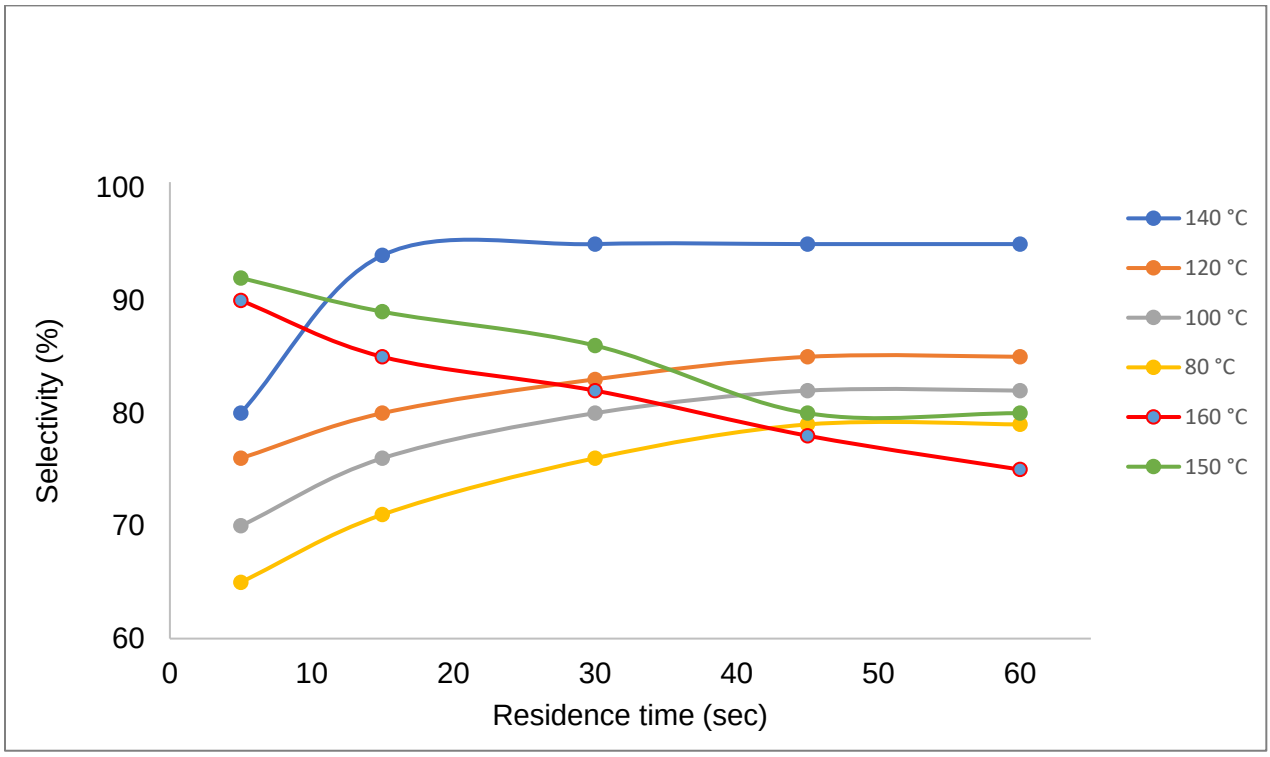


Figure 30: *Effect of residence time on the selectivity towards 3,5-bis(bromomethyl)toluene **38** in Chemtrix Labtrix system.*

The temperature and residence time study shown in Figure 30 confirmed the rather unusual trend displayed in Figure 29. We observed that the selectivity towards the desired product 3,5-bis(bromomethyl)toluene **38** increases with an increase in temperature up to 140 °C. At 150 °C and 160 °C, good selectivity values of 92% and 90% respectively were initially achieved at 5 seconds, but the selectivity surprisingly dropped as the residence time was increased. We also observed that selectivity towards the by-product 1,3,5-tris(bromomethyl)benzene **54** gradually increased from 140 °C to 160 °C as the residence time was increased (from a 5% increase between 140 °C–160 °C at 5 seconds residence time to 20% increase at 60 seconds residence time) suggesting that temperatures higher than 140 °C favour the formation of the tribrominated by-product **54**.

Heat serves as the radical initiator for this reaction together with benzoyl peroxide, promoting the release bromine radicals into solution. The bromine radicals then attack the mesitylene **50** molecule at the benzylic position in the propagation step of the reaction mechanism. The rate of release of bromine radicals into solution will depend on the temperature and radical initiator used. The drop in the selectivity towards the desired product **38** at temperatures above 140 °C could be due to bromine radicals being formed much quicker and some of these free radicals attacking at all three benzylic sites on the mesitylene **50** moiety, resulting in the formation of more of the tribrominated by-product. The desired product **38** initially forms quicker (as seen in the high selectivity values of 92% and 90% at 150 °C and 160 °C respectively at the residence time of only 5 seconds) and then undergoes further bromination at the third benzylic carbon to form the tri-brominated by-product **54**, which is reflected in the decrease in selectivity towards **38** as the residence time is increased. At temperatures 80 °C, 100 °C and 120 °C the selectivity towards 3,5-bis(bromomethyl)toluene **38** gradually increased between 5 seconds and 45 seconds. This can be attributed to some of the mono-brominated by-product **53** initially forming, which then undergoes further bromination yielding more of the desired product **38**. Beyond 45 seconds, no increase in selectivity was observed.

Having established 140 °C as the best temperature for the selective synthesis of 3,5-bis(bromomethyl)toluene **38**, we went on to investigate the effect of varying the molar ratios of the reactants on the conversion towards the desired product 3,5-bis(bromomethyl)toluene **38**. Also, the shortest residence time with the highest selectivity of 95% at 140 °C was 15 seconds (beyond 15 seconds at 140 °C, residence time had no effect on selectivity within the range investigated). Noting this, we decided to continue with 15 seconds as the residence time for the rest of our optimization studies.

For the molar equivalent study, the concentration of mesitylene **50** was kept constant at 0.0125 M and molar equivalents of NBS **45** with respect to mesitylene **50** was increased from 1:2 (effectively 1:1 since two moles of NBS **45** are required per mole of mesitylene **50** to achieve the desired product **38**), to 1:2.5 equivalents (effectively 1:1.25 equiv. w.r.t. **50**) and 1:3 (effectively 1:1.5 equiv. w.r.t. **50**). The concentration of the catalyst benzoyl peroxide was kept constant at 0.00125 M (0.1 equiv. w.r.t. **50**). The effect of increasing the molar equivalent of NBS on the selectivity

was observed. The residence time was kept constant at 15 seconds the results of the study are displayed in Figure 31 below.

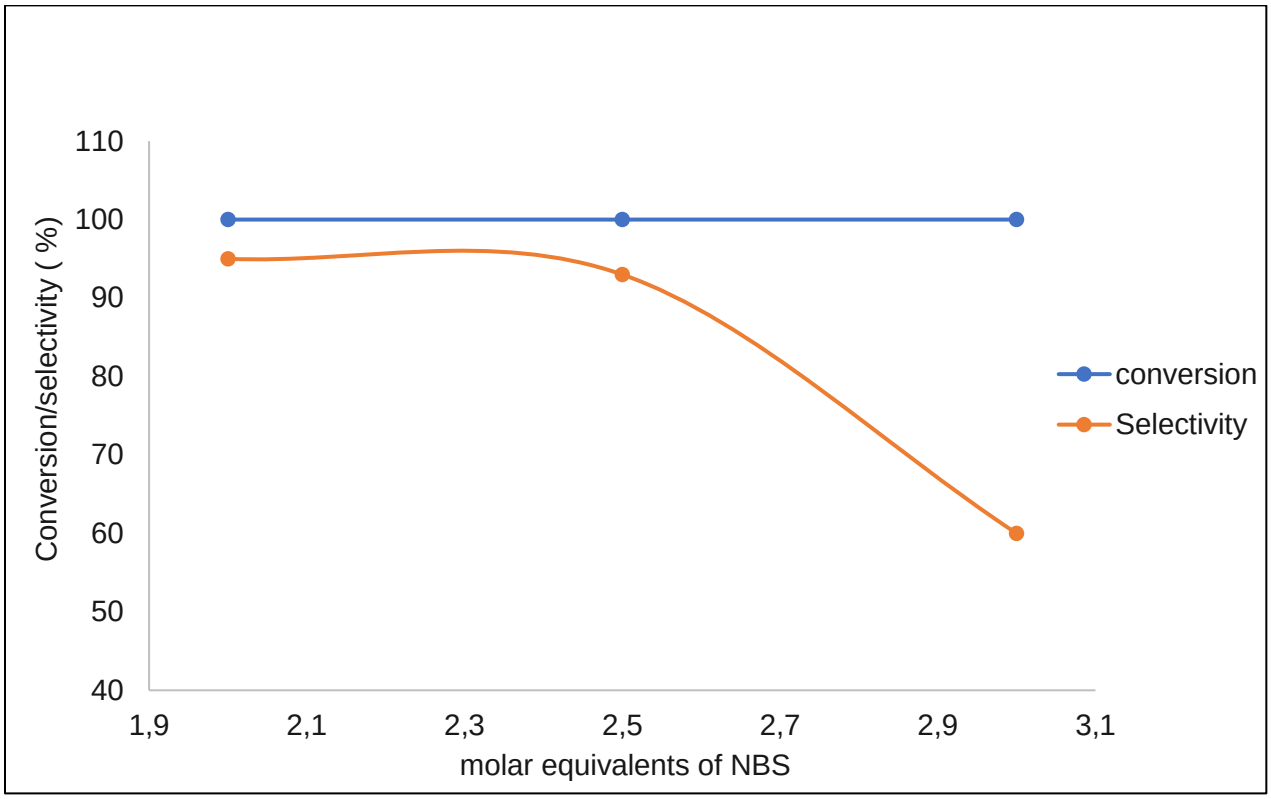


Figure 31: *Effect of the molar equivalents of NBS* ***45*** *on the bromination of mesitylene* ***50*** *towards 3,5-bis(bromomethyl)toluene* ***38****.*

The results show a decrease in selectivity toward the desired product **38** as the molar equivalents NBS is increased. An increase in the molar equivalents of NBS to 2.5 (effectively 1.25 w.r.t. **50**) resulted in a slight drop in selectivity from 95% to 93%. Further increasing the molar equivalents of NBS to 3 (effectively 1.5 equiv. w.r.t. **50**) led to further decrease in the selectivity towards **38** to 60%. The drop in the selectivity towards 3,5-bis(bromomethyl)toluene **38** as the molar equivalents of NBS is increased was attributed to an increase in the formation of the tri-brominated side product **54**. This means the mesitylene **50** reacts with this higher molar equivalent of NBS, resulting in some of the mesitylene **50** molecules being brominated at all 3 benzylic sites on the mesitylene **50** molecule and yielding the tri-brominated by-product **54**. From this observation, we deduced that increasing the molar equivalent of NBS would be detrimental to the optimization process. Therefore, we decided to keep the molar ratios of mesitylene **50** to NBS **45** at 1:2

respectively (effectively 1:1 since two moles of NBS **45** are needed per mole of mesitylene **50**). We also noticed that the conversion of mesitylene **50** was 100% at the temperature of 140 °C and 15 seconds for all molar equivalents in NBS investigated. This very high conversion could be due to very effective mixing in the Chemtrix micro reactor and the high temperatures employed.

We were also curious to understand the effect that the concentration of the catalyst, benzoyl peroxide, would have on the selectivity towards 3,5-bis(bromomethyl)toluene **38**, as well as the conversion of mesitylene **50**. The pre-determined conditions for optimum selectivity were adopted for this study *i.e.* temperature was kept at 140 °C, concentration of mesitylene **50** was kept constant at 0.0125 M, NBS was kept constant at 0.025M, (2 equiv. w.r.t. **50**) and the amount of the catalyst was varied between 0.00125 M (0.1 equiv. w.r.t. **50**) and 0.01 M (0.8 equiv. w.r.t. **50**). The residence time was kept constant at 15 seconds. The results of the study are displayed in Figure 32 below.

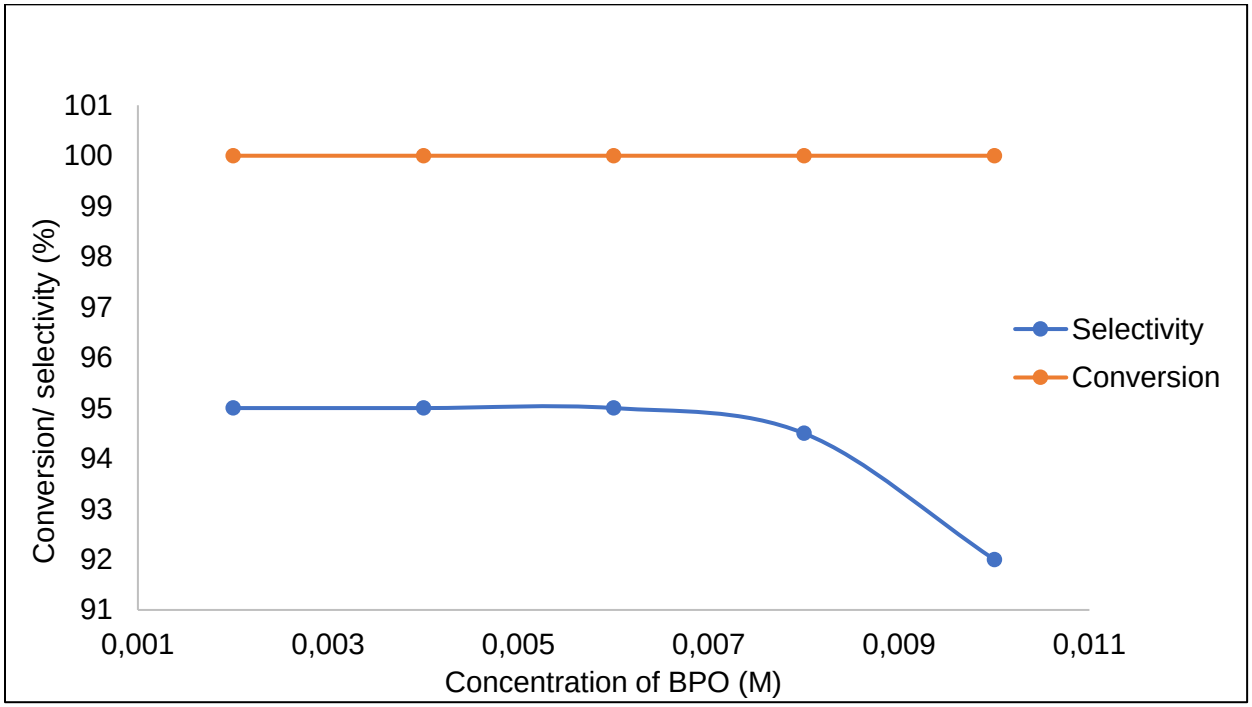


***Figure 32**: Showing the effect of catalyst concentration on the selectivity towards 3,5-bis(bromomethyl)toluene **38**.*

We observed that the selectivity remained constant at 95% from (0.00125 M, 0.1 equiv. w.r.t. **50**) to about 0.00625 M (0.6 equiv. w.r.t. **50**), then the selectivity started dropping. Benzoyl peroxide

forms benzoyloxy radicals readily upon application of heat, which are very stable radicals due to resonance stabilization.[90] The benzoyloxy radicals then initiate the formation of more bromine radicals during the initiation phase of the mechanism, which in turn attack the mesitylene **50** molecule at benzylic sites.[90,91,92] The drop in selectivity of **38** at high BPO concentration could be attributed to quicker release of bromine radicals into solution when the concentration of the radical initiator increased, resulting in the bromination reaction towards the formation of **38** occurring faster, and some of the desired product **38** formed undergoing further bromination to achieve the tribrominated by-product **53**. This implies that the desired product **38** becomes a substrate for further bromination, resulting in some of **38** being converted into the tribrominated product **54**. After we had investigated the effect of temperature, molar equivalents of reactants and molar equivalents of the catalyst, we were curious to understand the effect that different solvents have on the reaction. In addition to acetonitrile, two more solvent, dichloromethane and benzene, were investigated. The temperature was kept at the previously optimized value of 140 °C, the concentration of mesitylene **50** was kept constant at 0.0125 M, NBS was kept constant at 0.025 M, (2 equiv. w.r.t. **50**) and the amount of the catalyst was kept at the previously determined optimum of 0.00125 M(0.1 equiv. w.r.t. **50**). The residence time was kept constant at 15 seconds. The results of the study are shown in Figure 33 .

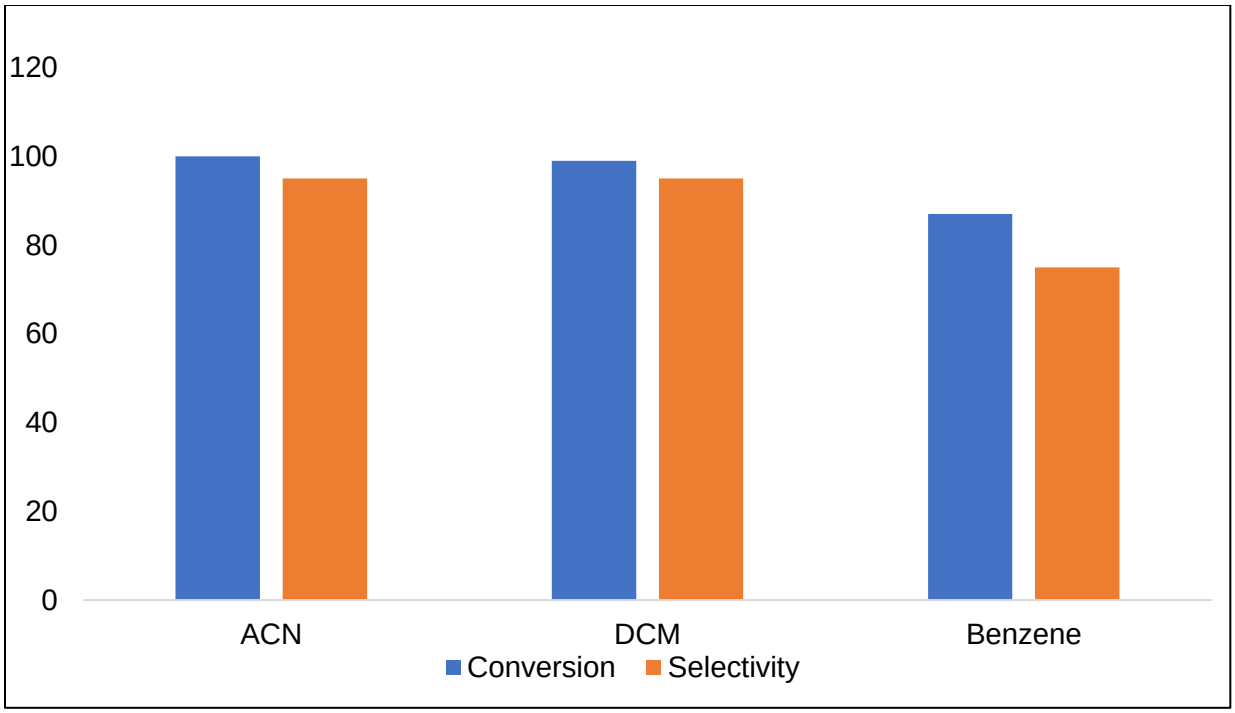


***Figure 33**: Showing the effect of different solvents: dichloromethane, acetonitrile and benzene on the conversion and selectivity of **50** towards **38**.*

From Figure 33, we deduce that acetonitrile and dichloromethane (DCM) are very good solvents for the reaction, both achieving 95% selectivity with 100% conversion and 99% conversion, respectively. Drops in conversion and selectivity to 87% and 75% respectively, were observed when benzene was used as solvent. Due to the very low boiling point of DCM (40 °C), we decided to continue with acetonitrile as solvent. This is because using DCM as solvent will result to more pressure in the system as the system will need to be pressurized even more using back pressure regulators for the reaction to occur at 140 °C.

The synthesis of **38** was therefore successfully optimized for temperature, residence time, molar equivalents of reactants, molar equivalents of the catalyst and the effect of different solvents, with 100% conversion of mesitylene **50** and 95% selectivity towards 3,5-bis(bromomethyl)toluene **38** at 140 °C and 15 seconds residence time. This translates to a throughput of 0.206 g/h of the product **38** formed using the Chemtrix unit.

3.1.1.2 Scale up synthesis of 3,5-bis(bromomethyl)toluene using Little Thing Factory reactors

Having optimized the bromination of mesitylene **50** towards 3,5-bis(bromomethyl)toluene **38** using the Chemtrix Labtrix system, by investigating the effect of temperature, molar equivalents of reactants, concentration of catalyst and effects of different solvents on the reaction, we decided to transfer the optimized parameters to the larger Little Things Factory (LTF) reactor. The setup was connected as shown in Figure 34 below.

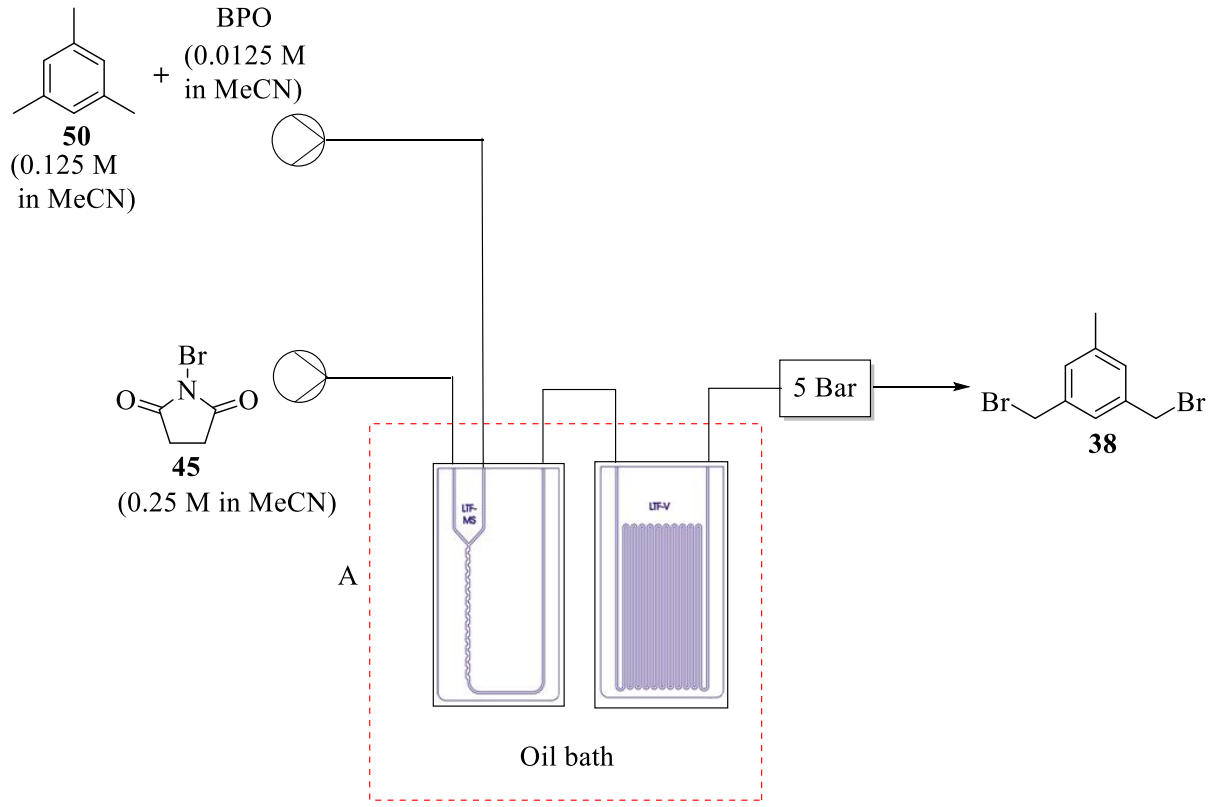


Figure 34: *Schematic setup for synthesis of 3,5-bis(bromomethyl)toluene **38** in Little Things Factory reactors.*

In the Chemtrix Labtrix system, it was necessary to use very low concentrations of the reactants to avoid blockages. Moving to the LTF reactors with larger channel sizes, we decided to increase the concentration of the reactants (tenfold), ensuring that we get a higher throughput. In this study, mesitylene **50** (0.125 M in acetonitrile), NBS **45** (0.25 M in acetonitrile, 2 equiv. w.r.t. **50**) and BPO (0.0125 M in acetonitrile, 0.1 equiv. w.r.t. **50**) were pumped through an LTF mixer reactor

(for mixing) then through a 1.7 mL LTF reactor connected in series as shown in Figure 34 above. An attempt to replicate the optimum residence time obtained in Chemtrix (15 seconds) in the larger LTF reactor resulted in leakages in the system due to high pressure induced by the high flow rates (*i.e.* the connecting tubing repeatedly disconnected from the LTF reactor). Consequently, the shortest residence time we could achieve in the LTF reactor was 1 minute. Therefore, the residence time was varied from 1 minute to 6 minutes. The results of this study are displayed in Figure 35 below.

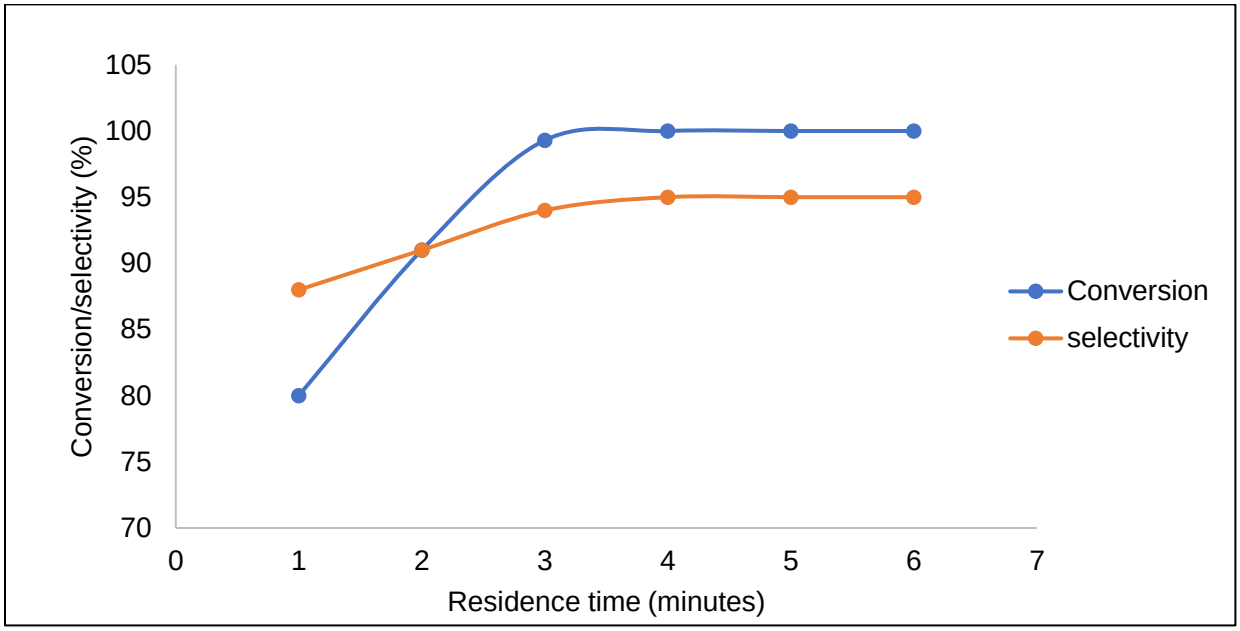


Figure 35:*Effect of residence time on the conversion of mesitylene* ***50*** *and selectivity towards 3,5-bis(bromomethyl)toluene* ***38*** *in a Little Things Factory reactor at 140 °C.*

The results obtained shows a general increase in conversion of mesitylene **50** between 1 minute and 3 minutes, ultimately achieving 100% conversion of **50** in about 3 minutes using the LTF reactor. This rapid increase in conversion can be attributed to the highly effective turbulent mixing achieved at the high flow rates used. In addition to this, the LTF reactors have staggered and ridged internal structure to enhance turbulent mixing. The combined effect of this staggered oriented ridges in the internal structure and the high flow rates employed both ensure very efficient turbulent mixing, which could explain the high conversions achieved between 1 minute and 3 minutes. Beyond 3 minutes, the conversion remained constant at 100% within the residence time range investigated.

The selectivity towards 3,5-bis(bromomethyl)toluene **38** also increased from 87% at 1 minute, to 95 % selectivity at 4 minutes residence time, and remained constant at 95% between 4 minutes and 6 minutes. This increase in selectivity was attributed be due to the initial formation of some monobrominated by-product **54**, which then undergoes further bromination at a second benzylic site to achieve 3,5-bis(bromomethyl)toluene **38**. Our optimum conditions in the LTF reactor were therefore 100% conversion of mesitylene **50**, with 95% selectivity towards the desired product 3,5-bis(bromomethyl)toluene **38** in 4 minutes. This translates to a throughput of 2.01 g/h.

3.1.1.3 Synthesis of 3,5-bis(bromomethyl)toluene by bromination of mesitylene in a photochemical reactor

As mentioned earlier, the formation of bromine radicals can be induced either using heat or by using UV light. We were curious to investigate the reaction using UV light as a radical initiator. A homemade photochemical reactor setup was used, consisting of a BLE-6T365 UV lamp and 3 mL volume PTFE coil, connected to a Chemyx pump and a T-mixer as shown in Figure 36 below.

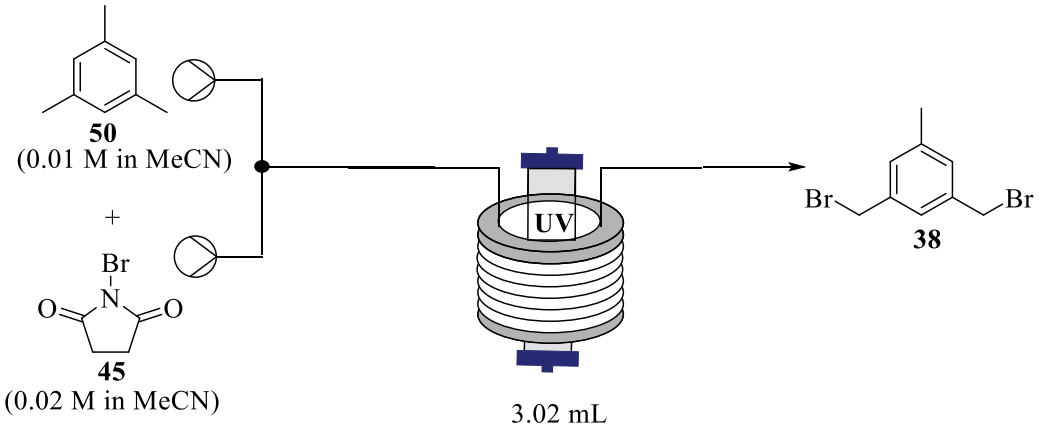


Figure 36: *Schematic setup for the synthesis of 3,5-bis(bromomethyl)toluene **38** in a photochemical reactor.*

The photochemical transformation was attempted in hope that a more cost-effective approach would be achieved. Doing the synthesis with photochemically–obtained bromine radicals will give an overall cleaner and cost-effective process due to lower temperatures and pressure in the system.[93] This makes photochemical transformations the centre of a great amount of interest in

organic synthesis, for both small scale and large scale synthesis.[94,95,91] Firstly, a concentration study was done to determine the concentration of the reactants that are suitable for the photochemical reaction. The molar equivalents of mesitylene **50** to NBS **38** was kept constant at a 1:2 ratio respectively (effectively 1 to 1 since moles of NBS are required per mole of mesitylene to obtain **38**). The concentrations of mesitylene **50** and NBS **45** were varied between 0.01 M:0.02 M and 0.1 M:0.2 M of mesitylene **50** to NBS, respectively. The conversion of mesitylene **38** was monitored on HPLC (*i.e.* we monitored the disappearance of the mesitylene peak only, no selectivity studies performed yet). The residence time was kept to 10 minutes and the photochemical transformation was done at room temperature. The results of the study are shown in Figure 37 .

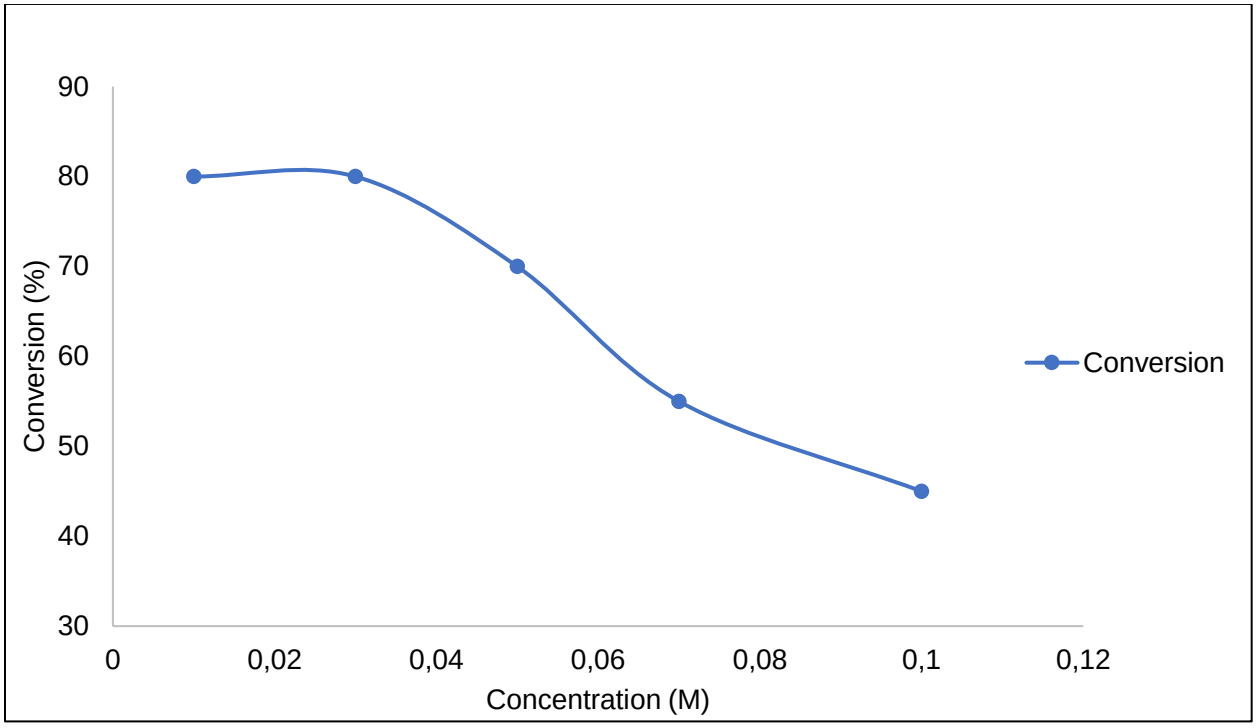


Figure 37: *Showing effect of the concentration of mesitylene **50** and NBS **45** on the conversion of mesitylene **50**.*

Photochemical reactions are often very dependent on the concentration of the reactants, as the concentration must allow for appropriate light penetration for the reaction to occur.[95,98] We observed that the highest conversion of mesitylene **50** was achieved at low concentrations (0.01 M:0.02 M and 0.03 M:0.06 M of mesitylene to NBS respectively). As the concentrations of the

reactants were increased, the conversion began to drop. This drop could be because at higher concentrations, less bromine radicals are formed due to less UV light penetration. The lower light penetration could be due to the higher concentration of reactant molecules obstructing the passage of light through the reaction mixture.[99,100] This results in a less homogenous irradiation inside the flow reactor leading to a drop in conversion. We decided to proceed with 0.03 M:0.06 M of mesitylene **50** to NBS **45** as the best concentration for our study at room temperature We then went on to do a more extensive residence time study and this time, both the conversion of mesitylene **50** and selectivity towards 3,5-bis(bromomethyl)toluene **38** were monitored.

In our study, a solution of mesitylene **50** in one syringe (0.03 M in acetonitrile), and a solution of NBS **45** in a second syringe (0.06 M in acetonitrile, 2 equiv. w.r.t. **50**) were simultaneously streamed through the 3 mL photochemical reactor and the residence time was varied from 5 minutes to 25 minutes. Both the conversion of mesitylene **50** and the selectivity towards 3,5-bis(bromomethyl)toluene **38** were monitored. The results of the study are shown in Figure 38 below.

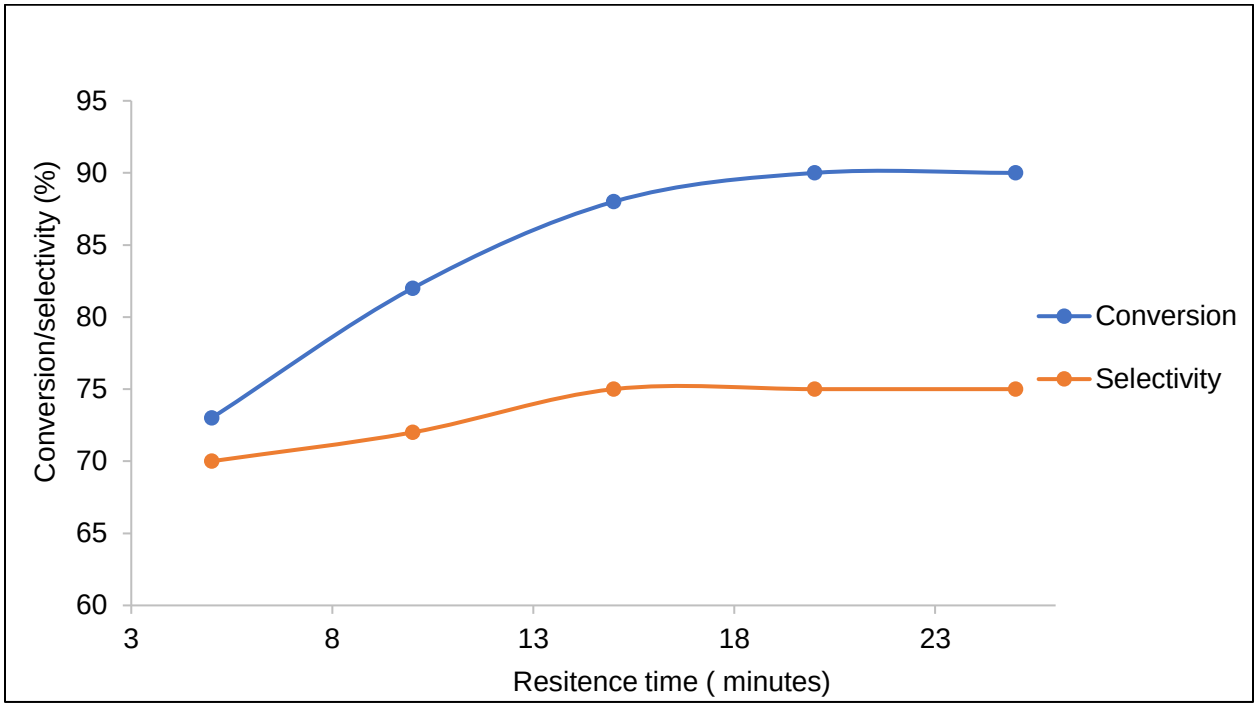


Figure 38: *Effect of residence time on the conversion of mesitylene **50** and the selectivity towards 3,5-bis(bromomethyl)toluene **38** in a photochemical reactor.*

The results obtained show that the conversion of mesitylene **50** increased with residence time from 73% at 5 minutes to 90% at 20 minutes residence time and remained constant at 90% when the residence time was increased to 25 minutes. A more rapid increase in conversion was observed between 5 minutes and 15 minutes, which can be attributed to better, more turbulent mixing with the higher flow rates of the fluid employed. Since the photochemical reaction was carried out at room temperature, the molecules will therefore possess lower kinetic energy and depend mostly on the mixing properties of the system to encounter each other.

The selectivity towards 3,5-bis(bromomethyl)toluene **38** also gradually increased from 70% selectivity at 5 minutes residence time, to 75% selectivity at 15 minutes residence time. This increase in selectivity can be attributed to the initial formation of some of the mono brominated by-product **53** which then undergoes further bromination at a second benzylic site to yield the desired product 3,5-bis(bromomethyl)toluene **38**, therefore increasing the selectivity towards **38**. HPLC analysis showed that the major by-product for the photochemical reaction was the mono brominated by-product **53**.

A 90% conversion was achieved in the photochemical reactor after 20 mins, with75 % selectivity towards **38**, which translates to a throughput (the expected mass per unit time) of 0.025 g/h. The highest throughput was therefore obtained with the Chemtrix reactor (2.06 g/h) where we obtained 100% conversion of **50** and 95% selectivity towards the desired product **38** in just 15 seconds.

3.1.2 Synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile in flow chemistry systems

Having successfully synthesized 3,5-bis(bromomethyl)toluene **38**, we moved on to the second step to synthesize 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**. The organic synthetic reaction towards 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **39** from 3,5-bis(bromomethyl)toluene **38** and NaCN is a phase transfer reaction, with tetrabutylammonium bromide as the phase transfer catalyst (PTC) in this case. In the batch synthesis of the diacetonitrile **39**, 3,5-bis(bromomethyl)toluene **38** was reacted with NaCN in DCM and water (2:1) as the biphasic solvent system, using tetrabutylammonium bromide as the PTC to give a good, isolated yield of 91% after 8 hours.

The reaction was adapted to flow reactors and investigated in both Chemtrix and LTF reactors. The effect of temperature, residence time (controlled by the flow rates of reactants), concentration

of PTC, molar equivalents of reactants and the effect of different solvents were all studied. Our initial plan was to optimize all reactions using the Chemtrix micro reactors to ensure very small amounts of reactants are used for the optimization, and then to transfer the optimized reaction conditions to the larger LTF reactor to scale up the reaction. However, we experienced some problems with the Chemtrix Labtrix system and consequently had to prematurely transfer some of the optimization studies to the LTF reactors. The parameters optimized using the Chemtrix Labtrix system were temperature and molar equivalents of reactants. Molar equivalents of PTC, solvent study, effect of different PTC and concentration studies were done using the LTF reactors.

3.1.2.1 Synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile using the Chemtrix Labtrix system

The reaction was investigated in flow chemistry systems to achieve optimal conditions for the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**. The Chemtrix system was initially used. The setup used is shown in Figure 39.

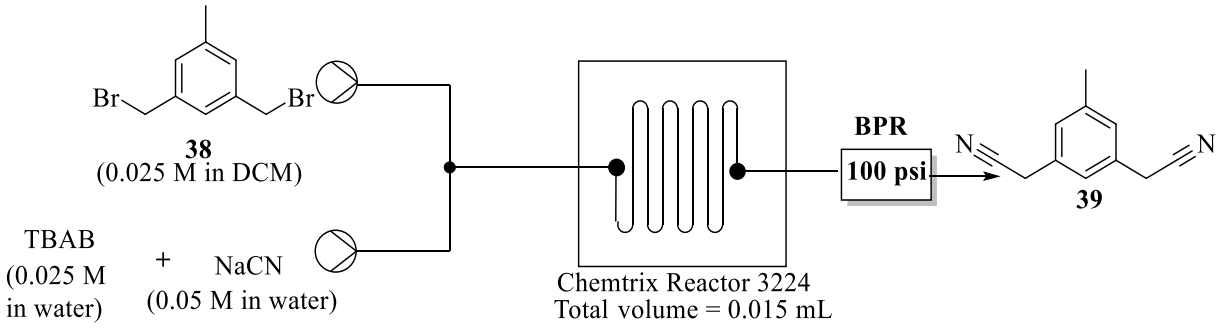


Figure 39: *Schematic Chemtrix setup for the synthesis and optimization of 2, 2'-(5-methyl-1,3-phenylene)diacetonitrile* ***39****.*

The reaction takes place in the organic solvent dichloromethane, as water is unable to dissolve the 3,5-bis(bromomethyl)toluene **38**. The low boiling point of the dichloromethane solvent (39.8 °C) is a limitation in batch, as the reaction cannot be done at temperatures higher than the boiling point of the solvent system. In flow chemistry reactors however, we were able to pressurize the system so that the reaction could be carried out safely at 190 °C, more than 4 times the boiling point of the organic solvent dichloromethane. This is one very important advantage of using flow chemistry, as the flow system can be pressurized so that reactions are safely carried out at

temperatures higher than the boiling point of the solvent, a feat that is not possible with batch chemistry.

A preliminary temperature study was done to establish whether temperature has a significant effect on the reaction. In this study, 3,5-bis(bromomethyl)toluene **38** (0.025 M in DCM) was reacted with NaCN (0.05 M, 2 molar equiv. w.r.t. **38**) with tetrabutylammonium bromide (0.0025 M in water, 0.01 equiv. w.r.t. **38**) as PTC (although we eventually used 0.025 M of the PTC (0.1 equiv. w.r.t. **38**), in this preliminary study we first attempted the use same molar equivalent of PTC used in batch (0.01 equiv. w.r.t. **38**, 0.0025 M)). The residence time was kept constant at 30 seconds. It was necessary to use these very low concentrations of reactants as blockages ensured at even slightly higher concentrations. The temperature was varied between 50 °C-150 °C. Unfortunately, the reaction did not work in flow under these conditions, as we got very low conversions at all temperatures, as shown in Figure 40 below.

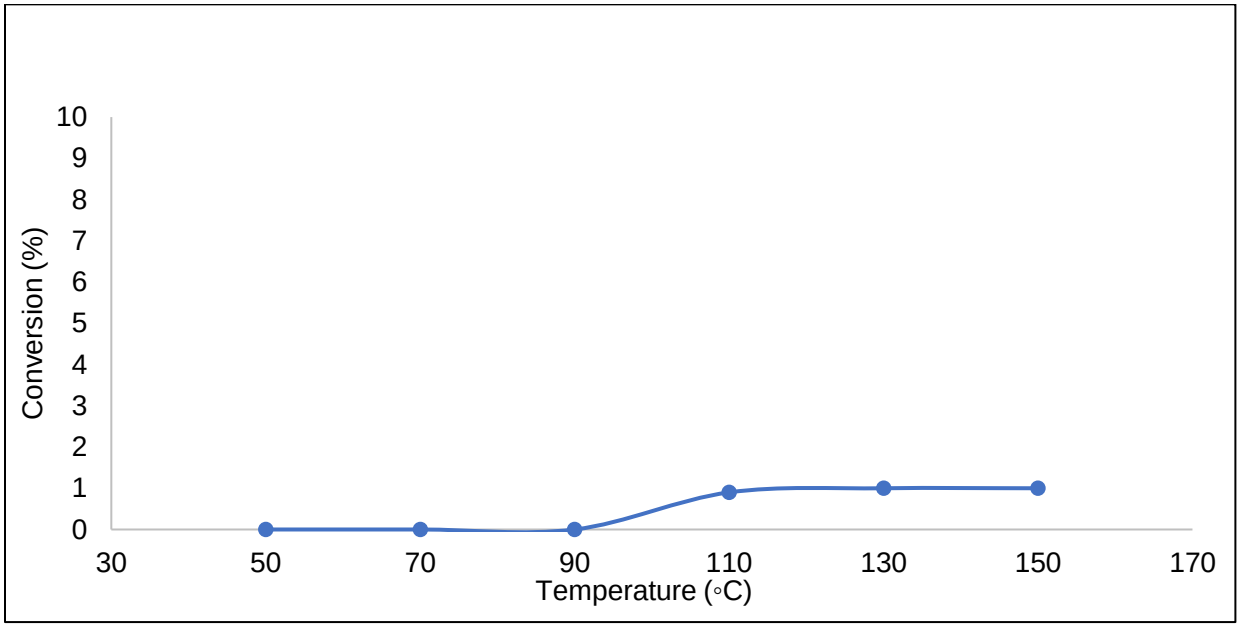


***Figure 40**: First preliminary temperature study towards the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**.*

For an S_N2 reaction, both the concentration of the nucleophile and the concentration of the substrate are important.[97] In two phase catalysis, the amount of the PTC will affect the amount of nucleophile available for the reaction. This is because the PTC is responsible for shuttling the nucleophile from

the aqueous phase to the organic phase where the reaction takes place. The general mechanism of action of a PTC is shown in Figure 41 below.

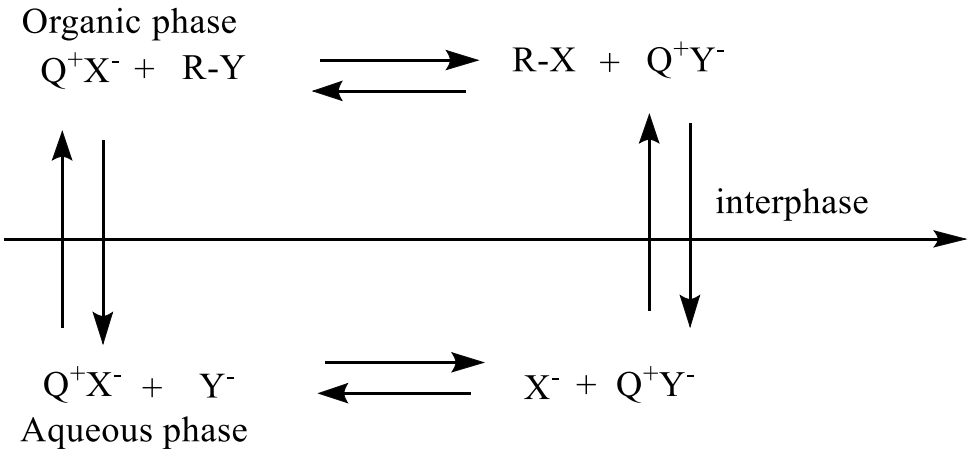


Figure 41: *Mechanism of action of phase transfer catalysts.*

In the figure above, Q^+X^- is the quaternary ammonium salt, which is dissolved in the aqueous phase (tetrabutylammonium bromide in this case) and serves as a PTC and Y^- is the nucleophile (cyanide ion in this case). Q^+Y^- is the ion pair formed between the nucleophile and the quaternary ammonium ion which crosses easily into the organic phase due to its lipotropic nature. R-Y represents the organic halide (**38** in this case) which undergoes substitution reaction to yield the product R-X (**39**) and corresponding side product Q^+Y^- (TBAB in this case). The side product Q^+Y^- is same as the PTC for this reaction because the halogen (bromine) present in the quaternary ammonium salt is the same as the leaving group halide (Y^-) in this case. Increasing the amount of PTC will increase the amount of the nucleophile (cyanide ion) being shuttled to the aqueous phase organic phase and this would better the chances of the reaction working.

An attempt to directly increase the concentration of the reactants 3,5-bis(bromomethyl)toluene **38** and NaCN resulted in blockages, but no blockages were observed with the increase in concentration of the PTC (tetrabutylammonium bromide). We therefore decided to initially use one molar equivalent (0.025 M, 1 equiv. w.r.t. **38**) of the PTC to optimize the reaction for temperature, molar equivalents of reactants and residence time. Once these other parameters had been optimized, we did a PTC equivalents study, where we carefully reduced the amount of the PTC and monitored the effect on conversion.

In the second temperature study, 3,5-bis(bromomethyl)toluene (0.025 M in DCM) was reacted with NaCN (0.05 M, 2 equiv. w.r.t. **38**, in water) in the presence of tetrabutylammonium bromide (0.025 M in DCM, 1 equiv. w.r.t. **38**). The residence time was kept constant at 30 seconds. The results of this study are shown in Figure 42 below.

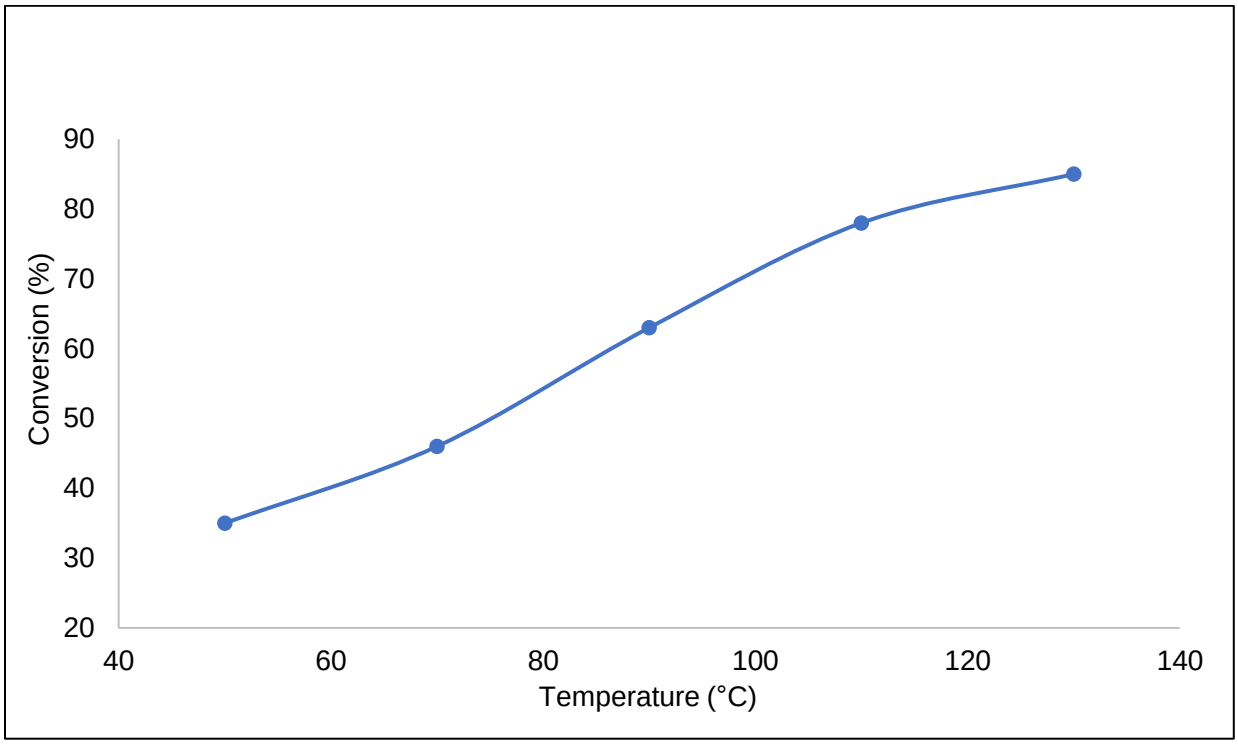


Figure 42: *Preliminary temperature study for the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**.*

From this study we see clearly that temperature has a significant effect on the conversion of the reaction. Having established this, we went on to do a more comprehensive and extensive temperature and residence time study. In this study, 3,5-bis(bromomethyl)toluene **38** (0.025 M in DCM)) was reacted with NaCN (0.05 M in water, 2 equiv. w.r.t. **38**) with TBAB (0.025 M in water, 1 equiv. w.r.t. **38**) as PTC. The temperature range monitored was between 50 °C to 190 °C, and the residence times were varied between 5 seconds and 30 seconds. The results obtained are shown in Figure 43 below.

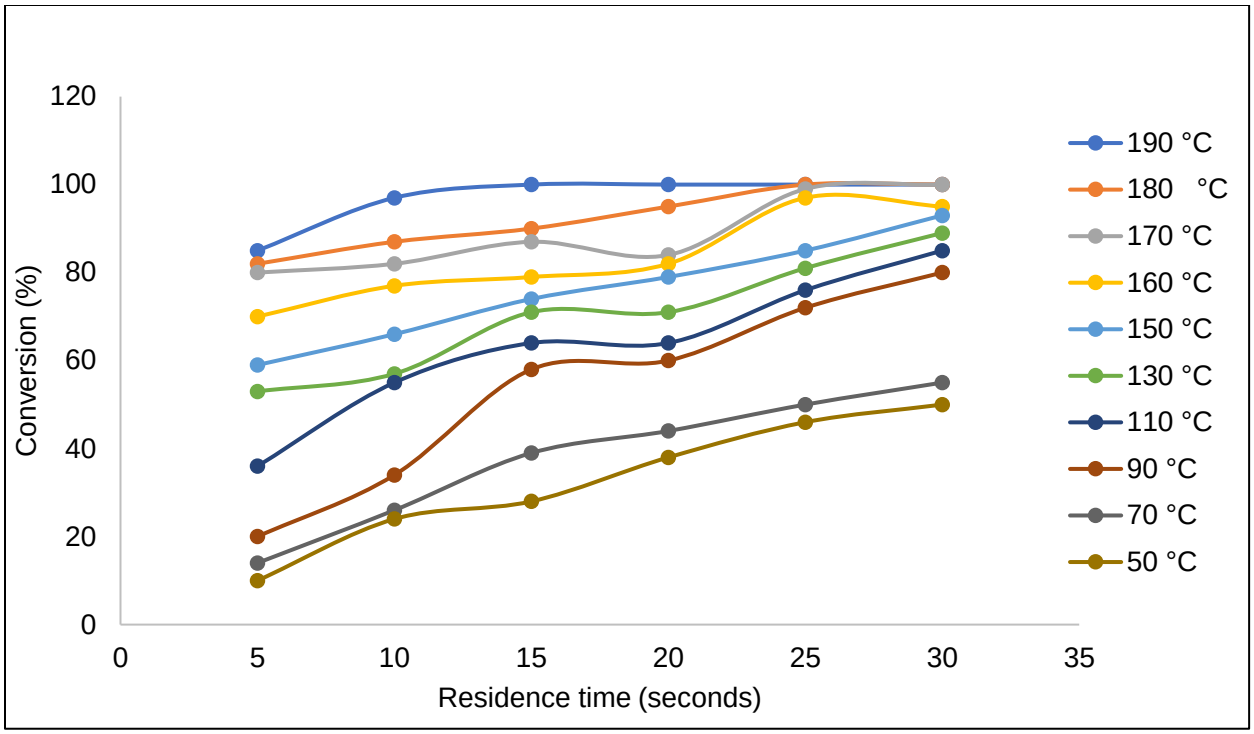


Figure 43: *Effect of temperature on the conversion of 3,5-bis(bromomethyl) toluene **38** to 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**.*

The molar ratio of 3,5-bis(bromomethyl)toluene **38** to NaCN was kept constant at 1:2 (0.025 M :0.05 M respectively). For this reaction, this is effectively a 1:1 mole ratio because two moles of the cyanide are needed per mole of 3,5-bis(bromomethyl)toluene **38** to form the desired diacetonitrile **39**. The amount of the PTC tetrabutylammonium bromide used was also kept constant at 0.025 M (1 equiv. w.r.t. **38**). The graph shows a general increase in the conversion as the temperature is increased. A plausible mechanism for the reaction is shown in the Figure 44 below.

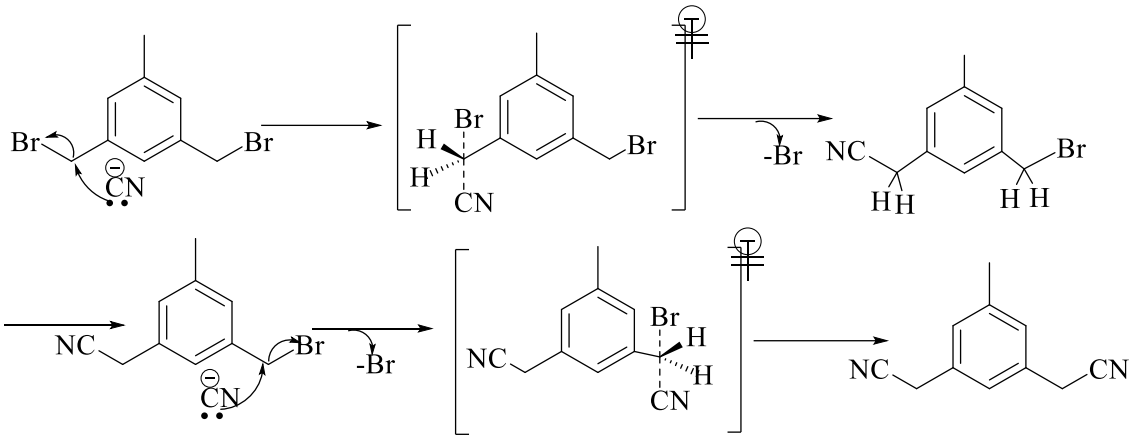


Figure 44: *Plausible reaction mechanism for the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** from 3,5-bis(bromomethyl)toluene **38** and NaCN.*

Figure 44 shows a plausible reaction mechanism, which shows that the cyanide ion, which is a very good nucleophile, forms and substitutes the bromide ion, which is an excellent leaving group. The high temperatures in the flow system make the substitution reaction much faster. Figure 43 shows that the conversion increases as the temperature is increased. The synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** in batch was carried out at 50 °C, giving a good yield of 91% in 9 hours. The temperature is a measure of the kinetic energy of the molecules. An increase in the kinetic energy of the molecules leads to an increase in the rate of collisions between the molecules, which in turn results in an increase in the conversion.[97] This increase in conversion as the temperature is increased is consistent with what is expected from theory, as the collision theory expresses that reactants in a reaction must have enough energy to collide and also have sufficient energy for a reaction to occur.[98] This means the higher the kinetic energy of the reactant molecules, the higher the contact between reactants leading to an increase in conversion as the temperature is increased. In addition, the very small channel sizes in the Chemtrix micro reactors ensure very good heat transfer, mass transfer and very efficient mixing which further increasing the rate of contact between the reactant molecules and resulting in higher conversions. In addition to this, the very small micro reactor channels promote exceptionally good mixing which translates into high conversions towards 3,5-bis(cyanomethyl)toluene **38**.[97]

In Figure 43, we also see that the conversions increase rapidly from 5 seconds to 30 seconds residence times. This could be because at very high flow rates like those employed to achieve

residence times between 5 seconds and 30 seconds, the high velocities of the reactant solutions ensure turbulent flow which results in good mixing, ultimately leading to better conversions. The results obtained indicate that the optimum temperature within the range investigated in 190 °C.

Having established that 190 °C was the optimum temperature for the reaction within the temperature range investigated, we went on to do a molar equivalents study, where we carefully monitored the effect of varying the molar ratios of the reactants on the conversion. 3,5-bis(bromomethyl)toluene **38** is the limiting reagent in this reaction. We investigated the effect of adding an excess of NaCN on the conversion of **38** towards the desired diacetonitrile **39**. The molar equivalent of 3,5-bis(bromomethyl)toluene **38** was kept constant while the molar equivalents of the cyanide was increased and the effect of this increase on the conversion was carefully observed. The previously optimized temperature of 190 °C was used and the molar equivalents of 3,5-bis(bromomethyl)toluene **38** to NaCN was varied between 1:2 and 1:3. The residence time was varied between 5 seconds and 25 seconds. The results are shown in Figure 45.

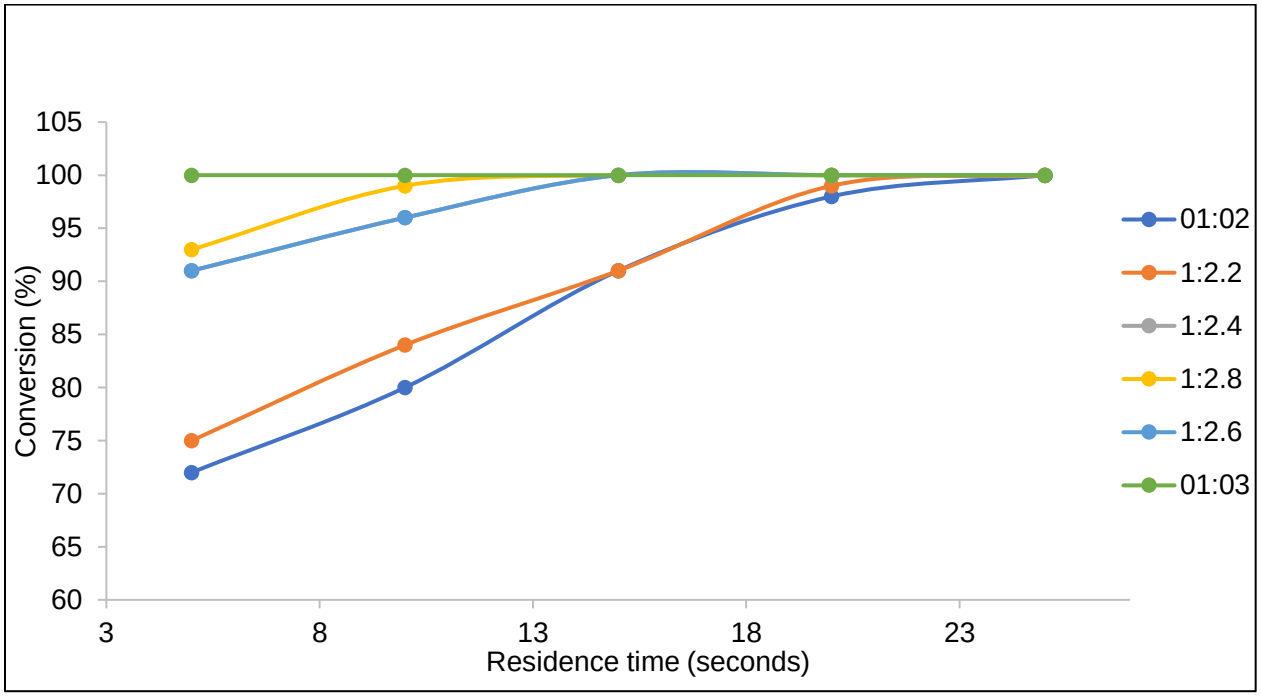


Figure 45: *Effect of increasing molar equivalents of NaCN at 190 °C.*

Figure 45 shows that the conversion towards the diacetonitrile **39** increases with increase in the molar equivalents of NaCN. This means that adding an excess of NaCN increases the conversion

of **38** towards the diacetonitrile **39**, at the previously determined optimum temperature of 190 °C. Two moles of the NaCN are required per mole of 3,5-bis(bromomethyl)toluene **38** to achieve the desired diacetonitrile **39**. By increasing the molar equivalents of NaCN 1.5-fold, that is from 1:2 to 1:3 (3,5 bis(bromomethyl)toluene: NaCN), we achieved 100% conversion in only 5 seconds. Upon attempting to reduce residence time to 2.5 seconds, we observed that the pressure increase induced by the high pump flow rates caused leakages in the connectors and syringes. We therefore could not investigate shorter residence times. For an S_N2 reaction like this one, the concentration of the nucleophile has a major effect on the conversion.[97] From theory, it is expected that increasing the concentration of the nucleophile will result in an increase in the conversion. The result obtained concur with this expectation from theory.

Having optimized the reaction for temperature and molar equivalents of NaCN, we went on to do a catalyst equivalents study, to carefully reduce the amount of PTC while carefully monitoring the effect on the conversion. At this point however, we were unable to continue optimizing the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** from 3,5-bis(bromomethyl)toluene **38** and NaCN using the Chemtrix Labtrix system, due to the thermal control unit of the instrument malfunctioning (resulting in it not going beyond a temperature of 100 °C anymore). We were forced to prematurely move the rest of the optimization reactions to the Little Things Factory reactors.

3.1.3.2 Synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile using Little Things Factory (LTF) reactor

The investigations done using the Little Things Factory reactors were the effects of different amount of the PTC, solvent study, comparing two different PTCs and the concentration studies. The LTF setup used for these studies is shown in Figure 46 below.

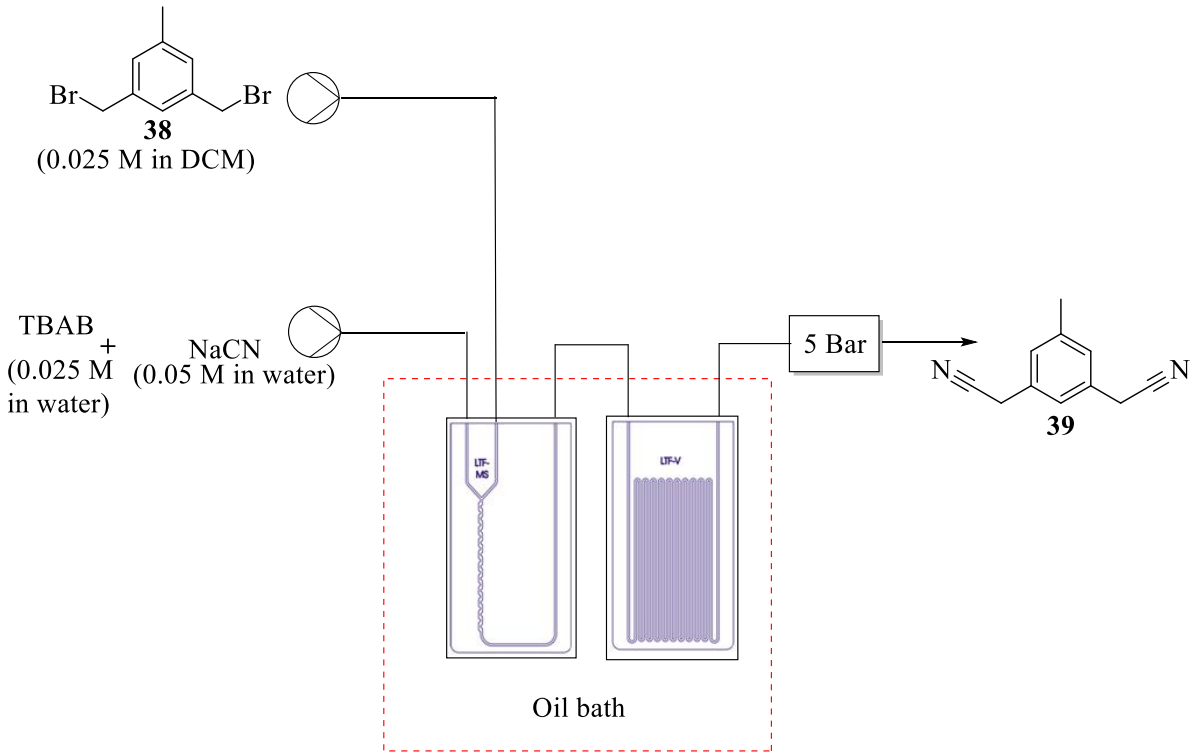


Figure 46: *Flow setup for the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** using the Little Things Factory reactors.*

As mentioned earlier, the amount of the PTC initially added for the other optimisation reactions was 1 equiv. (w.r.t. **50**). The amount of the PTC present determines the amount of the nucleophile that will be present in the organic phase for the reaction. This is because the PTC is responsible for shuttling the nucleophile from the aqueous phase to the organic phase of the two-phase system, where the reaction takes place. It was therefore necessary to do a study, where we carefully reduced the amount of PTC to a more acceptable molar equivalent. Reducing the amount of PTC will also make the process cheaper, as the quantity of the PTC wasted will be reduced. The molar equivalents of the reactant 3,5-bis(bromomethyl)toluene **38** to the PTC tetrabutylammonium bromide was varied between 1:0.1, 1:0.05, 1:0.025 and 1:0125 respectively. The pre-determined optimum temperature of 190 °C was used and the molar ratio of 3,5-bis(bromomethyl)toluene **38** to NaCN was kept at pre-determined optimum of 1 to 3 (effectively 1 to 1.5, as two equivalents of NaCN are needed for the synthesis) respectively. The effect of varying the molar equivalents of the PTC on the conversion to **39** was monitored and the results of this study are shown in Figure 47 below.

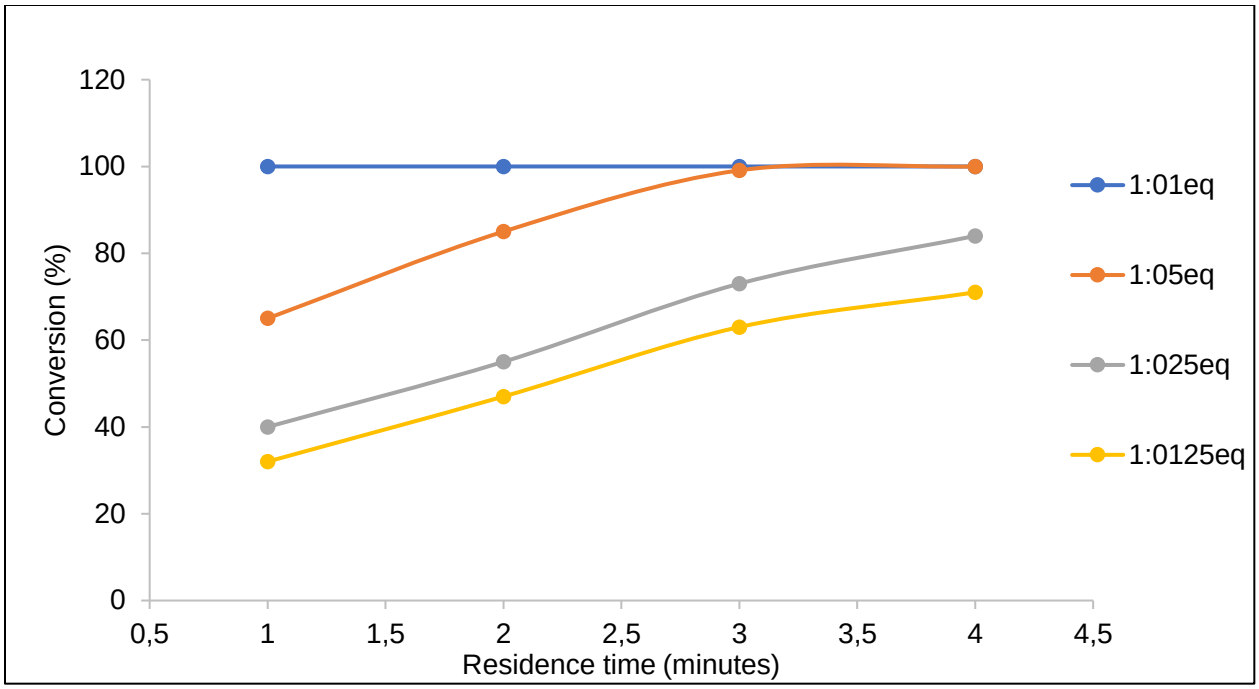


Figure 47: *Effect of the concentration of the phase transfer catalyst on the conversion of 3,5-bis(bromomethyl)toluene* ***38*** towards 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** at 190 °C.

The role of the PTC in this reaction is to transfer the nucleophilic agent (cyanide ion) from the aqueous phase to the organic phase where the displacement reaction takes place, since the NaCN salt is insoluble in the organic solvent. This means that the amount of the nucleophile available for the S_N2 reaction depends on the amount or concentration of the PTC present. The results obtained show that as the amount of PTC is increased, the conversion towards 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** also increases. This can be because the greater the amount of the PTC present in solution, the greater the amount of the nucleophile being transported into the organic phase for the reaction, leading to higher conversions. The results show a steady increase in conversion as the concentration of PTC increase, ultimately achieving 100% conversion when 1:0.1 molar equivalents of the reactant 3,5-bis(bromomethyl)toluene **38** to the PTC respectively in just 1 minute. We were unable to investigate shorter residence times as the pressure induced by the high flow rate of the pumps caused the connection pipes to disconnect from the reactors.

Having established that 0.1 molar equivalents of the PTC to 3,5-bis(bromomethyl)toluene **38** was best for the reaction, we went on to compare two different phase transfer catalysts. We already obtained 100% conversion using tetrabutylammonium bromide as PTC at the shortest time being

investigated, which was 1 minute. Therefore, the purpose of comparing the PTC was not to find a PTC that would result in faster reaction, but rather an attempt to find a PTC cheaper than TBAB, which would give similar results to those obtained when using TBAB as PTC.

For this study, a second PTC, tetrabutylammonium hydrogen sulfate, was investigated in comparison to TBAB. Only the effect residence time was varied, all other parameters were kept at the previously optimized conditions. That is, the temperature was kept constant at 190 °C, the concentration of the PTC for both PTCs was kept constant at 0.0025 M, the molar ratio of 3,5-bis(bromomethyl)toluene **38** to NaCN was kept at 1 to 3 (effectively 1 to 1.5). The residence time was varied from 1 minute to 5 minutes. The results of this study are shown in Figure 48.

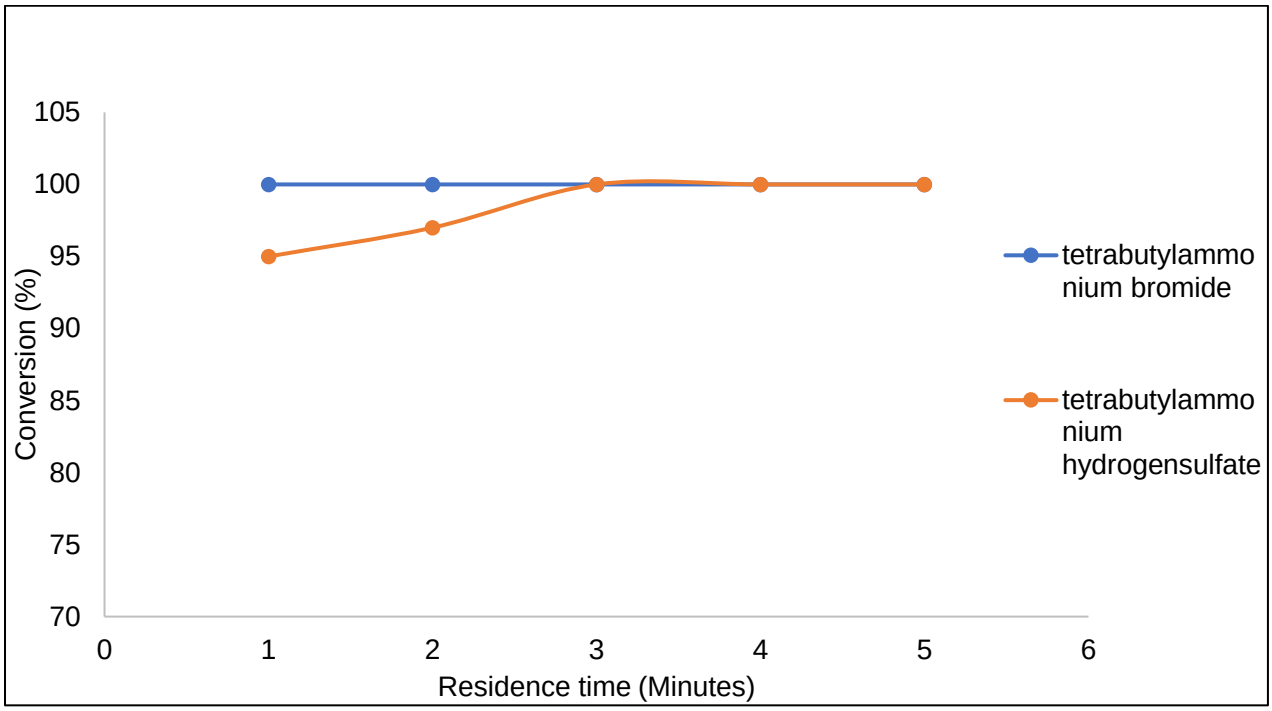


Figure 48: *Showing the effect of two different catalysts; tetrabutylammonium bromide and tetrabutylammonium hydrogen sulfate on the conversion of 3,5-bis(bromomethyl)toluene* ***38*** *towards 2,2'-(5-methyl-1,3-phenylene)diacetonitrile* ***39****.*

The results obtained show that both tetrabutylammonium bromide and tetrabutylammonium hydrogen sulfate are good catalysts for the reaction. Tetrabutylammonium bromide seems to be a better catalyst for the reaction as we achieved 100% conversion even at 1 minute residence time, compared the 95% conversion obtained with tetrabutylammonium hydrogen sulfate. We therefore

decided to continue with tetrabutylammonium bromide for this study. We were also eager to understand the effect that different solvents on the reaction. In the case of a reaction like this one, it was important to only investigate solvents that are immiscible with water. In addition to dichloromethane as a point of reference(since dichloromethane was used in batch), we investigated three more solvents: 2-methyltetrahydrofuran, toluene and chloroform. We investigated the effect that these different solvents have on the conversion towards the desired diacetonitrile **39**. Keeping all the previously determined optimum conditions *i.e.* temperature 190 °C, with 3,5-bis(bromomethyl)toluene **38** and NaCN in a 1:3 molar equivalents (effectively 1 to 1.5 equivalents) respectively, with tetrabutylammonium bromide (0.0025 M, 0.1 equiv. w.r.t. **38**) as catalyst. The residence time was kept constant at 1 minute. The results obtained are shown in Figure 49 below.

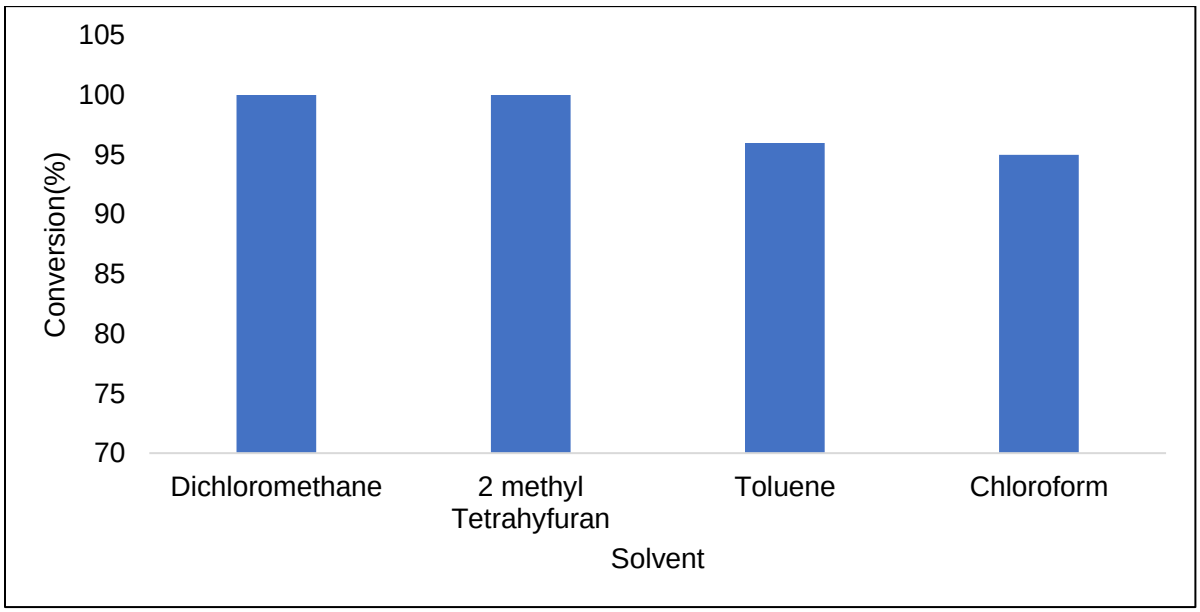


Figure 49: *Showing the effect of different solvents on the conversion of 3,5-bis(bromomethyl)toluene **38** towards 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **39**.*

From Figure 49 we see that all the solvents being investigated yielded good conversions at the shortest residence investigated of one minute. For an S_N2 reaction, a polar solvent is needed to dissolve the ionic nucleophile, as polar solvents have high dielectric dipole and are good at insulating ions. Non-polar solvents have low dielectric dipole and are not good at solvating ions.[97,98] In addition to being a polar solvent, aprotic solvents are preferred to protic solvents for

S_N2. This is because polar protic solvents have acidic protons which can solvate the nucleophile and reduce its nucleophilicity. Aprotic solvents on the other hand bind with the cation bound to the nucleophile, hence freeing the nucleophile.[97] Polar aprotic solvents are therefore ideal for this reaction.

The reactions done in toluene and chloroform as solvents yielded 88% and 90% conversion respectively. Toluene and chloroform are both non-polar solvents. As already explained, polar aprotic solvents are best for S_N2 reactions. The drop in conversion experienced with these two solvents can be attributed to the fact that they are both not ideal for the reaction, as they are not polar aprotic solvents.

With dichloromethane and 2-methyltetrahydrofuran, a conversion of 100% was achieved in one minute for both. These are both polar aprotic solvents and are therefore suitable for this reaction. 2-Methyltetrahydrofuran (2-Me-THF) is a greener solvent and safer to use than dichloromethane, for both the synthetic process and for the environment.[97] Also, 2-methyltetrahydrofuran has a boiling point of 80.2 °C in contrast to 39.8 °C for dichloromethane. The higher boiling point will imply a reduction in the overall pressure in the system, given that the system needs to be pressurized using back pressure regulators for the reactions to occur at temperatures higher than the boiling point of the solvent. A back pressure regulator with lower pressure will be required for 2-methyltetrahydrofuran, than for dichloromethane due to its higher boiling point, hence reducing the pressure in the system. This is especially significant at the very high temperature of 190 °C used for this reaction. We therefore decided to proceed with 2-Me-THF for the synthesis of 3,5-bis(cyanomethyl)toluene **39** from 3,5-bis(bromomethyl)toluene **38** and NaCN.

We were also curious to establish the effect that increasing the concentrations of the starting materials has on the conversion towards **39**. As a result of the initial optimization reactions being done using the Chemtrix Labtrix system, we were forced to start use very low concentrations of starting material (0.025 M 3,5-bis(bromomethyl)toluene **38** and 0.05 M NaCN) to avoid blockages, since the Chemtrix reactor channels are very small. With the LTF reactors however, we were able to significantly increase the concentrations of the starting materials with a much lower risk of clogging due the larger channel sizes of these reactors. It was especially important to increase the concentration of starting material so as to also increase the throughput (*i.e.* the amount of product

produced per unit time). The very low concentrations used until now imply that only very small amounts of products will be made per unit time even though 100% conversion was achieved. We therefore attempted increasing the concentrations of 3,5-bis(bromomethyl)toluene **38** and NaCN. The molar equivalents of the catalyst were constant at 0.1 equiv. (w.r.t. **50**) and the solvent used was 2-Me-THF the results obtained are shown in Table 3 below.

Table 3: *Showing the effect of increasing the concentration of reactants on the conversion towards 2,2'-(5-Methyl-1,3-phenylene) diacetonitrile **39**.*

Concentration ratio of 3,5-bis(bromomethyl)toluene to sodium cyanide, respectively	**Conversion (%)**
0.2M:0.6M	100%
0.4M:0.12M	100%
0.6M:1.8M	100%

For an S_N2 reaction, the conversion is expected to increase with increase in concentration of the reactant, since the rate of an S_N2 depends on both the concentration of the nucleophile and the substrate.[97] However, our aim was not to improve the conversions, as we were already achieving 100% conversion with 0.025 M and 0.075 M of 3,5-bis(bromomethyl)toluene **38** and NaCN respectively. Our objective was to increase the throughput and hence make the process more sustainable and cost-effective. The results obtained show that the reaction consistently yielded 100% conversion up to the maximum concentration being investigated of 0.6 M:1.8 M of 3,5-bis(bromomethyl)toluene **38** and NaCN respectively. This is made even better by the turbulent mixing experienced at the short residence time of 1 minute and the increased kinetic energy of the molecule at the high temperature of 190 °C resulting in the good conversions of 100% observed. This translates to a good throughput of 5.2 g/h when 0.6 M:1.8 M of **38** and NaCN were used, respectively.

3.1.3 Synthesis and optimization of 3,5-bis(1-cyano-1-methylethyl)toluene in a PTFE coil reactor

Having successfully synthesized and optimized the diacetonitrile **39**, we went on the third step of our synthetic route; the methylation of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** to obtain 3,5-bis(1-cyano-1-methylethyl)toluene **40** in flow. The reaction was investigated and optimized using the PTFE coil reactor, as it could not be done using the Chemtrix Labtrix system or LTF reactors due to clogging problems. The setup used for the reaction is shown in Figure 50 below.

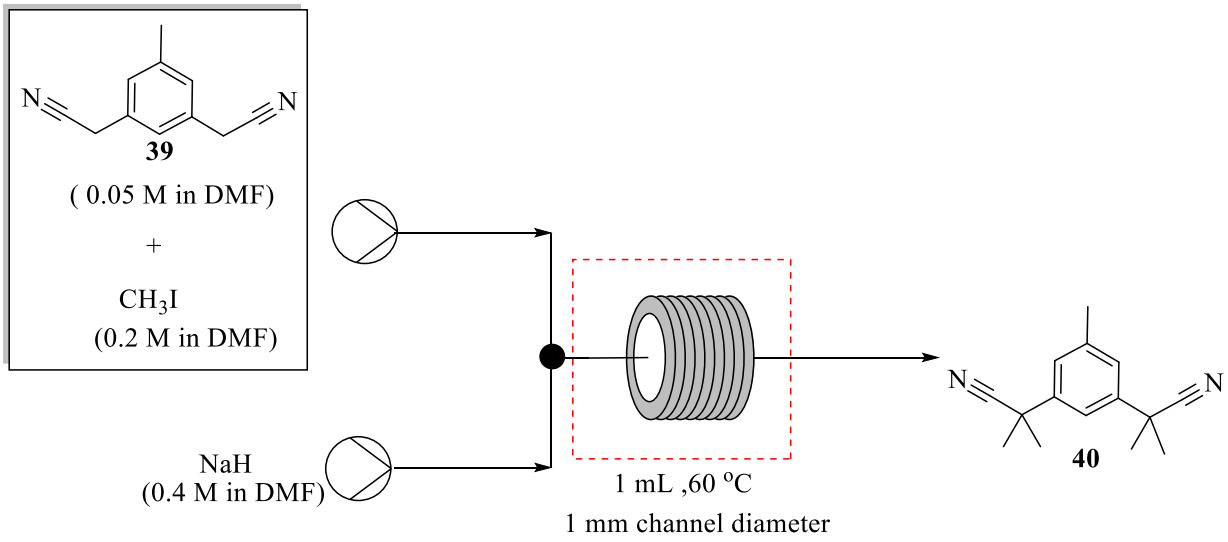


Figure 50: *Schematic of setup for the synthesis and optimization of 3,5-bis(1-cyano-1-methylethyl)toluene **40**.*

Batch synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene **40** from methylation of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** using methyl iodide and sodium hydride (NaH) as a base, in dimethyl formamide gave the product **40** with a yield of 67% after 6 hours. The reaction was then transferred to flow chemistry for synthesis and optimization.

Firstly, a quick preliminary temperature study was done to determine if temperature has a significant enough effect on the reaction. In this preliminary temperature study, 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **39** (0.05 M in DMF) was reacted with methyl iodide (0.2 M in DMF, 4 equiv. w.r.t. **39**) and NaH (0.4 M in DMF, 8 equiv. w.r.t. **39**). Due to the highly viscous nature of NaH in solution, as well as the high risk of clogging, we decided to use these low concentrations of reactants. The molar equivalents of the reactants and base were same as those used in batch, as

a point of reference. The residence time was kept to 5 minutes and the temperature range investigated was between 0 °C and 80 °C. The results of the study are shown in Figure 51 below.

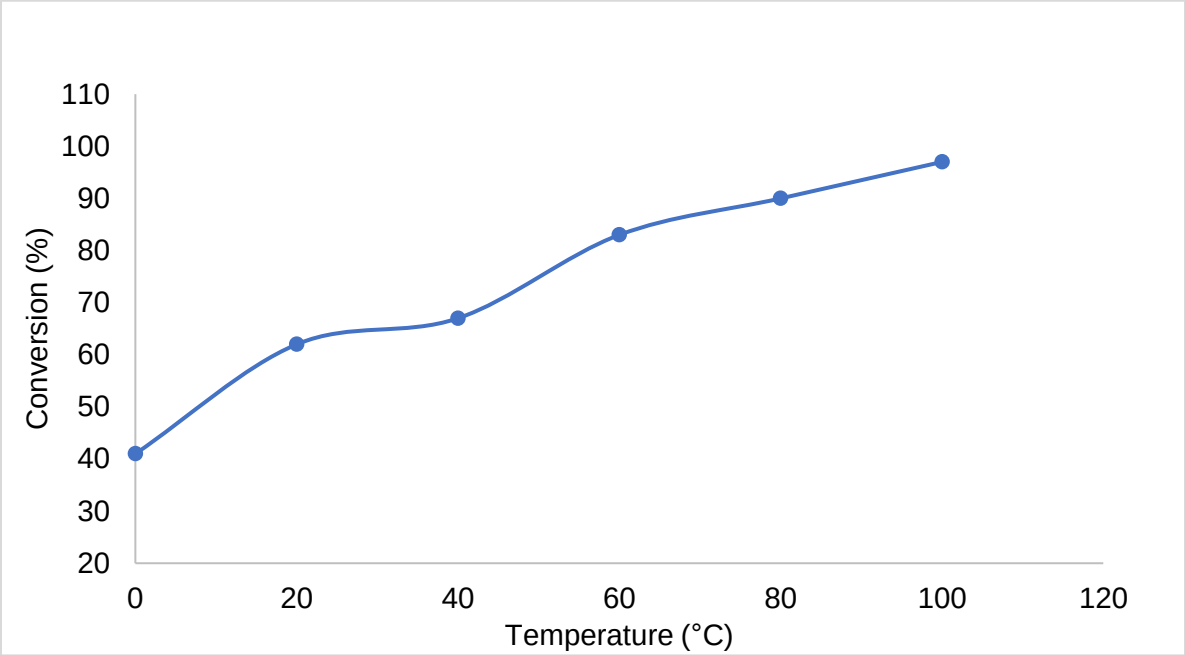


***Figure 51**: Preliminary temperature study for the synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene **40**.*

The preliminary study shows that temperature clearly has a significant effect on the reaction, as an increase in the conversion is observed as the temperature is increased. Having established this, we went on to do a more comprehensive temperature and residence time study. In this study, methylation of 2,2'-(5-methyl-1,3-phenylene) diacetonitrile **39** (0.05 M in DMF) and methyl iodide (0.2 M, 4 equiv. w.r.t. **39**) in one syringe, and NaH (0.4 M, 8 equiv. w.r.t. **39**) in another syringe were simultaneously streamed through the 1 mL PTFE coil reactor. It is important to reiterate that though the molar equivalents of **39** to methyl iodide was 1:4 respectively, this is effectively a 1:1 molar ratio because 4 moles of the methyl iodide are required per mole of **39** to obtain the desired product. The temperature range investigated was between 0 °C and 100 °C. The temperature study was limited to 100 °C due to the potentially explosive nature of NaH at elevated temperatures.[101] The residence time was varied between 5 minutes and 25 minutes. The results of the study are shown in Figure 52 below.

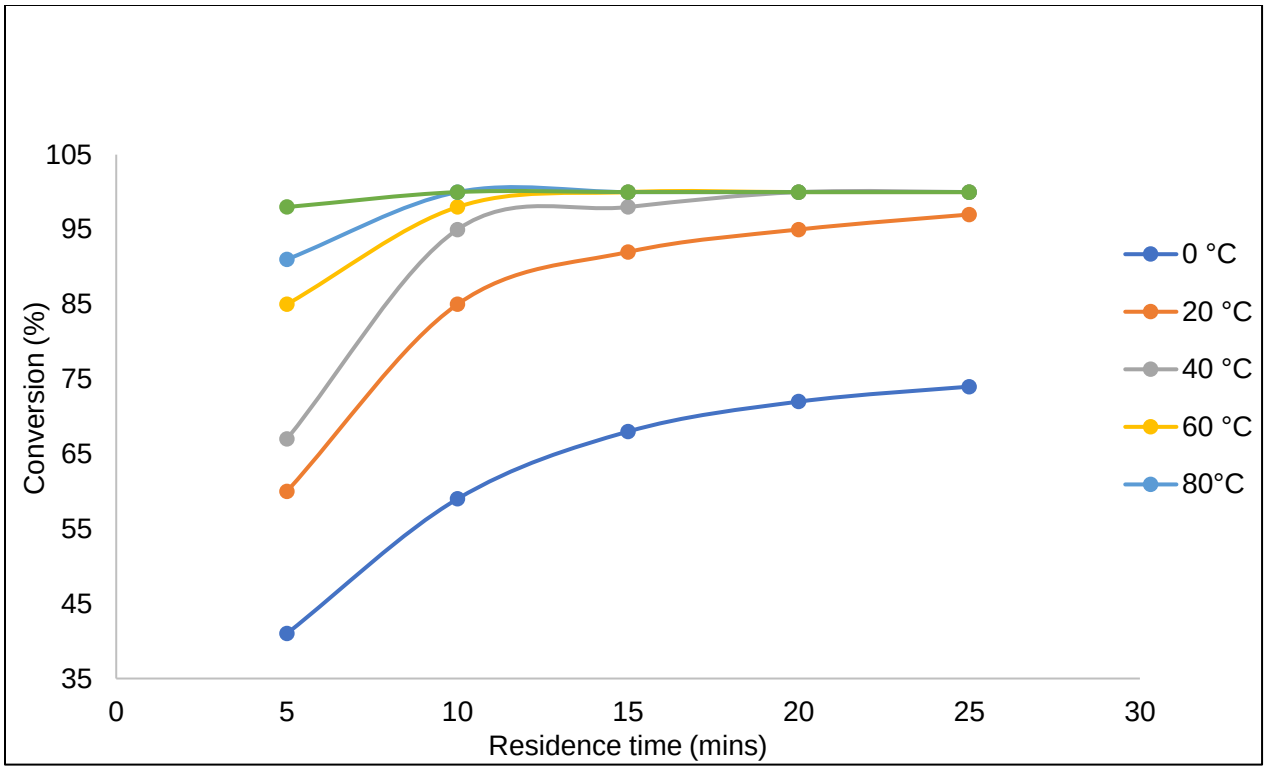


Figure 52: *Effect of temperature on the synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40****.*

The results from the study show that the conversion of the diacetonitrile **39** towards the desired propionitrile **40** generally increases with an increase in temperature. A plausible reaction mechanism is shown in Figure 53 below.

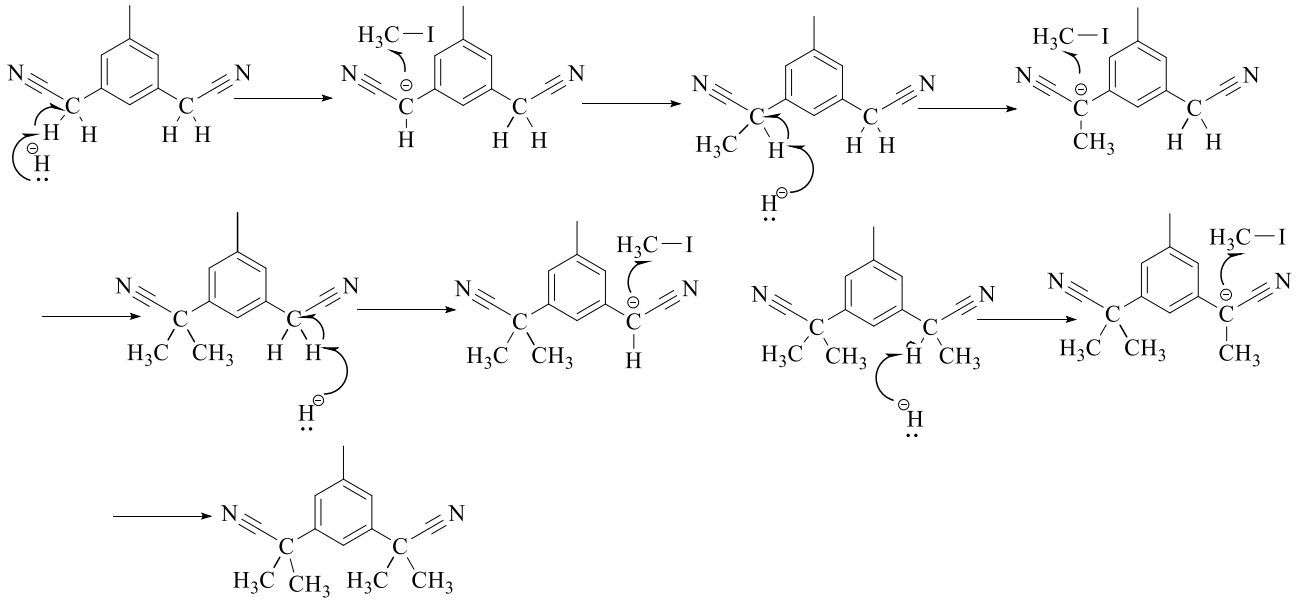


Figure 53: *Plausible reaction mechanism for the synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40.***

From the trends in Figure 52 we can deduce that the S_N2 reaction is favored at higher temperatures, as we observed an increase in the conversion of **39** towards **40** as the temperature was increased. A possible reason for this is that the molecules possess higher kinetic energy at higher temperatures, leading to more contact between molecules of the reactants. The ability for the reaction to be carried out at higher temperature in flow reactors highlights some of the advantages of flow chemistry over batch chemistry. This is because the reaction could only be carried out at low temperatures in batch (between 0 °C and 25 °C) due to the high risk of explosion of NaH at higher temperatures.[102] In flow systems however, the high volume to surface area ratio ensures the quick dissipation of heat, enabling the reaction to be carried out safely at higher temperatures. In addition to this, NaH decomposes when exposed to moisture.[103] The closed end to end flow reactors provide a safer a more air-tight environment for NaH, preventing its decomposition and leading to the improvement in yield and safety of the reaction. At 80 °C and 100 °C, the conversion increased from 90% and 87% respectively at 5 minutes residence time to 97% at 10 minutes for both temperatures. Beyond 10 minutes, the conversion remained constant at 97% for both 80 °C and 100 °C. We observed an increase in conversion at 60 °C, from 67% at 5 minutes residence time to a good conversion of 96% at 10 minutes residence time, then a plateau of 96-98% was observed beyond 10 minutes residence time. At 40 °C, we observed a rapid increase in conversion

from 74% at 5 minutes residence time to 92% at 10 minutes. A plateau of 92% to 95% was observed between 10 minutes and 25 minutes. At 0 °C and 20 °C, the conversion increased rapidly from 41% and 65% at 5 minutes residence time to 65% and 85% conversion at 10 minutes residence times, respectively. Plateaus of 65-71% for 0 °C and 80-85% for 20 °C were observed beyond 10 minutes residence time (from 15 minutes - 25 minutes).

Even though the highest conversion of 98% was achieved in just 10 minutes at 80 °C and 100 °C, milder conditions are preferred for the process from a scaling up and industrial perspective, especially when dealing with hazardous component like NaH. The potentially explosive danger of NaH is magnified at higher temperatures, making the reaction even more dangerous. Even though the continuous flow systems offer more efficient heat transfer due to the high volume to surface area ratio making the process safer, we decided that it will be even safer to continue with a milder temperature of 40 °C for this reaction, where a good conversion of 94% was observed at 10 minutes residence time. Milder temperatures will also cut cost since lower energy input will be required, especially at the industrial level. We also noticed that beyond 10 minutes residence time, the increase in conversion was very little for 0 °C, 20 °C and 40 °C and no increase in conversion was observed beyond 10 minutes for 80 °C and 100 °C. Following this observation, we decided to limit our residence time to 10 minutes for the remainder of the optimization studies. Having established that 40 °C was the best temperature for the reaction, we went to investigate the effect of the molar equivalents of methyl iodide on the reaction. Four moles of methyl iodide are required per mole of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** to achieve the desired propionitrile **40**. The concentrations **39** and NaH were kept constant at 0.05M and 0.4 M respectively, while concentration of methyl iodide was varied. The molar equivalents of **39** w.r.t. methyl iodide was varied from 1:4 (1:1 effectively since 4 moles of methyl iodide are required per mole of **39** to achieve the desired product), 1:6 (effectively 1:1.5) and 1:8 (effectively 1:2) respectively. The temperature was kept to 40 °C and the residence time was varied from 5 to 10 minutes. The results of the study are shown in Figure 54 below.

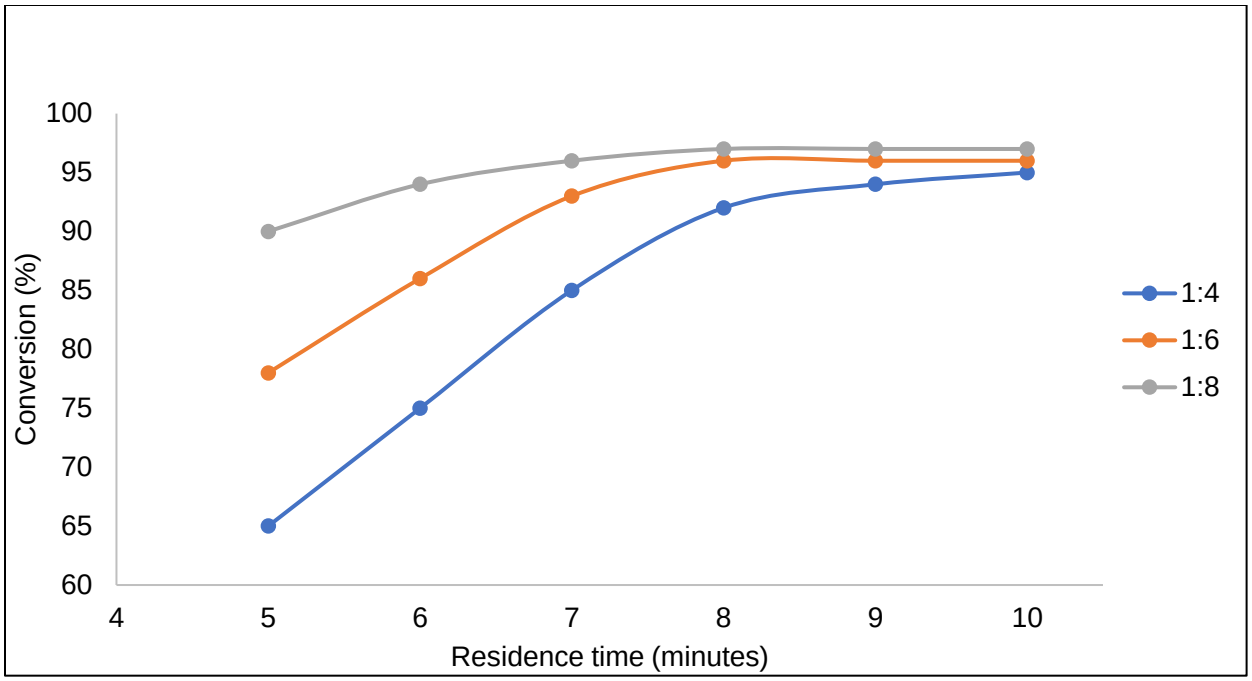


Figure 54: *Effect of increase in the molar equivalents of the methyl iodide on the conversion of* ***39*** *towards 3,5-bis(1-cyano-1-methylethyl)toluene* ***40****.*

The results obtained show that, as expected, an excess of methyl iodide improves the conversion towards 3,5-bis(1-cyano-1-methylethyl)toluene **40**. Varying the molar ratio of **39** to the non-limiting reagent methyl iodide from 1:4 (effectively 1:1 w.r.t. to **39**) to 1:6 (effectively 1:1.5 w.r.t. to **39**) led to a 13% increase in conversion at 5 minutes residence time. An additional 12% increase in conversion was observed when the molar equivalents of methyl iodide was increase from 1:6 (effectively 1:5 w.r.t. **39**) to 1:8 (effectively 1:2 w.r.t. **39)** at 5 minutes residence time. The conversion of **39** towards **40** also increased as the residence time was increased**,** attaining 95% and 96% conversion in 8 minutes for 1:6 and 1:8 molar equivalents, respectively. At 1:4 molar equivalents the conversion increased rapidly as the residence time was increased to 92% after 7 minutes, then a plateau was observed between 92% and 94% conversion was observed beyond 7 minutes residence time. We also noticed that there was no increase in conversion beyond 8 minutes residence time for both the 1:6 molar ratio and the 1:8 molar ratio. Therefore, we decided to adopt 8 minutes residence time for the remainder of our optimization studies. Also, given that increasing the molar equivalents of **39** to methyl iodide from 1:6 to 1:8 led to only very slight increase in conversion at 8 minutes residence time (from 95-96%), we reckoned that it would be best to continue with 1:6 molar equivalents for the rest of the optimization process.

We then went on to investigate the effect of the equivalents of the base NaH on the conversion towards the desired product 3,5-bis(1-cyano-1-methylethyl)toluene **40**. The concentration of NaH was varied between 0.2 M, 0.3 M, 0.4 M and 0.5 M. The concentration of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** was kept constant at 0.2 M, methyl iodide concentration was kept constant at 1.2 M (effectively 1.5 equiv. w.r.t. **39**) and the residence time was kept constant at 8 minutes. The results of the study a shown in Figure 55.

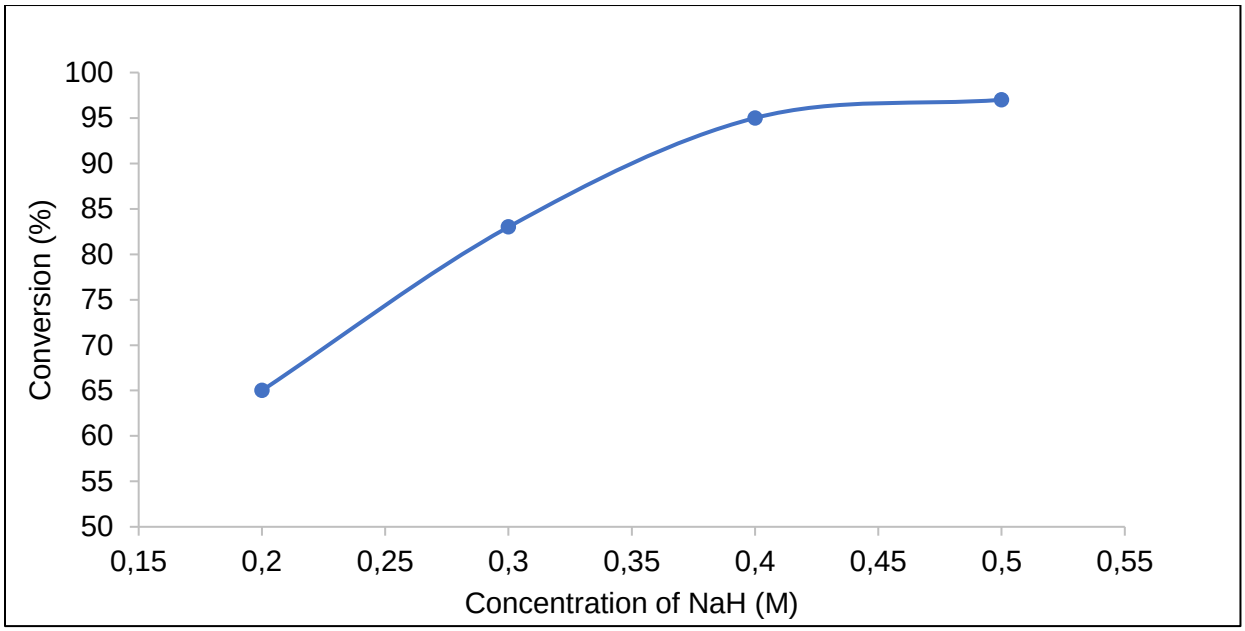


Figure 55: *Effect of NaH concentration on the conversion of **39** towards 3,5-bis(1-cyano-1-methylethyl)toluene **40**.*

Figure 55 shows that the conversion of **39** towards our desired product **40** generally increases as the concentration of the NaH is increased within the concentration range investigated. Only a small increase in conversion was observed from 65% at 0.2 M (4 equiv. w.r.t. **39**) to 83% at 0.3 M NaH(6 equiv. w.r.t. **39**).A further increase in conversion to 95% was observed when the concentration of NaH was increased to 0.4 M (8 equiv. w.r.t. **39**). A very slight increase in conversion of 2% (from 95% to 97%) was observed when the concentration of NaH was increased from 0.4 M to 0.5 M. Given that Increasing the concentration of NaH from 0.2 M to 0.5 molar led to only a 2% increase in conversion, we deduced that the best concentration of NaH for the reaction was 0.4 M (8 equiv. w.r.t. **39**), where we achieved 95% conversion in 8 minutes.

Having established our optimum concentration and molar equivalents of the base NaH, we were curious to see the effect that a different base will have on the reaction. We investigated the effect of a second base, lithium diisopropylamide (LDA) on the conversion of **39** towards our desired product 3,5-bis(1-cyano-1-methylethyl)toluene **40**. NaH, while being an good base for this reaction, poses significant problems in organic synthesis due to its highly exothermic and hazardous properties.[98,99] Also, NaH forms a slurry in solution ,which is a major concern in flow, especially at higher NaH concentration or when scaling up, due to the difficulty of pumping the viscous fluid through the reactors.[104,105] We therefore thought it necessary to investigate the effect of another base on the reaction of **39** towards the desired product **40**. 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** (0.05 M) and methyl iodide (3 M, 6 equiv. w.r.t. **39**(effectively 1.5 equiv. w.r.t. **39** since 4 moles are required for each mole of **39**)) and LDA(0.4 M, 8 equiv. (effectively 2 equiv.) w.r.t. **39**) in another syringe were simultaneously streamed through the 1 mL PTFE coil reactor. The temperature was kept at the previously determined optimum temperature of 40 °C, and the residence time was kept to 8 minutes. The results of the study are sown in Figure 56.

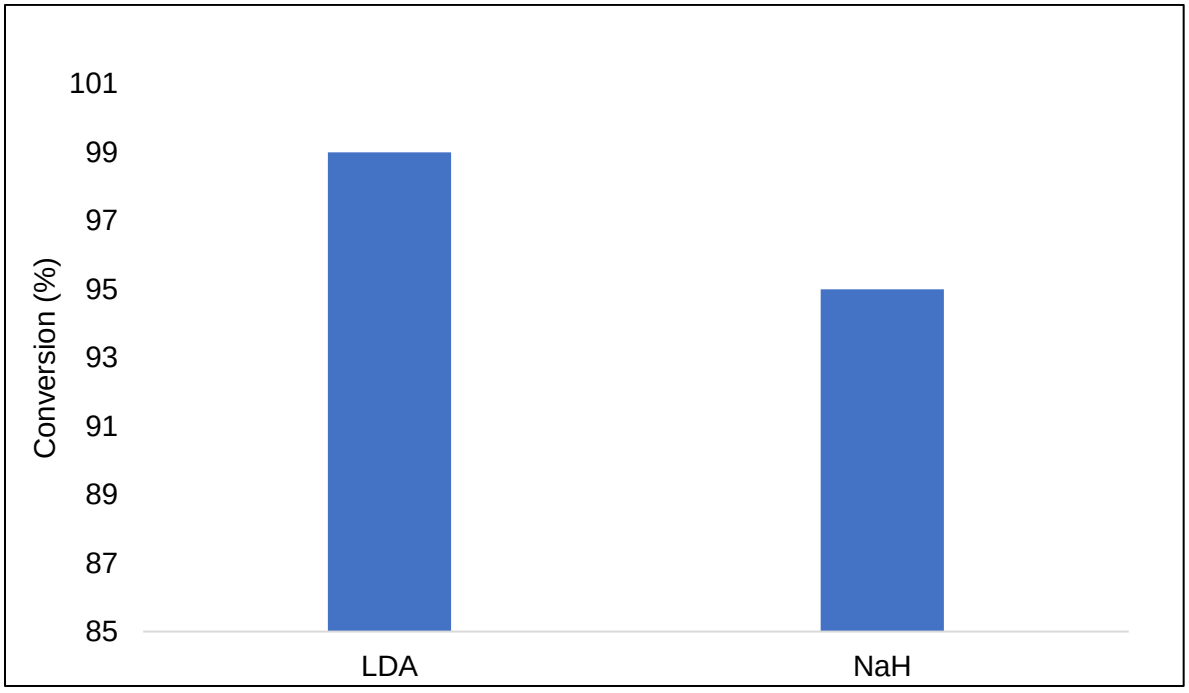


Figure 56: *Showing the effect of NaH and LDA on the conversion towards 2,2'-(5-methyl-1,3-phenylene)di(2-methylpropiononitrile* ***40.***

From Figure 56 we observe that a descent conversion of 99% was obtained when LDA was used as base. Compared to NaH, which is also an increase in conversion (compared to NaH) since 95 % conversion was obtained with NaH as base. The problems associated with the difficulty of pumping the NaH slurry through the flow reactors remain, especially at higher concentration of NaH and when scaling up. Furthermore, the slurry leads to a more inefficient mixing due to increase in the viscosity of the fluid. Reynold's formula shows that as viscosity of the fluid increases, turbulent mixing becomes reduced.[99] The increase on the conversion of **39** towards 3,5-bis(1-cyano-1-methylethyl)toluene **40** when LDA was used as base can be attributed to better, more turbulent mixing of the fluids due the to the lower viscosity of the solution.[99]

Therefore, the optimum conditions achieved for the synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene **40** in the PTFE tubing were 99% conversion at 40 °C and 8 minutes residence time using LDA as a base, With the molar ratio of **39** to methyl iodide kept at 1:6 respectively (effectively 1:1.5) and the molar equivalents ratio of the base to **39** was 1:8 (effectively 1:2).This translates to a throughput of 0.045 g/h.

3.1.4 Synthesis and optimization of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) in Little Things Factory reactor

Following the successful synthesis and optimization of 2,2'-(5-methyl-1,3-phenylene)di(2-methylpropiononitrile **40**, we moved on to the fourth step of our synthetic route to synthesize 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41**. The bromination of **40** to obtain 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41** was investigated and optimized in flow chemistry and all optimization reactions were done using a LTF reactor. The setup was connected as shown in Figure 57 .

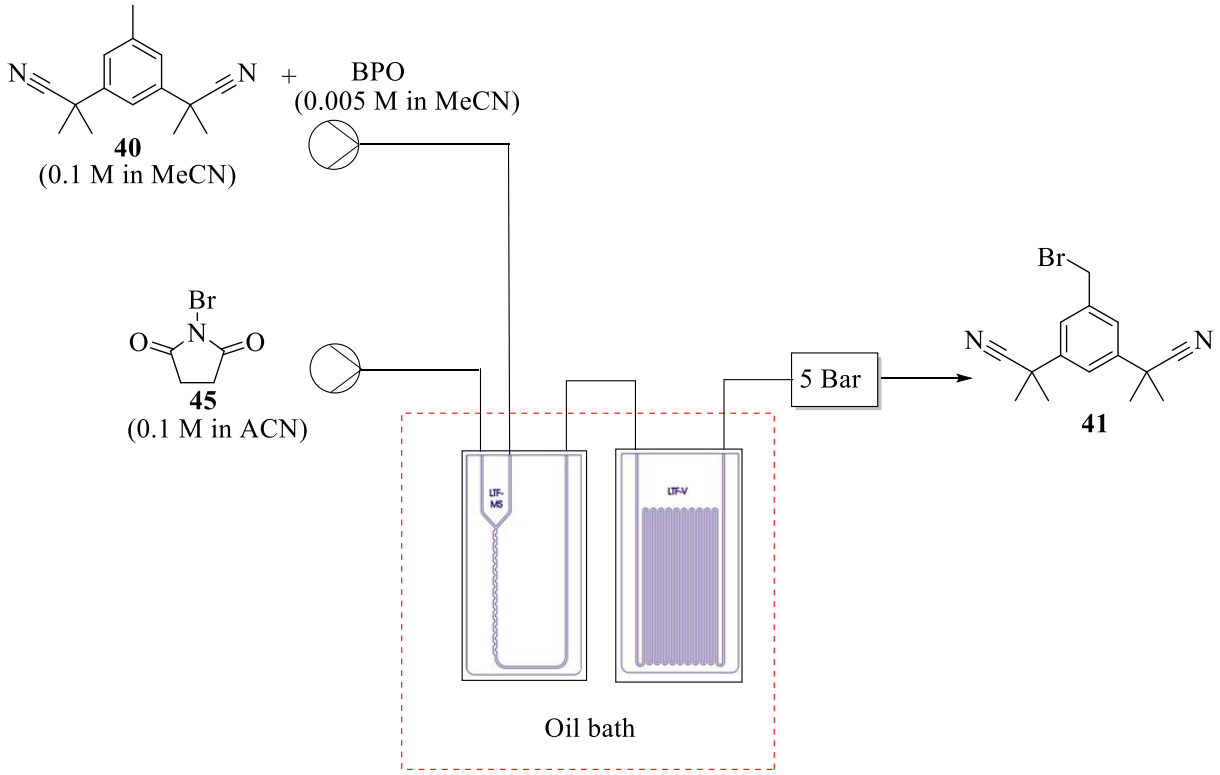


Figure 57: *Schematic setup for the synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile)**41** in a Little things Factory reactor.*

The batch synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41** gave a yield of 72% after 3 hours. The reaction was adapted to flow and optimized using the LTF reactor. The parameters investigated were the effect of temperature, residence time, molar equivalents of the reactants and concentration of the catalyst. Firstly, a quick preliminary temperature study was done to establish if temperature has a significant effect on the reaction within the temperature range investigated. In this study, 2'-(5-methyl-1,3-phenylene)di(2-methylpropiononitrile) **40** (0.1 M in ACN) and BPO (0.005 M, 0.05 equiv. w.r.t. **40**) in one syringe was reacted with NBS **45 (**0.1 M, 1 equiv. w.r.t. **40**) in a second syringe. Both solutions were streamed through the LTF reactor and the temperature was varied from 80 °C to 120 °C. The residence time was kept constant at 5 minutes. The results of the study are displayed in Figure 58.

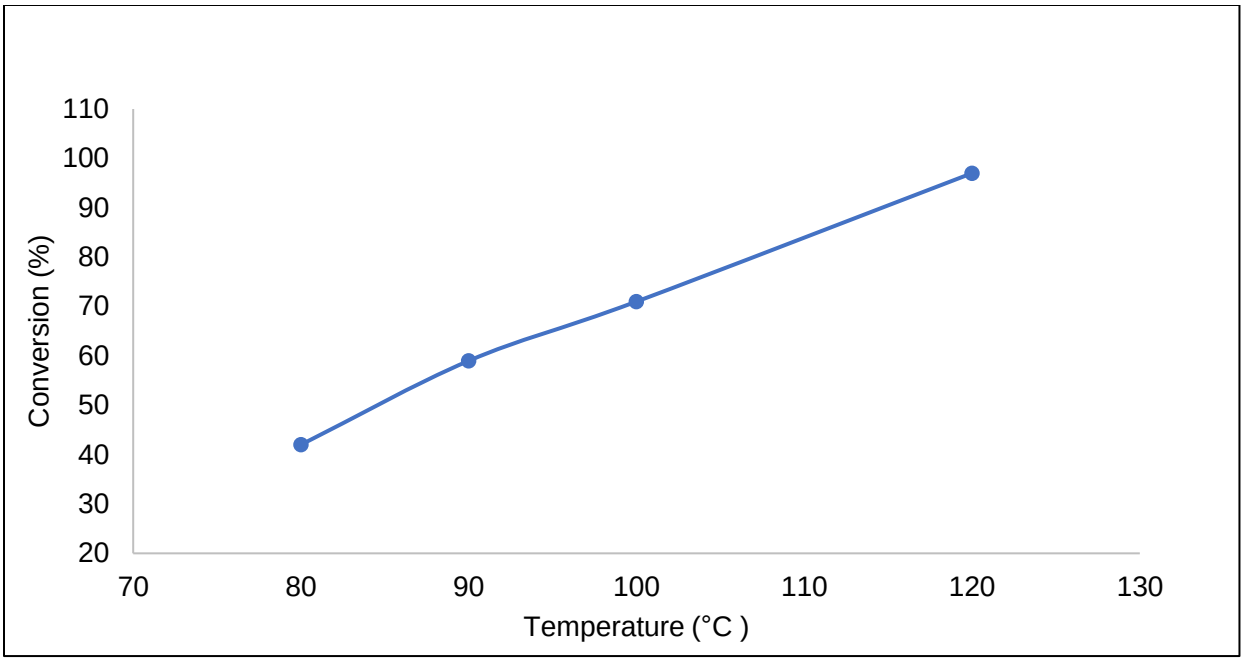


Figure 58: *Preliminary temperature study towards the synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile)* ***41***.

The results obtained clearly reveal that the temperature has a significant effect on the conversion of **40** towards 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41** within the temperature range investigated, as the conversion increased as the temperature is increased. Having established that the temperature significantly affects the reaction, we went to do a more extensive temperature and residence time study. In this study, 2'-(5-methyl-1,3-phenylene)di(2-methylpropiononitrile) **40** (0.1 M in ACN) was reacted with NBS **45 (**0.1 M, 1 equiv. w.r.t. **40**) with BPO (0.005 M, 0.05 equiv. w.r.t. **40)** as catalyst. The temperature was varied from 80 °C to 140 °C and the residence time was varied from 2 minutes to 10 minutes. The results of the study are displayed in Figure 59 below.

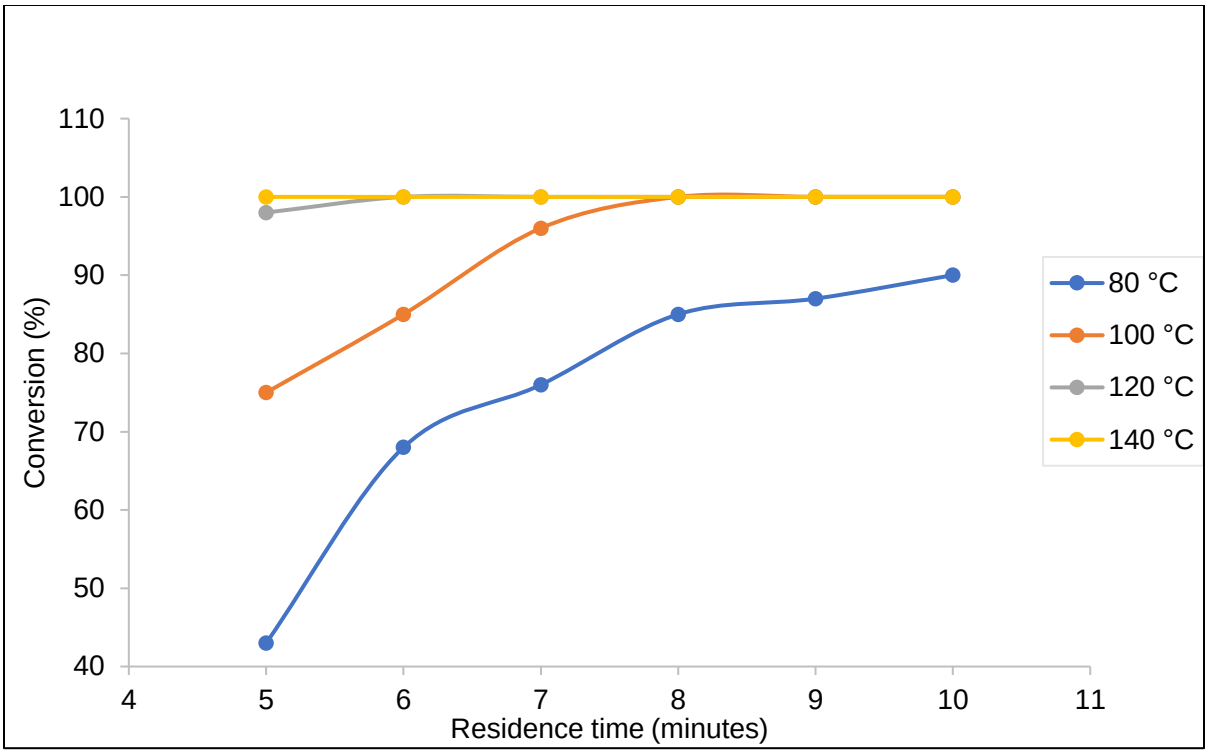


***Figure 59**: Effect of temperature and residence time on the conversion of **40** towards 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41**.*

Figure 59 shows that the conversion towards **41** generally increased with temperature within the temperature range investigated. The temperature also played an important role in the mechanism of the reaction. The reaction mechanism is same as the synthesis of 3,5-bis(bromomethyl)toluene **38** (section 2.5.2).

The increase in conversion as the temperature is increased can be attributed to the higher kinetic energy resulting in more collisions between the molecules. We observed that increasing the temperature from 80 °C to 100 °C led to a 33% increase in conversion (from 42% to 75% conversion of **40** towards **41**), and further increasing the temperature to 120 °C led to another 23% increase in conversion (from 75% to 98% conversion of **40** towards **41**).

The conversion of **40** towards **41** also increased as the residence time was increased within the range investigated. 100% Conversion was achieved in 5 minutes, 6 minutes and 8 minutes at 140 °C, 120 °C and 100 °C respectively. Even though the 100% conversion was achieved in the shortest time (5 minutes) at 140 °C, we decided to continue with 120 °C as the best temperature for the

reaction. This is because milder conditions are generally preferred as the make the process safer and cheaper (especially at large scale on the industrial level) and we also obtained very good conversions at 120 °C (98% conversion in 5 minutes and 100% conversions from 6 minutes to 10 minutes). Having established 120 °C as the best temperature for the reaction within the range investigated, we went on to do a molar equivalents study. In this study the molar equivalent of the limiting reagent **40** was constant while the molar equivalents of NBS **45** was increased. The molar ratios of **40** to NBS **45** respectively were varied as between 1:1 and 1:1.8. The concentration of the catalyst BPO was 0.005 M (0.05 equiv. w.r.t. **40**). The residence time was varied between 2 minutes and 6 minutes. The results are shown in Figure 60.

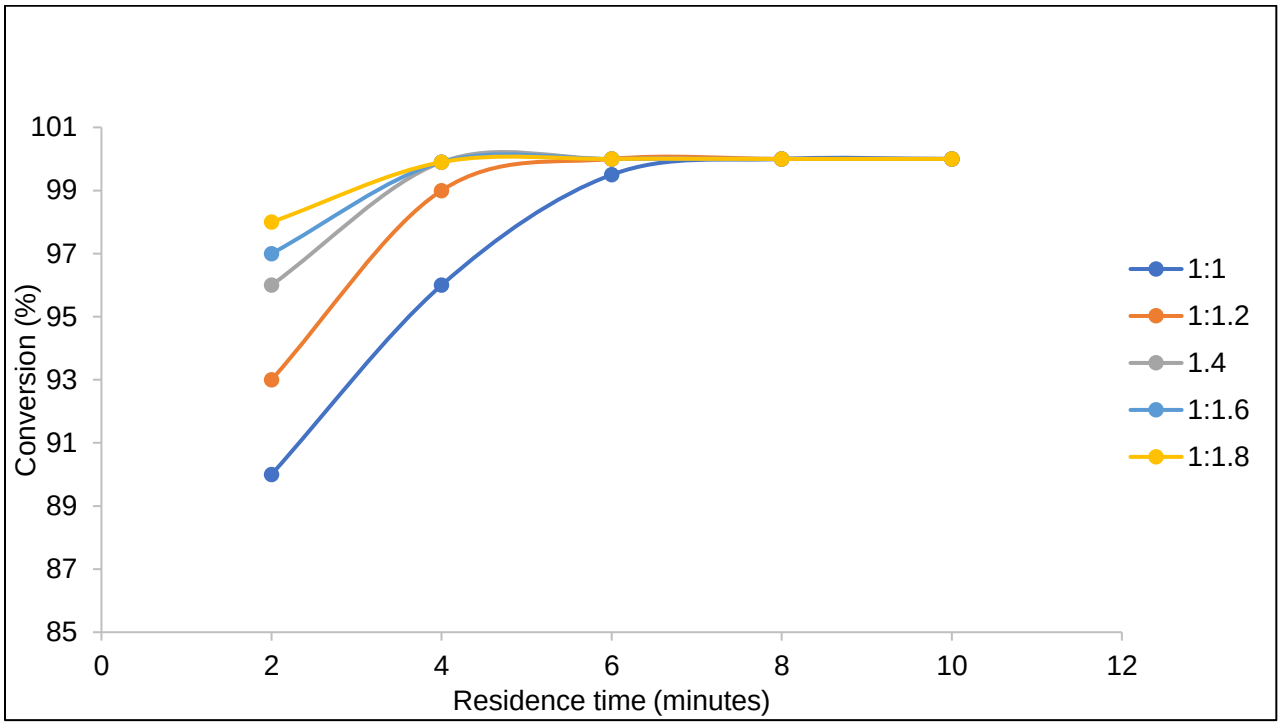


Figure 60: *Effect of increasing the molar equivalents of NBS **45** on the conversion of **40** towards 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41**.*

Figure 60 shows that the conversion towards **41** generally increased as the molar equivalents of NBS **45** is increased. Increasing the molar equivalents of NBS from 1:1 to 1:1.2 (of **40** to NBS **45** respectively) led to an increase in conversion by 3% (from 90% to 93% conversion) at 2 minutes residence time. A further increase from 1:2 to 1:4 led to another 3% increase in conversion (from 93% to 96% conversion) at 2 minutes residence. With molar ratio 1:1.6 only a 1% increase in

conversion was recorded (96%-97% conversion) and similarly at molar ratio 1:1.8, another slight 1% increase in conversion was observed. The conversions of **40** towards **41** generally increased as the residence time was increased within the residence time range investigated. Because only very slight increases in conversion we observed beyond 1: 1.4 molar equivalents (of **40** to NBS **45** respectively), we decided to proceed with the 1: 1.4 ratio (of **40** to NBS **45**) as the best molar ratio of reactants for the reaction.

Having established that 1: 1.4 molar equivalents of (**40** to NBS **45** respectively) was best for the reaction, we went on to investigate the effect of the concentration of the catalyst BPO on the conversion towards 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41**. In this study, the pre-determined optimum conditions of temperature and molar ratios of reactants were adopted *i.e.* temperature was kept at 120 °C, concentration of **40** was kept constant at 0.1 M, NBS **45** was kept constant at 0.14 M, (1.4 equiv. w.r.t. **40**) and the amount of the catalyst was varied between 0.005 M (0.05 equiv. w.r.t. **50**) and 0.03 M (0.3 equiv. w.r.t. **50**). The residence time was varied from 2 minutes to 6 minutes. The results of the study are displayed in Figure 61.

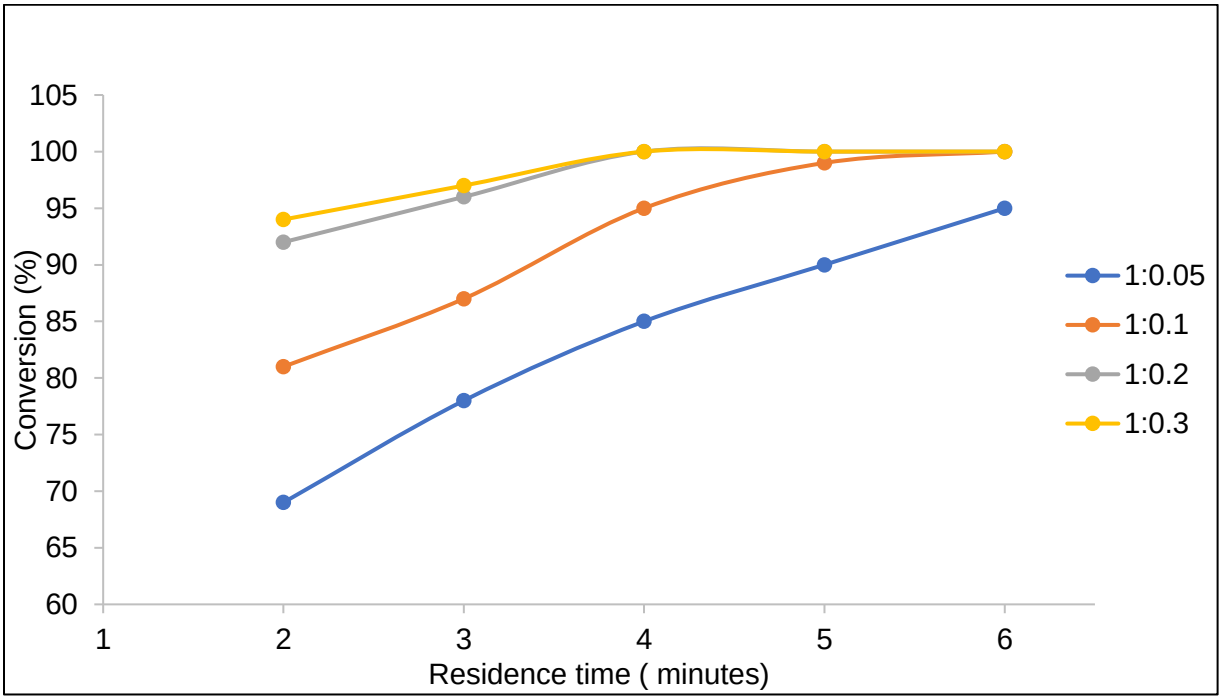


Figure 61: *Effect of the molar equivalents of the catalyst on the conversion of* ***40*** *towards 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile)* ***41****.*

From Figure 61 we see that the conversion of **40** towards 2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41** generally increases as the molar equivalents of the catalyst is increased. At 2 minutes residence, at 12% percent increase in conversion (from 69% to 81%) was observed when the molar equivalents of BPO was increased from 0.05 equiv. to 0.1 equiv. (w.r.t. **40**). Further increasing the molar equivalents of BPO to 0.2 equiv. (w.r.t. **40**) led to an 11% increase in conversion (from 81% to 92%). However, further increasing the molar equivalents of BPO to 0.3 (w.r.t. **40**) led to only a 2% increase in conversion. Observing this slight increase, we deduced that 0.02 equiv. of BPO (w.r.t. **40**) was best for the reaction. The conversion also generally increased as the residence time was increased, and 100% conversion was achieved at 0.2 equiv. of BPO (w.r.t. **40**) in 4 minutes. This translates to a throughput of 0.38 g/h.

Our optimum conditions for the synthesis of 2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) **41** were therefore 120 °C , with a 1:1.4 molar ratio of **40** to 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41** and 0.2 equiv. of the catalyst (w.r.t. **40**), with residence time of 4 minutes.

3.1.5 Continuous flow multistep synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile

Having successfully synthesized and optimized 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile) in continuous flow systems, we went on to combine the synthesis of 3,5-bis(bromomethyl)toluene **38** and 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** into a single continuous flow process. A major advantage of using continuous flow systems is that multistep synthesis can be carried out in a continuous manner without a need for product isolation or purification.[106,107,104] This eliminates dead-time between isolation of the products and the subsequent reaction step. Continuous multistep synthesis also guarantees safer handling of hazardous intermediates, as these intermediates can be generated in-situ and reacted in the next step within the closed system with no need for contact with the external environment.

The setup therefore included three LTF reactors, with two T mixers fitted with a 10 bar BPR. The first step, which involves the bromination of mesitylene was done using two 1.7 mL LTF reactors, while the cyanation reaction was done in one 1.7 mL LTF reactor, with a total residence time of 5 minutes for the multistep process. A solution of 3,5-bis(bromomethyl)toluene **38** (0.125 M) and benzoyl peroxide (0.0125 M, 0.1 equiv. w.r.t. **38**) in DCM were streamed through a T mixer then

through the first two LTF reactors at a flow rate of 0,425 mL/min. A second syringe containing NBS **45** solution (0.25 M , 2 equiv. w.r.t. **38**) in DCM was simultaneously streamed the T mixer and the first LTF reactors at a flow rate of 0.425 mL/min. The solution mixture emerging from the reactors was streamed through another T mixer and combined with a solution containing NaCN (0.19 M) and TBAB (0.019 M) being pumped at a flow rate of 0.85 mL/min. The setup was connected as shown in Figure 62.

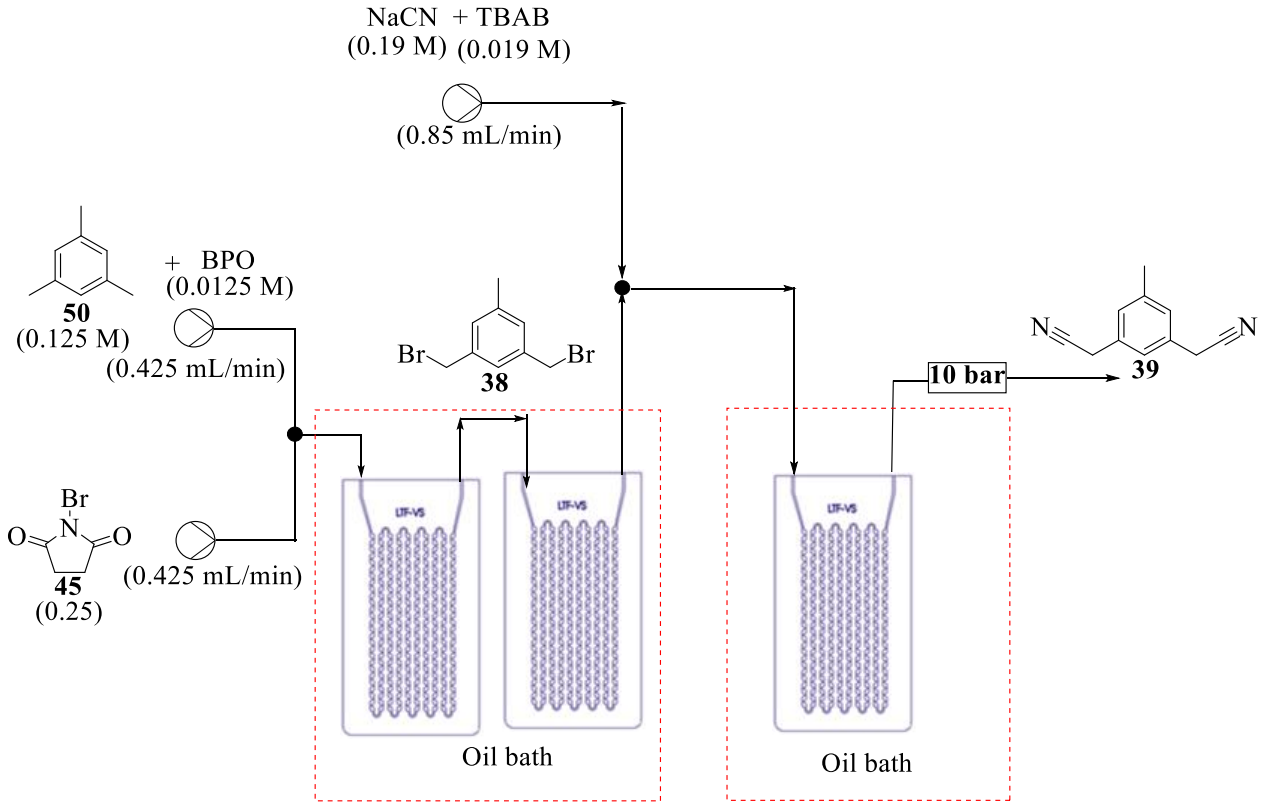


Figure 62: *Schematic setup for the multistep continuous flow synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39**.*

The two steps were successfully telescoped into one continuous flow process giving 94% conversion towards 3,5-bis(cyanomethyl)toluene **39** with a total residence time of 5 minutes (4 minutes for the first steps and 1 minute for the second step).

Chapter 4 - Conclusion

4.1 Conclusion

In this study, our objective to synthesize and optimize anastrazole intermediates in continuous flow systems was successfully achieved. As mentioned earlier, the batch procedures towards these intermediates are plagued with different limitations like poor selectivity, poor mass and energy transfer, problems during scaling up and safety concerns. Four anastrazole intermediates were successfully adapted to flow chemistry systems, resulting in safer, more energy and time efficient process with high throughputs.

The bromination of mesitylene to obtain 3,5-bis(bromomethyl)toluene **38** was successfully done in flow chemistry systems. Selectivity becomes an issue due to the likely formation of two byproducts (1-(bromomethyl)-3,5-dimethylbenzene and 1,3,5-tris(bromomethyl)benzene). The reaction was done in 15 µL Chemtrix reactor, 1.7 mL LTF reactor and a self-made 3.02 mL photochemical reactor made using PTFE tubing .The high surface area to volume ratio in the reactor which allowed for efficient mass and heat transfer, together with the capability for reaction parameters to be carefully controlled in flow chemistry reactors resulted in a good conversions and selectivity values being achieved. In both the Chemtrix and LTF reactors, 100% conversion was achieved with 95% selectivity. In the larger photochemical reactor, 100% conversion was achieved with 75% selectivity. The drop in selectivity was attributed to poorer mixing in the self-made photochemical reactor and insufficient light penetration.

The second step, which involved cyanation of 3,5-bis(bromomethyl)toluene **38** to obtain 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** was optimized in a 1.7 mL LTF reactor. Much higher temperatures and high turbulent effective mixing let to us achieving 100% conversion in a very short residence time.

The subsequent methylation of 3,5-bis(1-cyano-1-methylethyl)toluene **39** to obtain 3,5-bis(1-cyano-1-methylethyl)toluene **40** was done using a PTFE coil reactor. Safety concerns surrounding the hazardous nature of the NaH base used in the synthesis make this synthesis a dangerous process in batch. Consequently, the process is carried out at very carefully and at low temperatures in batch. In flow however, the high surface area to volume ratio guarantees quick heat dissipation, making such exothermic and potentially explosive rection much safer. The reaction was safely carried out at higher temperatures leading to increased safety when compared to the batch process

batch. Two bases were compared, NaH and LDA, achieving 95% and 99% respectively. The increase in selective with LDA was attributed to better mixing, as the LDA is much less viscous in solution than NaH.

The bromination of 3,5-bis(1-cyano-1-methylethyl)toluene **40** to obtain 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile) **41** was done in a 1.7 mL LTF reactor. Increasing the temperature resulted in significant increase in conversion with shorter residence times.

Finally, the two steps involved in the synthesis of 2,2'-(5-methyl-1,3-phenylene)diacetonitrile **39** were telescoped into a single continuous flow process. The system consisted of 3 LTF reactors, two T mixers and a 10 bar Zaiput back pressure regulator. A conversion of 94% was achieved for the telescoped process in a total residence time of 5 minutes.

In this study, we see plainly that the anastrazole intermediates were synthesized in flow systems with improved efficiency, safety, selectivity and throughput. Safety concerns surrounding the exothermic and potentially explosive nature of NaH were clearly more safely handled with flow chemistry. The reactions can be scaled up for industrial production locally, allowing for improved access to cheaper, locally made drug for Africa.

4.2 Future work

The synthesis of anastrazole intermediates could be optimized and scaled up in continuous flow systems to obtain a higher throughput. The remaining steps in the synthesis of anastrazole could be optimized and scaled up. The total synthesis of anastrazole could be optimized, telescoped into one continuous process and scaled up, resulting in a safe and highly effective process.

Chapter 5 - References

1 H. Nagai and Y. H. Kim, Cancer prevention from the perspective of global cancer burden patterns, *J. Thorac. Dis.*, 2017, **9**, 448–451.

2 G. M. Cooper and R.E. Hausman, *The Development and Causes of Cancer*, 8th ed.; Oxford University Press: New York, 2019.

3 G. Melmed, The War on Cancer: A Report from the Front Lines. *Baylor Univ. Med. Cent. Proc.* **2017**, *19* (4), 323–334.

4 S. H. Hassanpour and M. Dehghani, Review of cancer from perspective of molecular, *J. Cancer Res. Pract.*, 2017, **4**, 127–129.

5 M. Arruebo, N. Vilaboa, B. Sáez-Gutierrez and J. Lambea, Assessment of the Evolution of Cancer Treatment Therapies, *Cancers (Basel).*, 2011, **3**, 3279–3330.

6 L. Zhou, K. Nyberg and A. C. Rowat, Understanding diffusion theory and Fick's law through food and cooking, *Adv. Physiol. Educ.*, 2015, **39**, 192–197.

7 Sartorius K, Sartorius B, Govender PS and Sharma V, S. A. The Future Cost of Cancer in South Africa : An Interdisciplinary Cost Management Strategy. *South Africa Med. J.* **2016**, *106* (10), 949–950.

8 D.M. Parkin, F.I. Bray and S.S. Devesa, Cancer Burden in the Year 2000. The Global Picture.*Eur. J. Cancer* **2001**, *37*, 4–66.

9 J. V. Frangioni, New technologies for human cancer imaging, *J. Clin. Oncol.*, 2008, **26**, 4012–4021.

10 C. Jin, K. Wang, A. Oppong-Gyebi and J. Hu, Application of nanotechnology in cancer diagnosis and therapy - A mini-review, *Int. J. Med. Sci.*, 2020, **17**, 2964–2973.

11 L. G. Magalhaes, L. L. G. Ferreira and A. D. Andricopulo, Recent advances and perspectives in cancer drug design, *Ann. Braz. Acad. Sci.*, 2018, **90**, 1233–1250.

12 F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre and A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA. Cancer J. Clin.*, 2018, **68**, 394–424.

13 N. Harbeck, F. Penault-Llorca, J. Cortes, M. Gnant, N. Houssami, P. Poortmans, K.

Ruddy, J. Tsang and F. Cardoso, Breast cancer, *Nat. Rev. Prim.*, 2019, **5**, 1–31.

14 O. A. Zayas-Villanueva, L. D. Campos-Acevedo, J. D. J. Lugo-Trampe, D. Hernández-Barajas, J. F. González-Guerrero, M. F. Noriega-Iriondo, I. A. Ramírez-Sánchez and L. E. Martínez-De-Villarreal, Analysis of the pathogenic variants of BRCA1 and BRCA2 using next-generation sequencing in women with familial breast cancer: A case-control study, *BMC Cancer*, 2019, **19**, 1–8.

15 R. W. Hart, R. Adamson and D. Barnes, Chemical carcinogens: A review of the science and its associated principles. By the U.S. interagency staff group on carcinogens, *Environ. Health Perspect.*, 1986, **67**, 201–282.

16 P. A. Oliveira, A. Colaço, R. Chaves, H. Guedes-Pinto, L. F. P. De-La-Cruz and C. Lopes, Chemical carcinogenesis.*An. Acad. Bras. Cienc.*, 2007, **79**, 593–916.

17 A. R. Boobis, S. M. Cohen, V. L. Dellarco, J. E. Doe, P. A. Fenner-Crisp, A. Moretto, T. P. Pastoor, R. S. Schoeny, J. G. Seed and D. C. Wolf, Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, *Regul. Toxicol. Pharmacol.*, 2016, **82**, 158–166.

18 L. Falzone, S. Salomone and M. Libra, Evolution of cancer pharmacological treatments at the turn of the third millennium, *Front. Pharmacol.*, 2018, **9**, 1–19.

19 M.I Nounou, F. ElAmrawy, N. Ahmed, K. Abdelraouf , S. Goda and H. Syed-Sha-Qhattal , Breast cancer: conventional diagnosis and treatment modalities and recent patents and technologies. *Breast Cancer*. 2015,**9**,17-34.

20 A. M. Kabel, Tumor markers of breast cancer: New prospectives, *J. Oncol. Sci.*, 2017, **3**, 5–11.

21 H. Koyama, Current status of breast cancer chemotherapy in Japan. Recent Results Cancer Res. 1980;**70**:159-66

22 S. Puhalla, S. Bhattacharya and N. E. Davidson, Hormonal therapy in breast cancer: A model disease for the personalization of cancer care, *Mol. Oncol.*, 2012, **6**, 222–236.

23 P. Boyle ,T. Ngoma, R Sullivan and O Brawley, Cancer in Africa: the way forward, *ecancer*, 2019, **13**, 953-955.

24 W. Y. Joko-Fru, E. Jedy-Agba, A. Korir, O. Ogunbiyi, C. P. Dzamalala, E. Chokunonga, H. Wabinga, S. Manraj, A. Finesse, N. Somdyala, B. Liu, P. McGale, A. Jemal, F. Bray and D. M. Parkin, The evolving epidemic of breast cancer in sub-Saharan Africa: Results from the African Cancer Registry Network, *Int. J. Cancer*, 2020, **147**, 2131–2141.

25 S. N. Cumber, K. N. Nchanji and J. M. T.-Gwegweni, Breast cancer among women in sub-Saharan Africa: prevalence and a situational analysis, Southern African Journal of Gynaecological Oncology , 2017, **9**, 35-37

26 V. McCormack, F. McKenzie, M. Foerster, A. Zietsman, M. Galukande, C. Adisa, A. Anele, G. Parham, L. F. Pinder, H. Cubasch, M. Joffe, T. Beaney, M. Quaresma, K. Togawa, B. Abedi-Ardekani, B. O. Anderson, J. Schüz and I. dos-Santos-Silva, Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study, *Lancet Glob. Heal.*, 2020, **8**, e1203–e1212.

27 E. F. M. Hoen, T. Kujinga and P. Boulet, Patent challenges in the procurement and supply of generic new essential medicines and lessons from HIV in the southern African development community (SADC) region , *J. Pharm. Policy Pract.*, 2018, **11**, 1–8.

28 V.B. Kerry and K. Lee, TRIPS, the Doha declaration and paragraph 6 decision: what are the remaining steps for protecting access to medicines?. *Global Health*. 2007;3:3. Published 2007 May 24.

29 D. L. Riley and R. C. J. Strydom, Landscape and opportunities for active pharmaceutical ingredient manufacturing in developing African economies, *React. Chem. Eng.*, 2019, **4**, 457–489.

30 Y.M. Martei, A. Binagwaho and L.N. Shulman, Affordability of Cancer Drugs in Sub-Saharan Africa: Effects of Pricing on Needless Loss of Life. JAMA Oncol. 2017,**3**(10):1301-1302

31 J. Dong and Z. Mirza, Supporting the production of pharmaceuticals in Africa. Bull World Health Organ. 2016;94(1):71-72.

32 J. L. Carapinha, D. Ross-Degnan, A. T. Desta and A. K. Wagner, Health insurance systems in five Sub-Saharan African countries: Medicine Benefits and Data for Decision Making, *Health Policy* , 2011, **99**, 193–202.

33 United Nations, *International Trade Statistics Yearbook*, 2019, vol.I, https://www.un-ilibrary.org/content/books/9789210048323.

34 South Africa Imports of Pharmaceutical products, https://tradingeconomics.com/south-africa/imports/pharmaceutical-products, (accessed 15 September 2020).

35 P. Watts and C. Wiles, Micro Reactors , Flow Reactors and Continuous Flow Synthesis Micro reactors, flow reactors and continuous flow synthesis, *J. Chem.Res 2012,**36**,181-193.*

36 P. Watts, G. Pascali and P. Salvadori, Positron emission tomography radiosynthesis in microreactors, *J. Flow Chem.*, 2012, **2**, 37–42.

37 J. Zhang, C. Gong, X. Zeng and J. Xie, Continuous flow chemistry : New strategies for preparative inorganic chemistry,Cordination Chemistry Reviews.2016, **324**, 39–53.

38 J. C. Pastre, P. R. D. Murray, D. L. Browne, G. A. Brancaglion, R. S. Galaverna, R. A. Pilli and S. V. Ley, Integrated Batch and Continuous Flow Process for the Synthesis of Goniothalamin, *ACS Omega*, 2020, **5**, 18472–18483.

39 K Gernaey, Ask the experts: The challenges and benefits of flow chemistry to optimize drug development. Future Medicinal Chemistry,2012, **4**(14), 1780-1781.

40 M. Trojanowicz, Flow chemistry in contemporary chemical sciences: a real variety of its applications, *Molecules*, 2020, **25**, 1–52.

41 M. Guidi, P. H. Seeberger and K. Gilmore, How to approach flow chemistry, *Chem. Soc. Rev*, 2020, **49**, 8910–8932.

42 R. Van Kerrebroeck, P. Naert, T. S. A. Heugebaert, M. D'hooghe and C. V. Stevens, Electrophilic bromination in flow:a safe and sustainable alternative to the use of molecular bromine in batch, 2019, **24**, 2116-2119.

43 Y. D. Yoshida and A. Nagaki, continuous flow synthesis, *Drug Discov. Today Technol.*, 2013, **10**, e53–e59.

44 Rossetti Ilenia, New Concepts from batch to continuous organic chemistry, *Ind. Chem.*, 2016, **2**, 1–2.

45 W. C. Fu and T. F. Jamison, Modular continuous flow synthesis of Imatinib and analogues, *Org. Lett.*, 2019, **21**, 6112–6116.

46 C. Wiles and P. Watts, Continuous process technology: a tool for sustainable production, *Green Chem*, 2014, **15**, 55–62.

47 E. A.Mansur, Y. Mingxing, Y. Wang and Y. Dai, State-of -the-art review of mixing in Microfluid Mixers, *Chinese J. Chem. Eng.*, 2008, **16**, 503–516.

48 X. Chen, S. Liu, Yao Chen and S. Wang, A review on species mixing in droplets using passive and active micromixers, *International Journal of Environmental Analytical Chemistry*, **101**, 422-432

49 T.J. Ober, Foresti D and J.A. Lewis, Active mixing of complex fluids at the microscale. Proceedings of the National Academy of Sciences, *Proc. Natl. Acad. Sci.*, 2015, **112**, 12293-12298.

50 F. Z. Ward , Mixing in microfluidic devices and enhancement methods, *J Micromech Microeng*, 2015, **25**, 1-33.

51 C. Wiles, The use of Static Micro Mixers within Labtrix® Micro Reactors Mixing, https://www.chemtrix.com/img/library/1-Micro mixers.pdf

52 J. N. Tan and A. Neild, Microfluidic mixing in a Y-junction open channel microfluidic mixing in a Y-junction open channel, 2012, **2**, 1–13.

53 L. Malet-Sanz and S. Flavien, Continuous flow chemistry: a pharma perspective, *J. Med.Chem*, 2012, **59**, 4062–4098.

54 S. Taghavi-Moghadam, A. Kleeman and G. George, Microreaction technology as a novel approach to drug design, Process development and reliability, *Org. Process Res. Dev.*, 2001, **5**, 652–658.

55 A. Adeyemi, J. Bergman, J. Brånalt and J. S. Mats, Continuous flow synthesis under high-temperature/high-pressure conditions using a resistively heated flow reactor, *Org. Process Res. Dev.*, 2017, **21**, 947–955.

56 R. D. Souza and P. Watts, Flow Processing as a Tool for API Production in developing

economies, *J. Flow Chem.*, 2017, **7**, 146–150.

57 C. F. Carter, H. Lange, S. V Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode and N. L. Gaunt, ReactIR Flow Cell : A new analytical tool for continuous flow chemical processing , *Org. Process Res. Dev.*, 2010, **14**, 393–404.

58 H. Wang, M. Naghavi, C. Allen, M. Barber, Z. qar, A. Bhutta, A. Carter, M. A. Daniel, C. Casey, F. J. Charlson, Al. Z. Chen, M. M. Coates, M. Coggeshall, L. Dandona, D. J. Dicker, H. E. Erskine, A. J Ferrari, C. Fitzmaurice, K. Foreman, M. H. Forouzanfar, M. S. Fraser, N. Fullman, P. W. Geth, S. F. A. Deena Alasfoor, M. A. A. Aldridge, Z. A. A. Aleman, L. T. Alexander and S. Alhabib, Global , regional, and national life expectancy , all-cause mortality , and cause-specifi c mortality for 249 causes of death , 1980 – 2015: a systematic analysis for the Global Burden of Disease Study 2015, *the lancet*, 2016, **388**, 1980–2015.

59 T. A. Hamlin and N. E. Leadbeater, Real-time monitoring of reactions performed using continuous-flow processing : The Preparation of 3-Acetylcoumarin as an Example, *J. Vis. Exp.*, 2015, **105**, 1–7.

60 R. F. Tice, J. D. Song, H. Lyon, and A. D. Ismagilov, Formation of droplets and mixing in multiphase microfluidics at low values of the reynolds and the capillary numbers., *Langmuir*, 2003, **19**, 9127–9133.

61 Mixing and reaction technology pace setting technology, https://www.sulzer.com/-/media/files/products/staticmixers/mixing_and_reaction_technology_e_23270640.ashx?la=en, (accessed 15th April 2020).

62 I. M. Mándity, S. B. Ötvös and F. Fülöp, Strategic application of residence-time control in continuous-flow reactors, *chemistry open*, 2015, **4**, 212–223.

63 D. T. McQuade, B. P. Mason, K. E. Price, J. L. Steinbacher and A. R. Bogdan, Greener approaches to organic synthesis using microreactor technology., *Chem. Rev.*, 2007, **107**, 2300−2318.

64 A. A. Heredia, S. M. Soria-Castro, W. D. Castro-Godoy, I. D. Lemir, M. López-Vidal, F. R. Bisogno, J. E. Argüello and G. Oksdath-Mansilla, Multistep synthesis of organic selenides under visible light irradiation: a continuous-flow approach, *Org. Process Res.*

Dev., 2020, **24**, 540–545.

65 J. Britton and T. F. Jamison, The assembly and use of continuous flow systems for chemical synthesis, *Nat. Protoc.*, 2017, **12**, 2423–2446.

66 T. Welton, Solvents and sustainable chemistry, *Proc. R. Soc. A Math. Phys. Eng. Sci.*, 2015, **471**, 1–20.

67 M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley and C. V. Stevens, Taming hazardous chemistry by continuous flow technology, *Chem. Soc. Rev.*, 2016, **45**, 4892–4928.

68 D. M. Roberge, C. Noti, E. Irle, M. Eyholzer, B. Rittiner, G. Penn, G. Sedelmeier and B. Schenkel, Control of Hazardous Processes in Flow : Synthesis of 2-Nitroethanol, 2014, **4**, 26–34.

69 K. Hiebler, S. Soritz, K. Gavric, S. Birrer, M. C. Maier, B. Grabner and H. Gruber-Woelfler, Multistep synthesis of a valsartan precursor in continuous flow, *J. Flow Chem.*, 2020, **10**, 283–294.

70 M. Baumann, I. R. Baxendale, S. V Ley, C. D. Smith and G. K. Tranmer, Supporting information a fully automated continuous flow synthesis of 4,5- disubstituted oxazoles, *Org. Process Res. Dev.*, 2013, **17**, 1192–1208.

71 D. C. Stefan, Cancer care in Africa: an overview of resources, *J. Glob. Oncol.*, 2015, **1**, 30–36.

72 P. Kaur., 1 , 2 , 4-Triazole : A review of pharmacological activities, *Int. Res. J. Pharm.*, 2017, **8**, 1–29.

73 R. J. Santen, H. Brodie, E. R. Simpson, P. K. Siiteri and A. Brodie, History of aromatase: saga of an important biological mediator and therapeutic target, *Endocr. Rev.*, 2009, **30,** 343–375.

74 S. Chumsri, T. Howes, T. Bao, G. Sabnis and A. Brodie, Aromatase, Aromatase Inhibitors, and Breast Cancer, *J Steroid Biochem Mol Biol*, 2011, **125**, 13–22.

75 P. N. Edwards and M. S. Large, Substituted aralkyl) heterocyclic compounds, United

Kingdom, 1887.

76 A. Khile, N. Joshi, S. Bhirud, Process for preparing anastrozole and intermediates thereof. US; US20060189670A1, 2006.

77 J. Hăilóng, Synthesis of anastrozole. China; CN103554041B, 201375

78 A. Gaitonde, C. Vaidya and S. Pawar. Process for preparing anastrozole. UK; EP1758872A1, 2005.

79 S. C. Shah, V. Kayamba, R. M. Peek and D. Heimburger, Cancer control in low- and middle-income countries: is it time to consider screening?, *J. Glob. Oncol.*, 2019, **3**, 1–8.

80 D. A. Goldstein, J. Clark, Y. Tu, J. Zhang, F. Fang, R. Goldstein, S. M. Stemmer and E. Rosenbaum, A global comparison of the cost of patented cancer drugs in relation to global differences in wealth, *Oncotarget*, 2017, **8**, 71548–71555.

81 P.Watts, S.J. Haswell, The Application of micro reactors for organic synthesis. *Chem. Soc. Rev.* 2005, ***34***, 235–246.

82 K. F. Jensen, B. J. Reizman and S. G. Newman, lab on a chip, *R. Soc. Chem.*, 2014, **14**, 3206–3212.

83 Back pressure regulators, https://www.idex-hs.com/store/fluidics/valves/back-pressure-regulators.html, (accessed 15 September 2020).

84 Back pressure regulators, https://www.zaiput.com/product/back-pressure-regulators/

85 Chemyx Inc fusion 200 touchsyringe pump:precision dosing syringe pumps for research, https://www.fishersci.com/shop/products/fusion-200-touch-syringe-pump/NC0670590, (accessed 15 September 2020).

86 R. E. Pearson and J. C. Martin, The mechanism of benzylic bromination with *N*-bromosuccinimide, *J. Am. Chem. Soc.*, 1963, **85**, 354–355.

87 I. Saikia, A. J. Borah and P. Phukan, Use of bromine and bromo-organic compounds in organic synthesis, *Chem. Rev.*, 2016, **116**, 6837–7042.

88 J. Wegner, S. Ceylan and A. Kirschning, Flow chemistry - a key enabling technology for (multistep) organic synthesis, *Adv. Synth. Catal.*, 2012, **354**, 17–57.

89 G. B. Quartara, M. Altamura, A. Guerri, R. Nannicini, M. Gensini, Solvent dependent benzylic radical bromination of aromatic Sulfonyl Chlorides, *Lett. Org. Chem.*, 2006, **3**, 191–194.

90 D. S. Achilias and I. D. Sideridou, Kinetics of the benzoyl peroxide/amine initiated free-radical polymerization of dental dimethacrylate monomers: Experimental studies and mathematical modeling for TEGDMA and Bis-EMA, *Macromolecules*, 2004, **37**, 4254–4265.

91 C. Gardner Swain, W. H. Stockmayer and J. T. Clarke, Effect of structure on the rate of spontaneous thermal decomposition of substituted benzoyl peroxides, *J. Am. Chem. Soc.*, 1950, **72**, 5426–5434.

92 D. D. Tanner, T. C. S. Ruo, H. Takiguchi, A. Guillaume, D. W. Reed, b. p. setiloane, s. l. tan and c. p. Memtzer, on the mechanism of *n*-bromosuccinimide brominations. bromination of cyclohexane and cyclopentane with *N*-bromosuccinimide, *J. Org. Chem.*, 1983, **48**, 2743–2747.

93 R. L. Hartman, Flow chemistry remains an opportunity for chemists and chemical engineers, *Curr. Opin. Chem. Eng.*, 2020, **29**, 42–50.

94 C. Sambiagio and T. Noël, Flow photochemistry: Shine some light on those tubes!, *Trends Chem.*, 2020, **2**, 92–106.

95 S. Deshpande, B. Gadilohar, Y. Shinde, D. Pinjari, A. Pandit and G. Shankarling, Energy efficient, clean and solvent free photochemical benzylic bromination using NBS in concentrated solar radiation (CSR), *Sol. Energy*, 2015, **113**, 332–339.

96 A. S. Shaikh and C. J. Gohil, Photochemical reaction: a lightning phenomena, *Int. J. Pharm. Chem. Anal.*, 2016, **3**, 104-107.

97 T. H. Rehm, Flow photochemistry as a tool in organic synthesis, *Chem. - A Eur. J.*, 2020, **26**, 16952–16974.

98 Y. Nishina, B. Ohtani and K. Kikushima, Bromination of hydrocarbons with CBr_4,

initiated by light-emitting diode irradiation, *Beilstein J. Org. Chem.*, 2013, **9**, 1663–1667.

99 R. Saeed, F. Uddin and Z. Khalid, The kinetics of the photochemical reaction of methylene green with methylamine and ethylamine, *Turk. J. Chem.*, 2004, **28**, 351–367.

100 I. Abdiaj and J. Alcázar, Improving the throughput of batch photochemical reactions using flow: Dual photoredox and nickel catalysis in flow for C(sp2)C(sp3) cross-coupling, *Bioorg. Med. Chem.*, 2017, **25**, 6190–6196.

101 D. Hesek, M. Lee, B.C. Noll, J. F. Fisher, and S. Mobashery, Dual roles of sodium hydride as a base and as a reducing agent and as a reducing agent, *J Org Chem*, 2009, **74**, 2567–2570.

102 Q. Yang, M. Sheng, J. J. Henkelis, S. Tu, E. Wiensch, H. Zhang, Y. Zhang, C. Tucker and D. E. Ejeh, Explosion hazards of sodium hydride in dimethyl sulfoxide, *N*, *N*-dimethylformamide, and *N*, *N*-dimethylacetamide, *Org. Process Res. Dev.*, 2019, **23**, 2210–2217.

103 D. A. Sheppard, T. D. Humphries and C. E. Buckley, Sodium-based hydrides for thermal energy applications, *Appl. Phys. A Mater. Sci. Process.*, 2016, **122**, 1–13.

104 F. Bossler, L. Weyrauch, R. Schmidt and E. Koos, Influence of mixing conditions on the rheological properties and structure of capillary suspensions, *Colloids Surf.. Eng.*, 2017, **518**, 85–97.

105 T. Shende, V. J. Niasar and M. Babaei, Effective viscosity and reynolds number of non-newtonian fluids using meter model, *Rheol. Acta*, 2021, **60**, 11–21.

106 V. R. L. J. Bloemendal, M. A. C. H. Janssen, J. C. M. Van Hest and F. P. J. T. Rutjes, Continuous one-flow multi-step synthesis of active pharmaceutical ingredients, *React. Chem. Eng.*, 2020, **5**, 1186–1197.

107 J. Britton and C. L. Raston, Multi-step continuous-flow synthesis, *Chem. Soc. Rev.*, 2017, **46**, 1250–1271.

Chapter 6 - Appendix

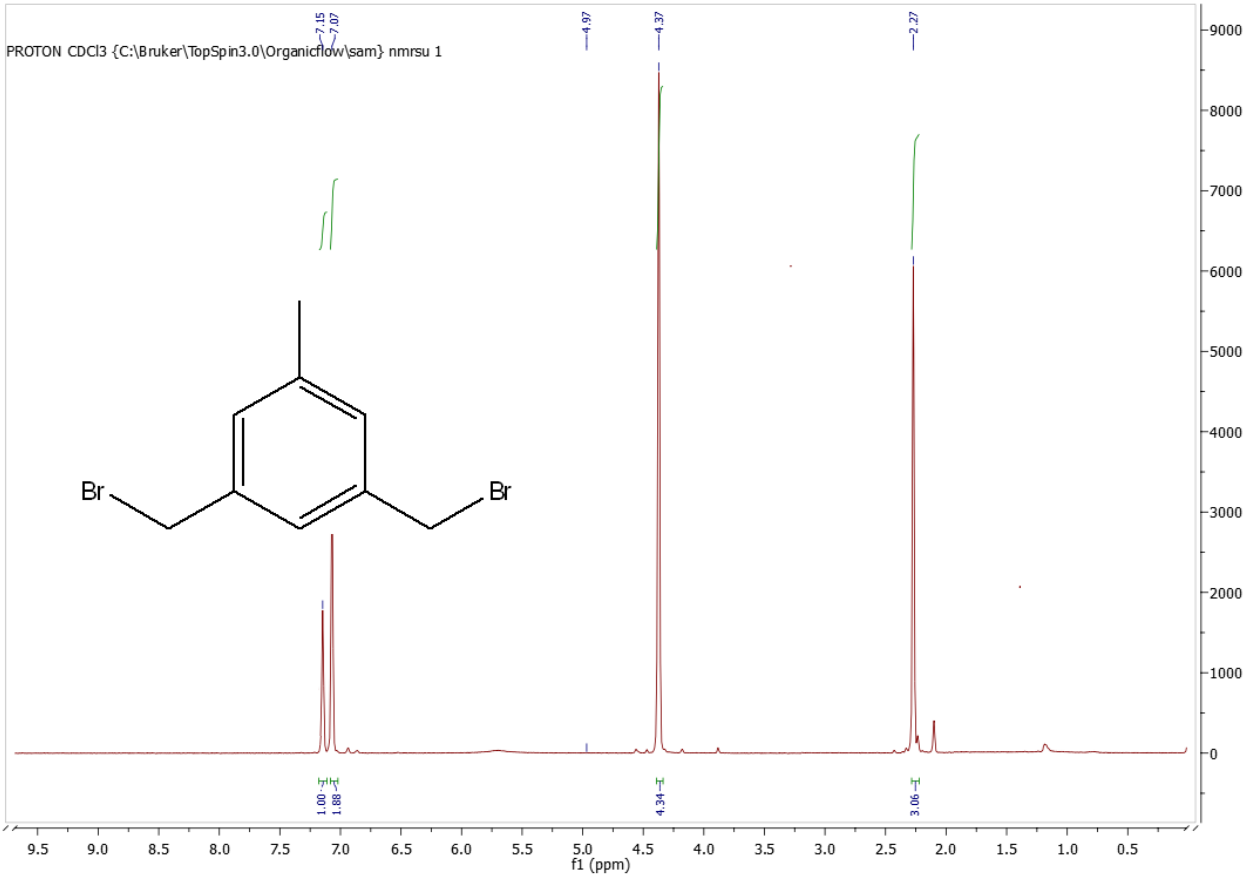


Figure 63: *^{1}H NMR obtained for 3,5-bis(bromomethyl)toluene* ***38****.*

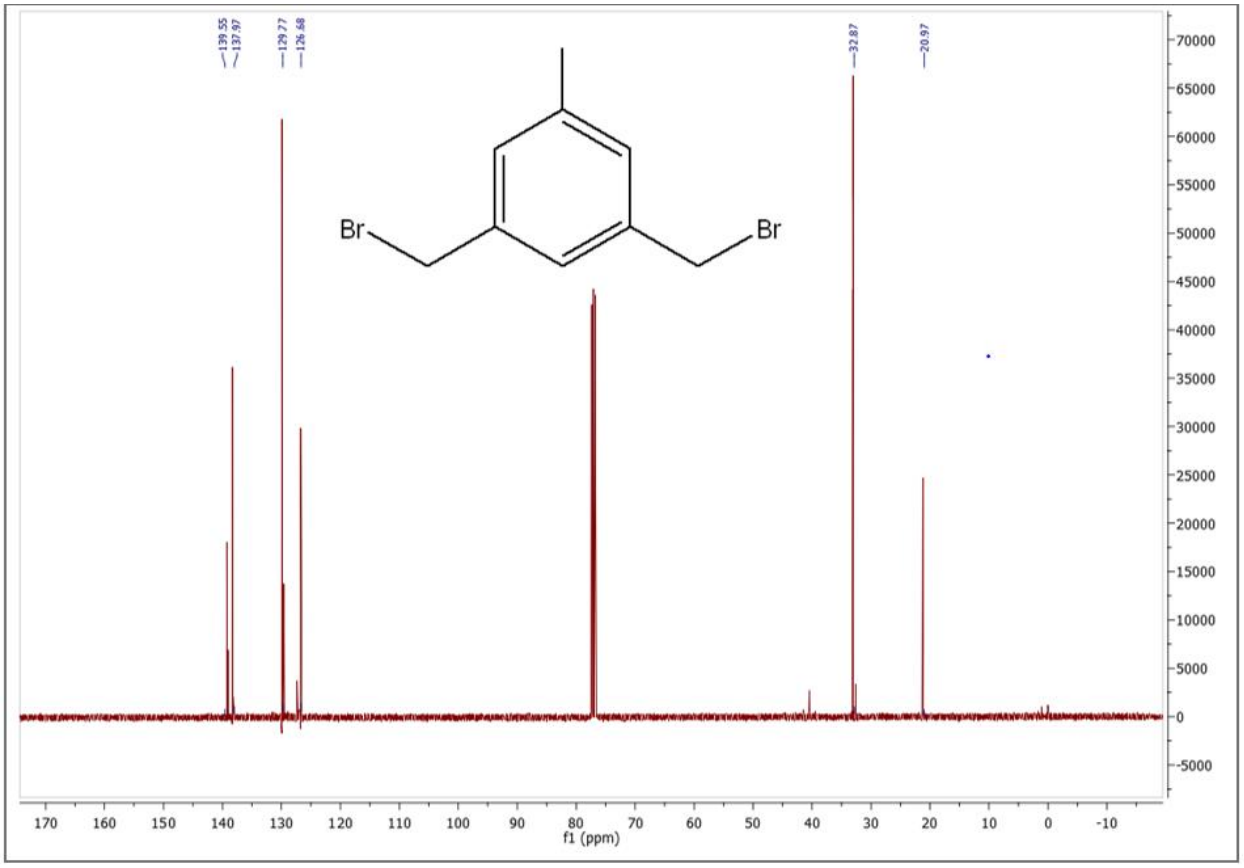


Figure 64: *^{13}C NMR obtained for 3,5-bis(bromomethyl)toluene **38**.*

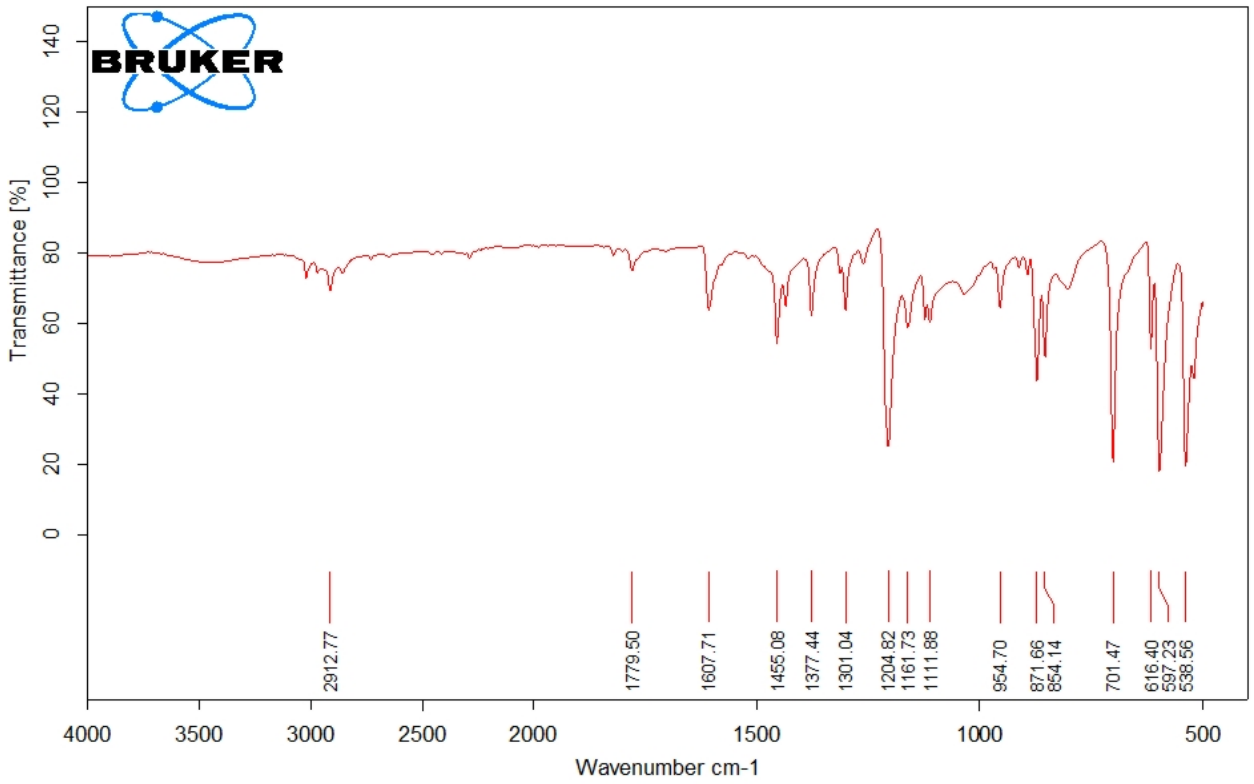


Figure 63: *FT-IR obtained for 3,5-bis(bromomethyl)toluene* ***38****.*

Figure 64: *^{1}H NMR obtained for 1,3,5-tris(bromomethyl)benzene* ***54****.*

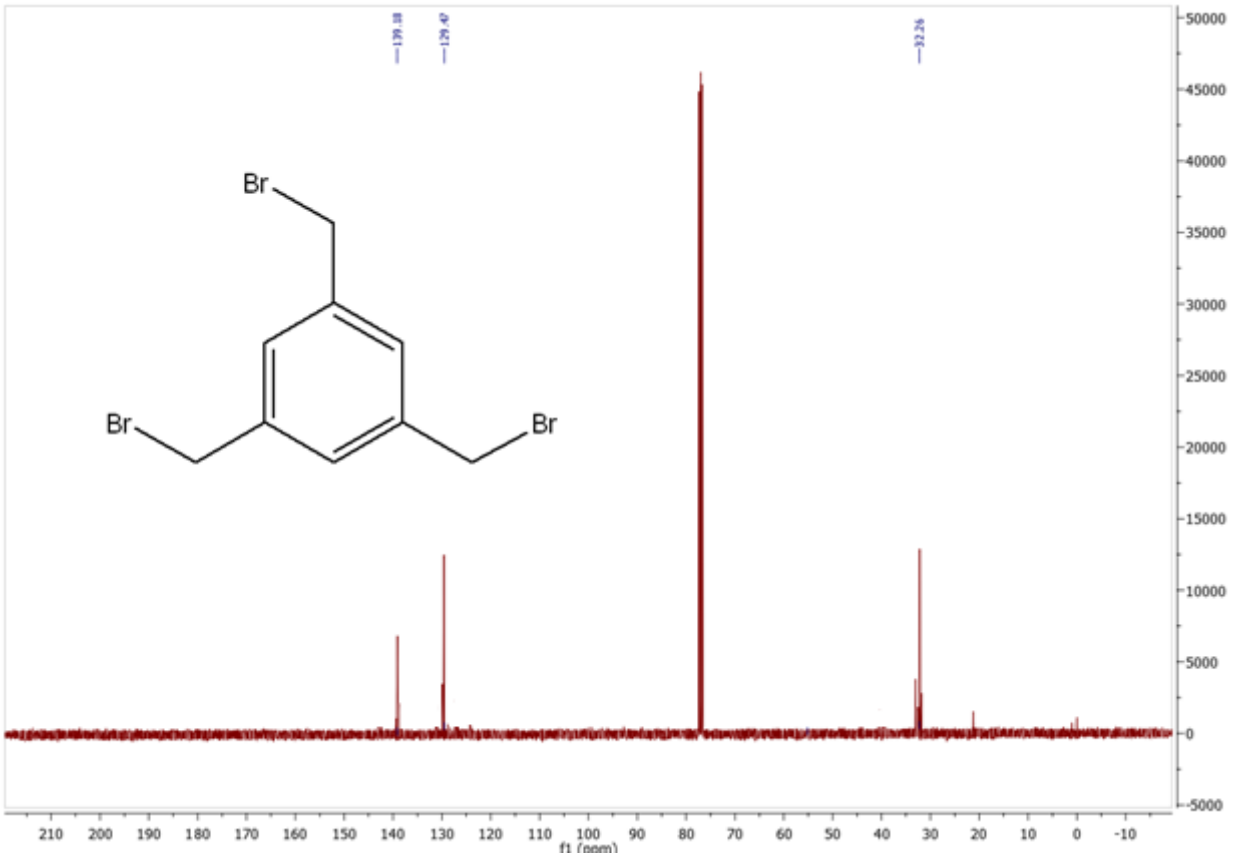


Figure 65: *^{13}C NMR obtained for 1,3,5-tris(bromomethyl)benzene* ***54****.*

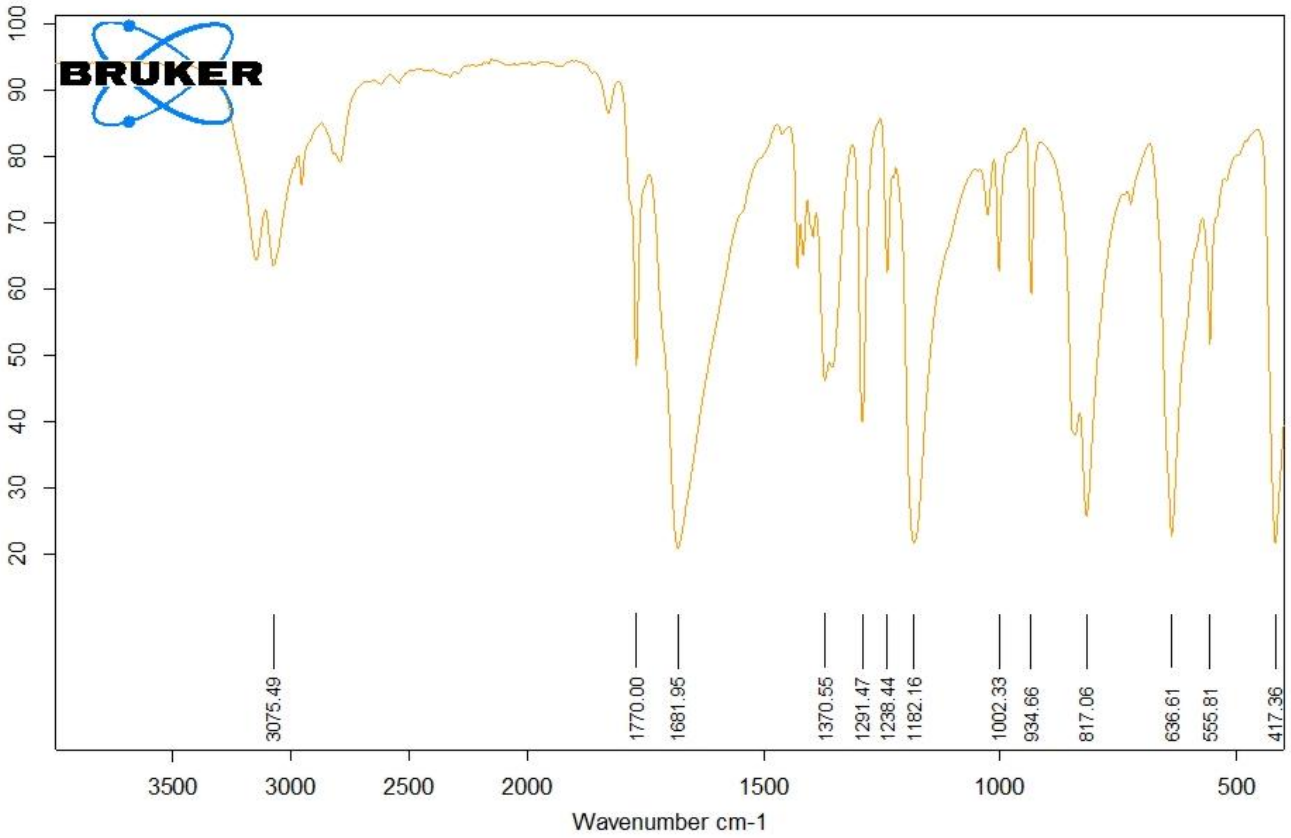


Figure 66: *FTIR obtained for 1,3,5-tris(bromomethyl)benzene* ***54****.*

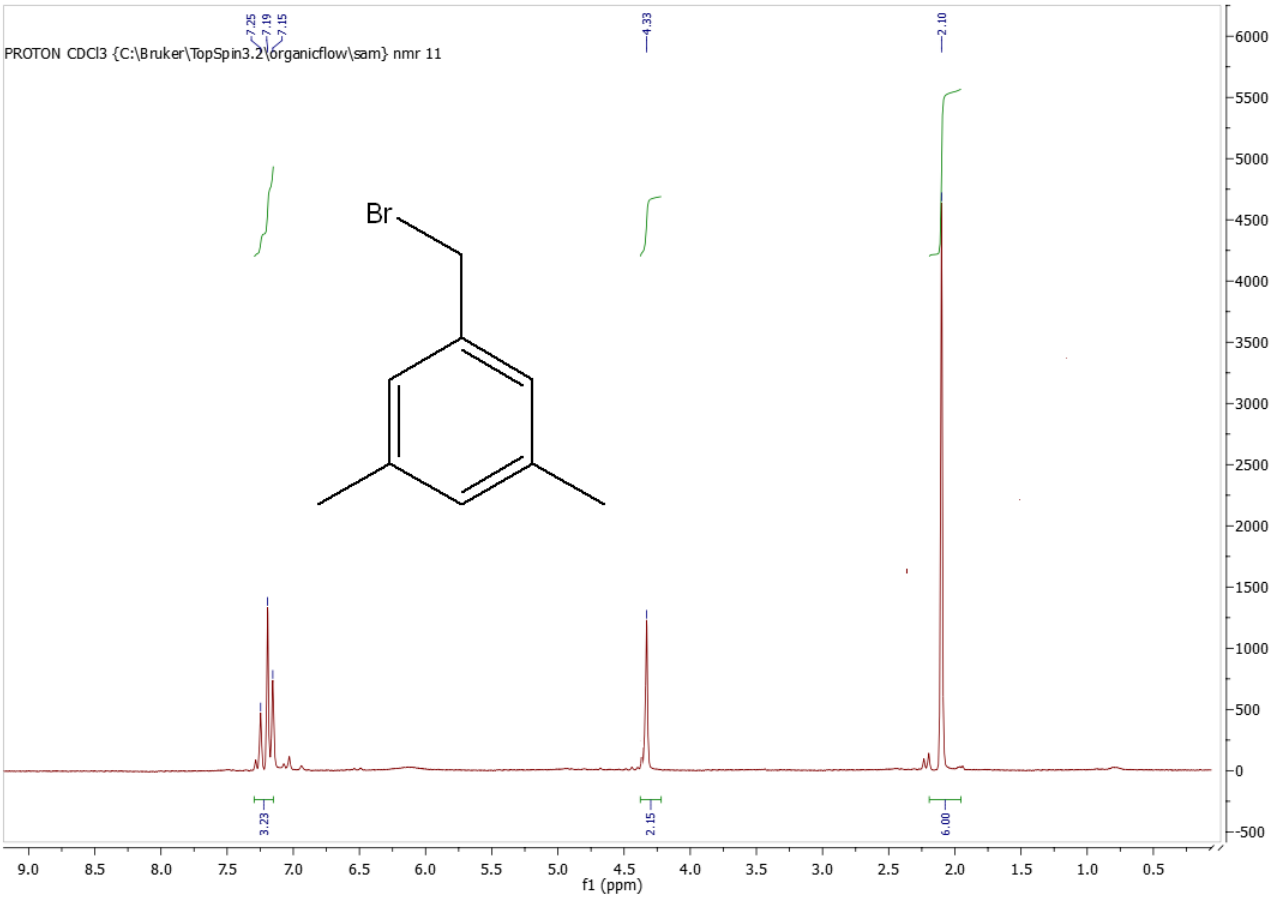


Figure 69: *^{1}H NMR obtained for 1-(bromomethyl)-3,5-dimethylbenzene* ***53****.*

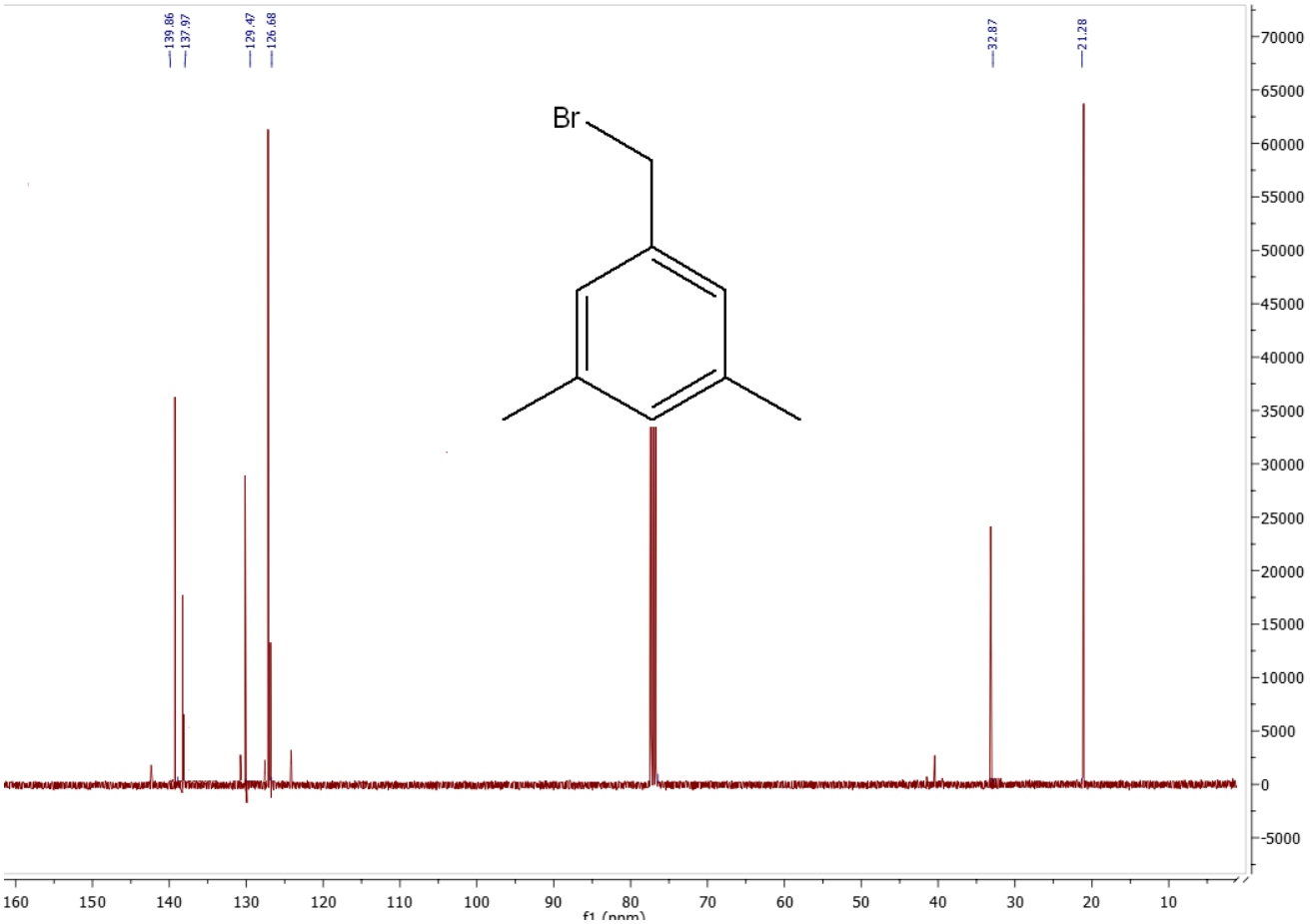


Figure70: *^{13}C NMR obtained for 1-(bromomethyl)-3,5-dimethylbenzene* ***53****.*

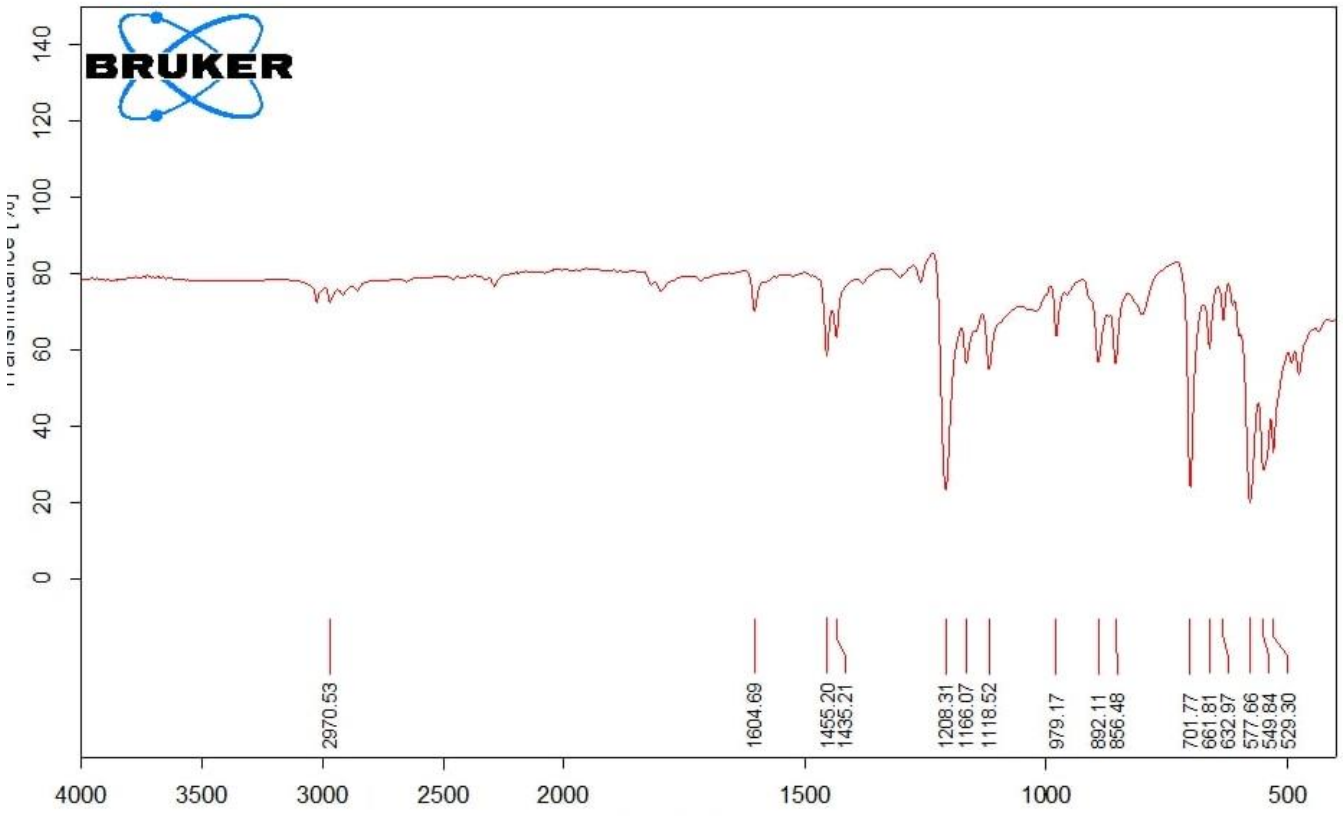


Figure 67: *FT-IR obtained for 1-(bromomethyl)-3,5-dimethylbenzene* ***53****.*

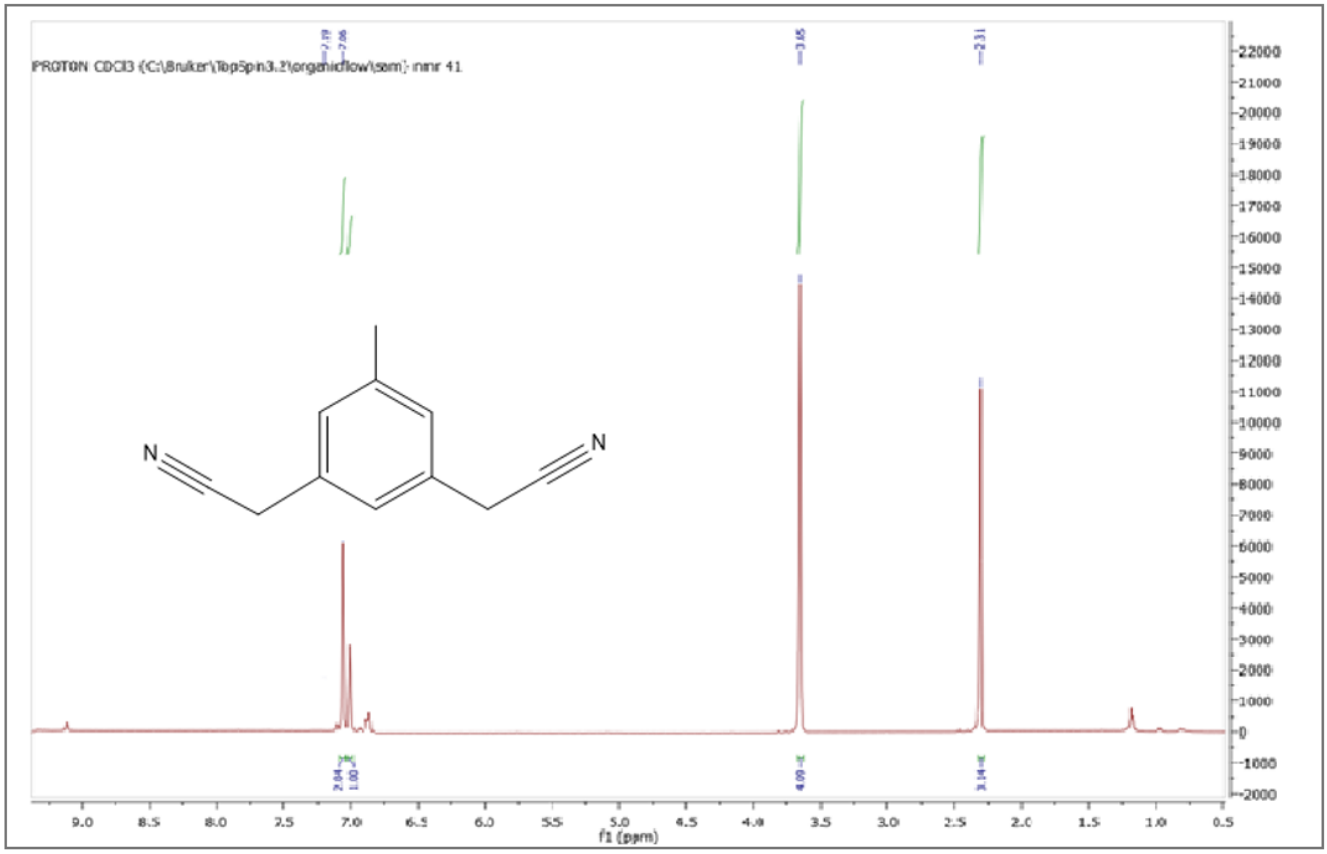


Figure 68: *^{1}H NMR obtained for 2,2'-(5-Methyl-1,3-phenylene)diacetonitrile* ***39****.*

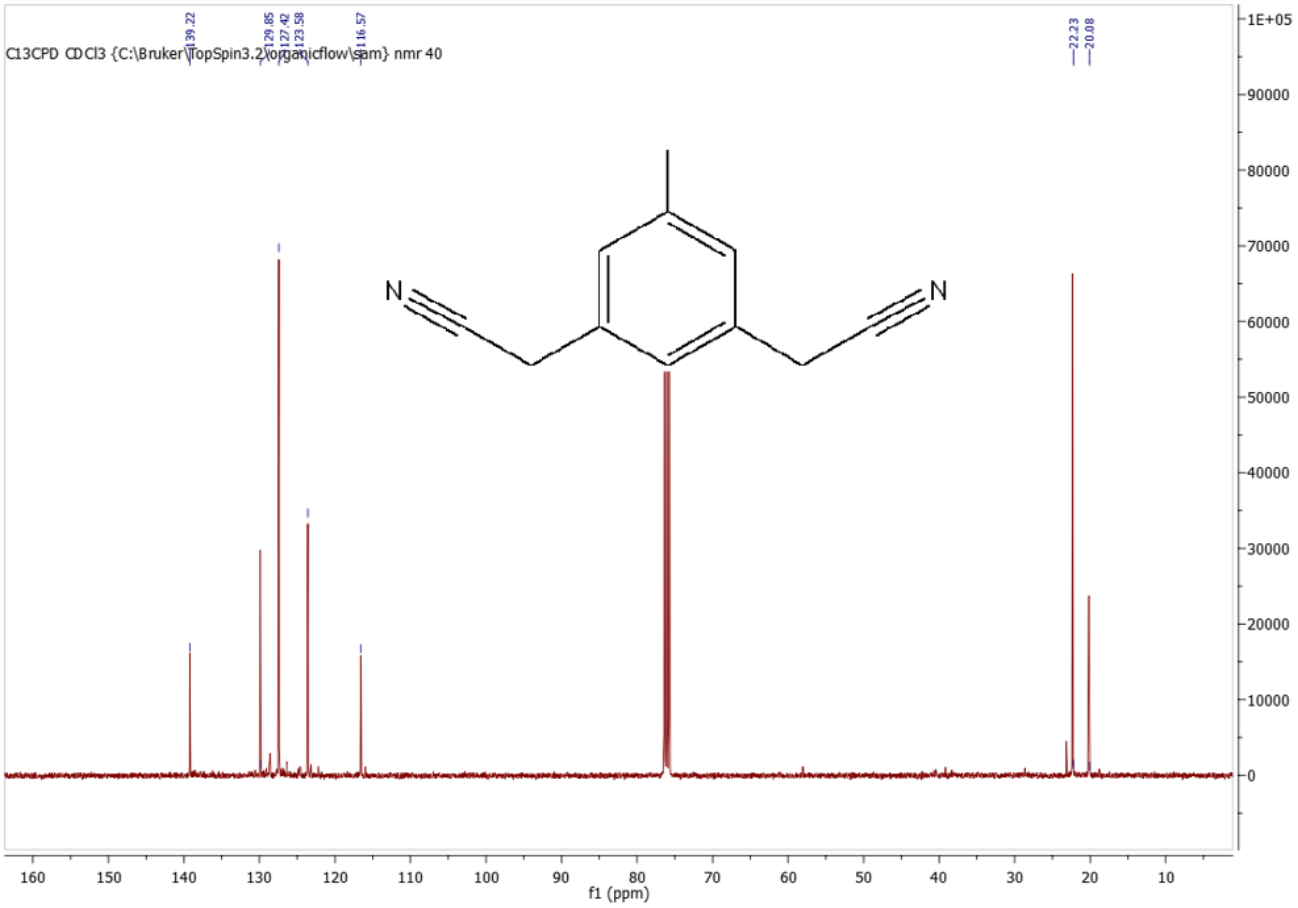


Figure 69: *^{13}C NMR obtained for 2,2'-(5-Methyl-1,3-phenylene)diacetonitrile* ***39****.*

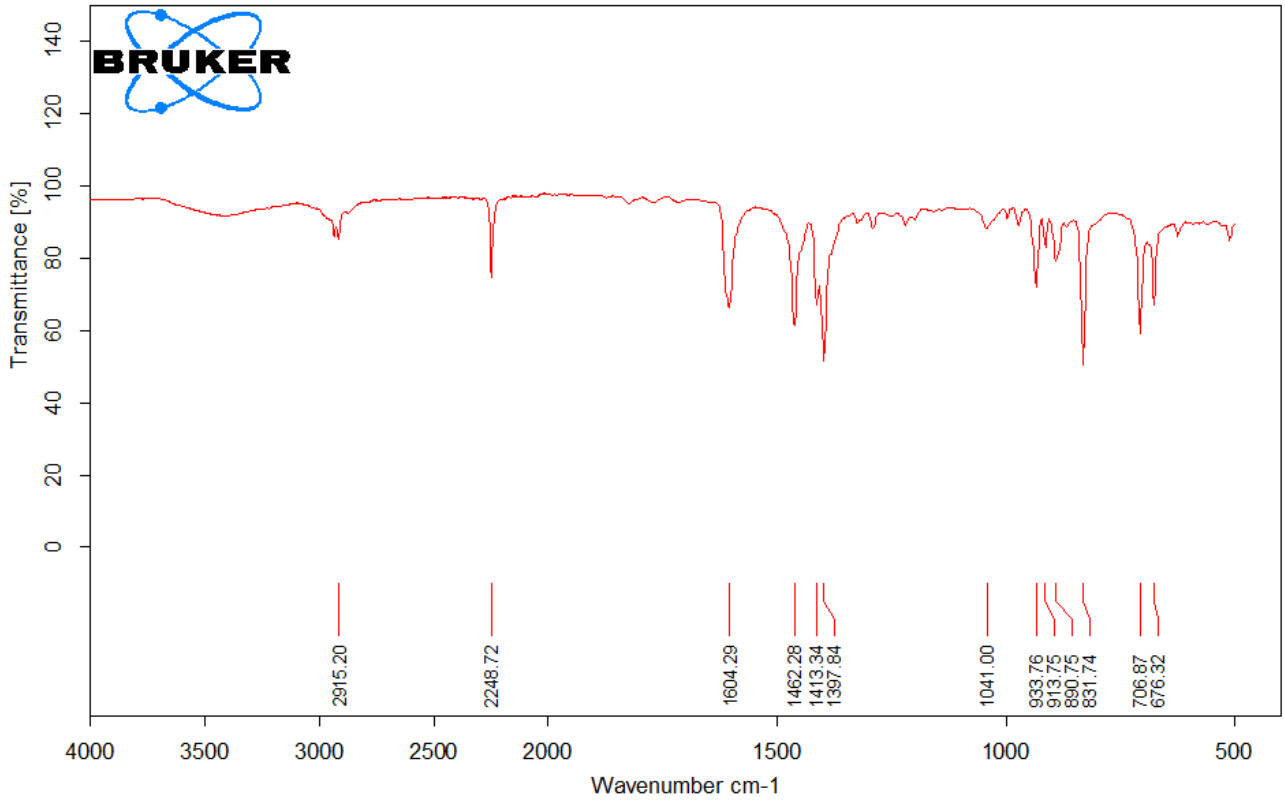


Figure 70: *FT-IR obtained for 2,2'-(5-Methyl-1,3-phenylene)diacetonitrile* ***39****.*

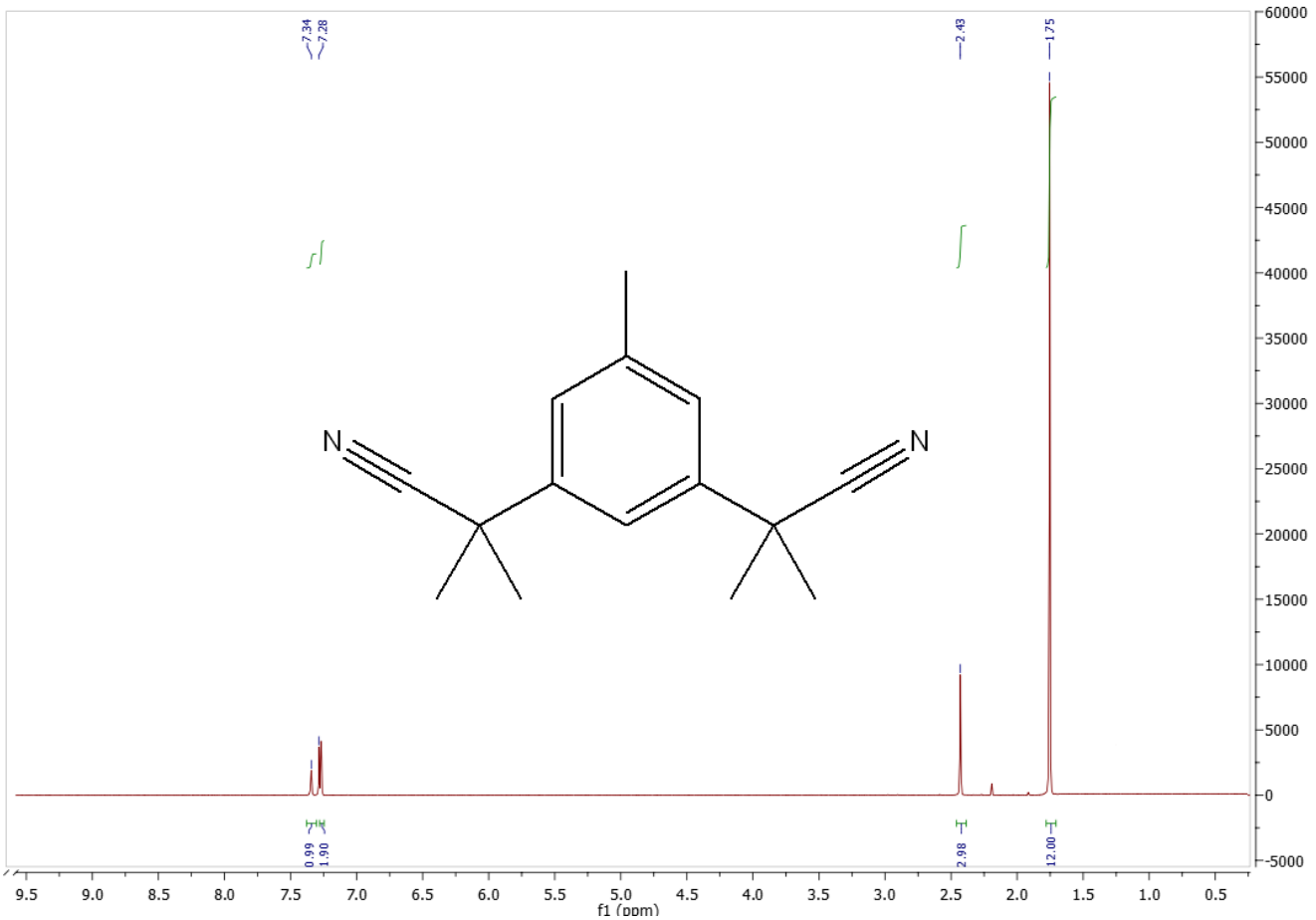


Figure 71: *^{1}H-NMR obtained from the batch synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40****.*

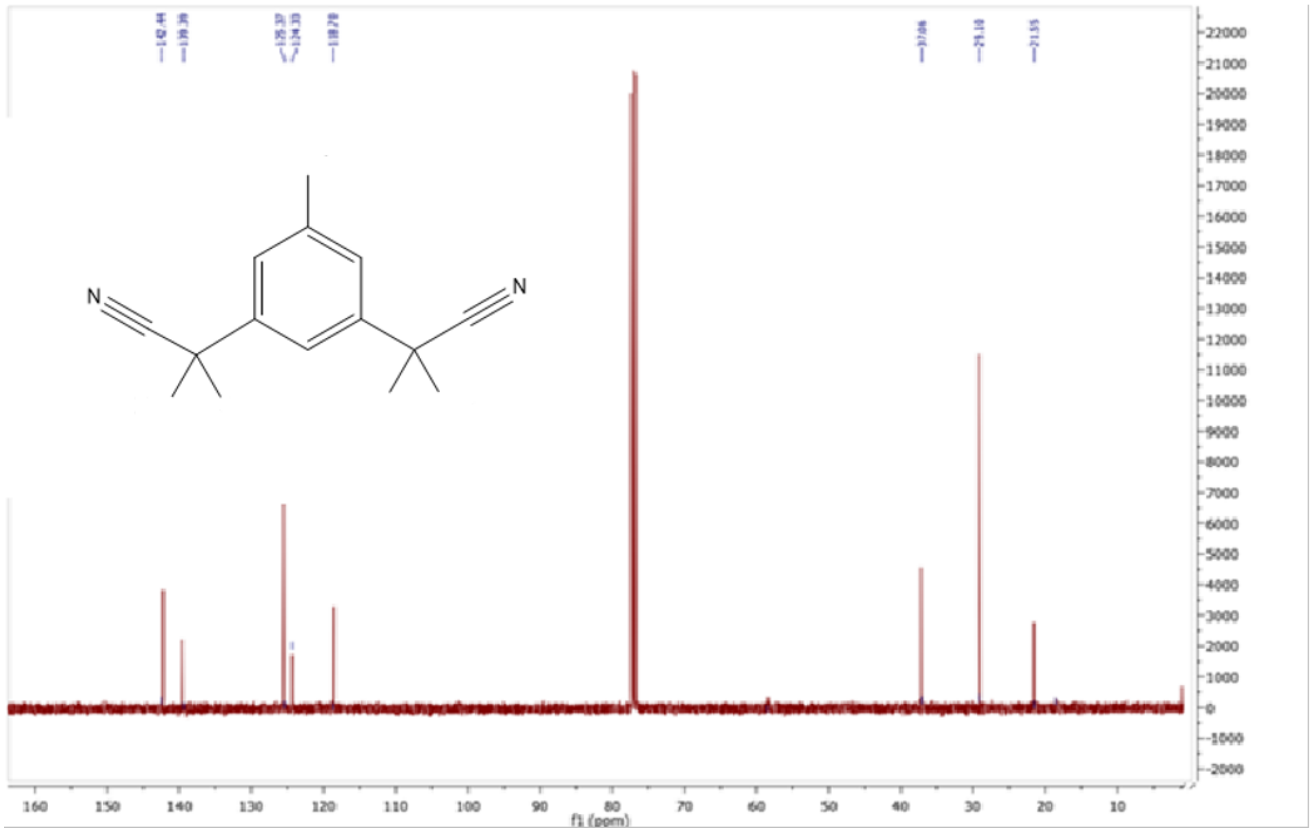


Figure 72: *^{13}C-NMR obtained from the batch synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40****.*

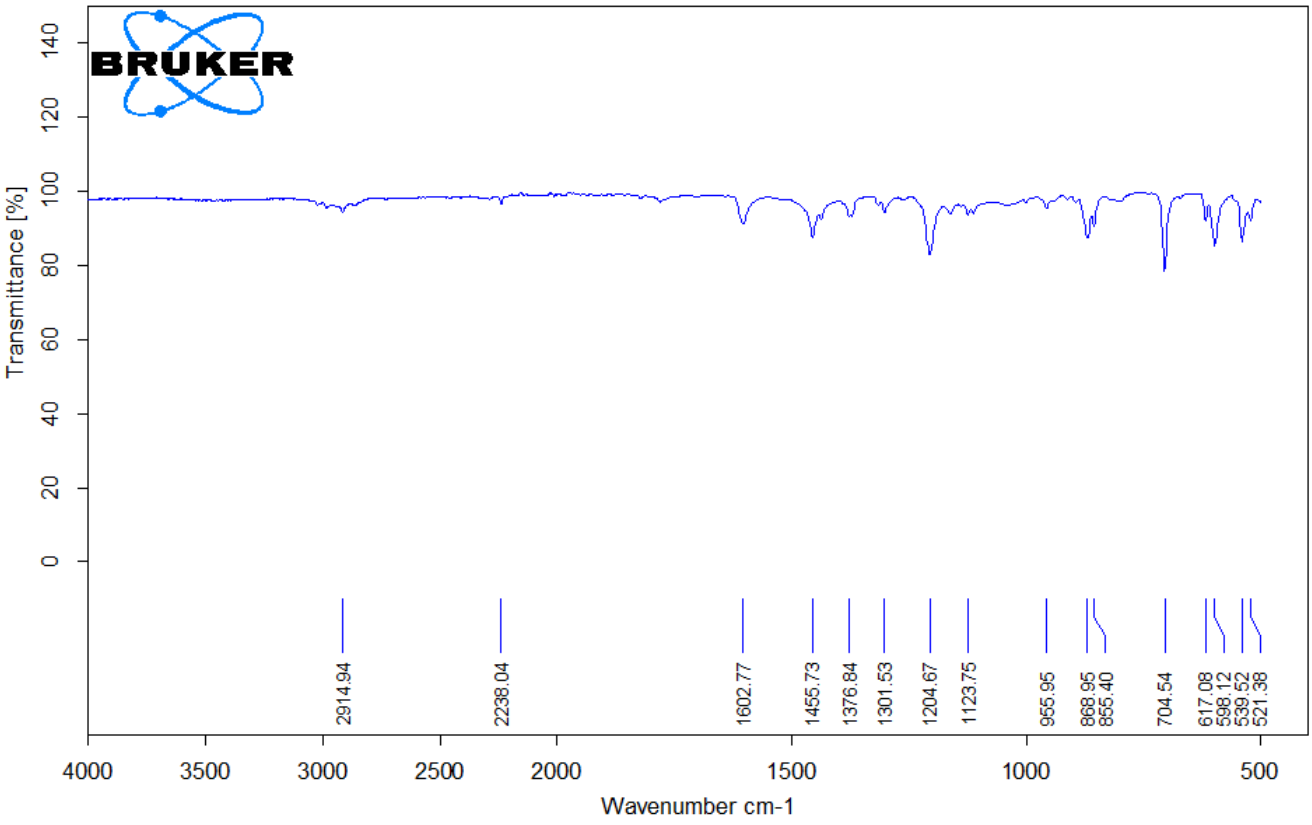


Figure 77: *FT-IR obtained from the batch synthesis of 3,5-bis(1-cyano-1-methylethyl)toluene* ***40****.*

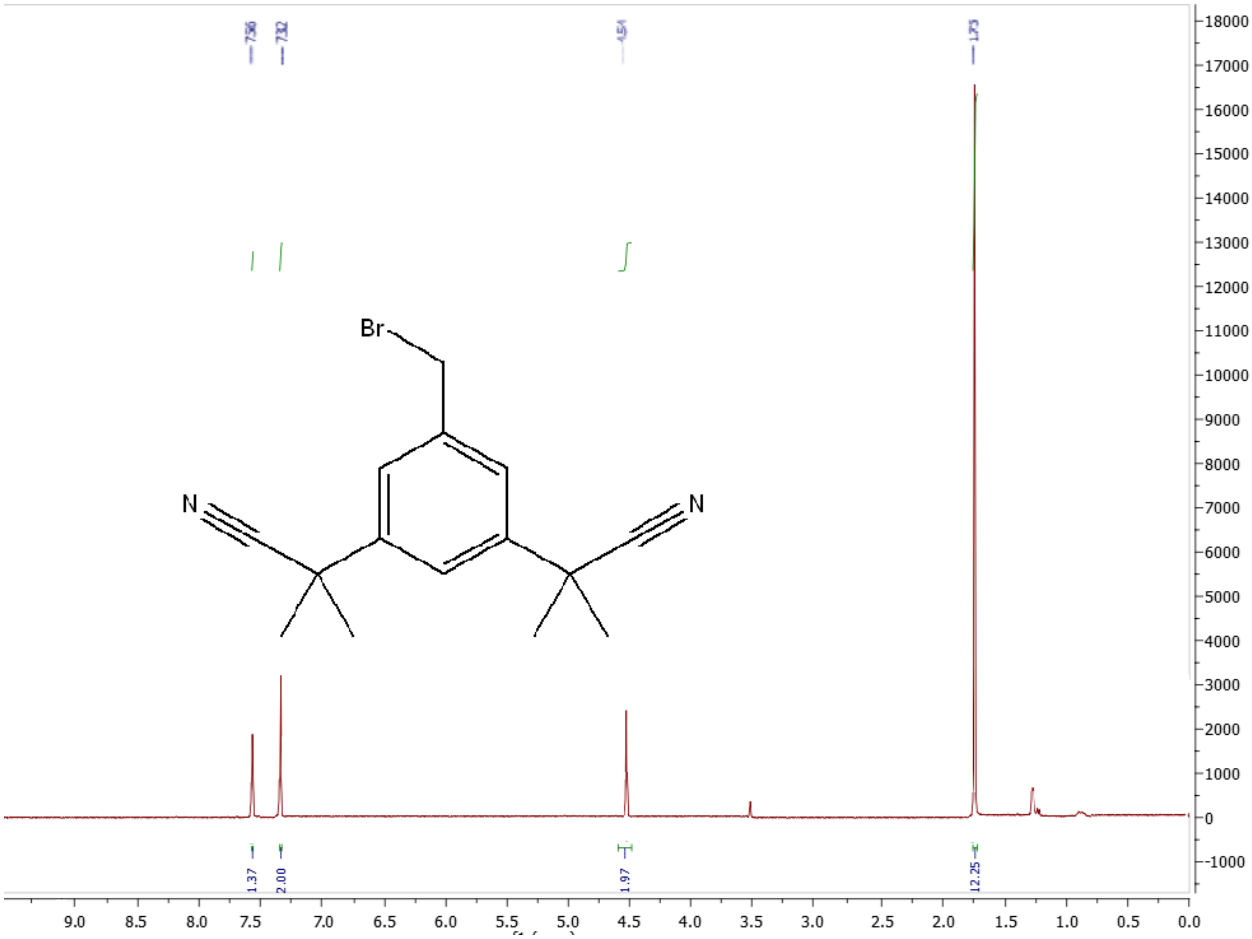


Figure 78: *^{1}H-NMR obtained from the batch synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile)* ***41***.

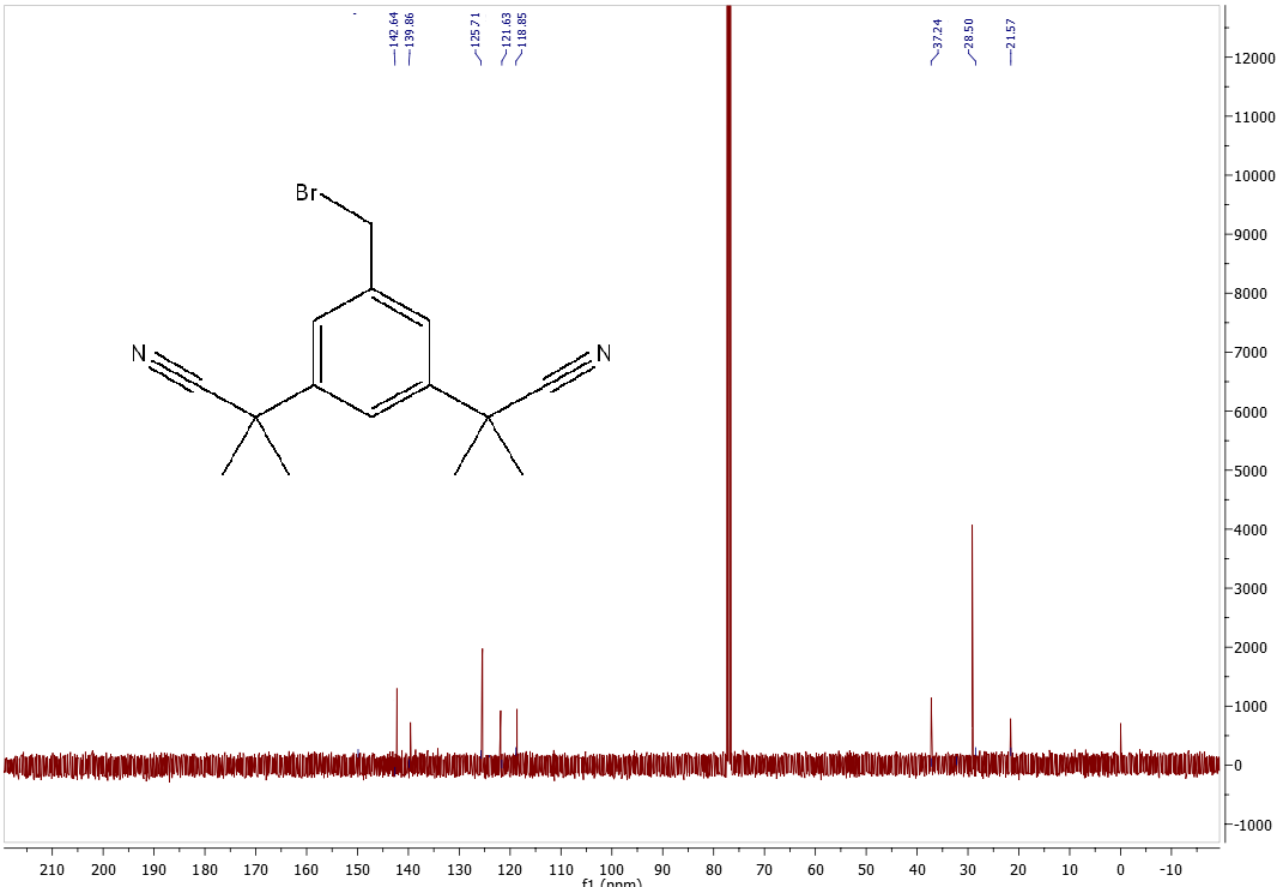


Figure 79: *^{13}C NMR obtained from the batch synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methylpropionitrile)* ***41***.

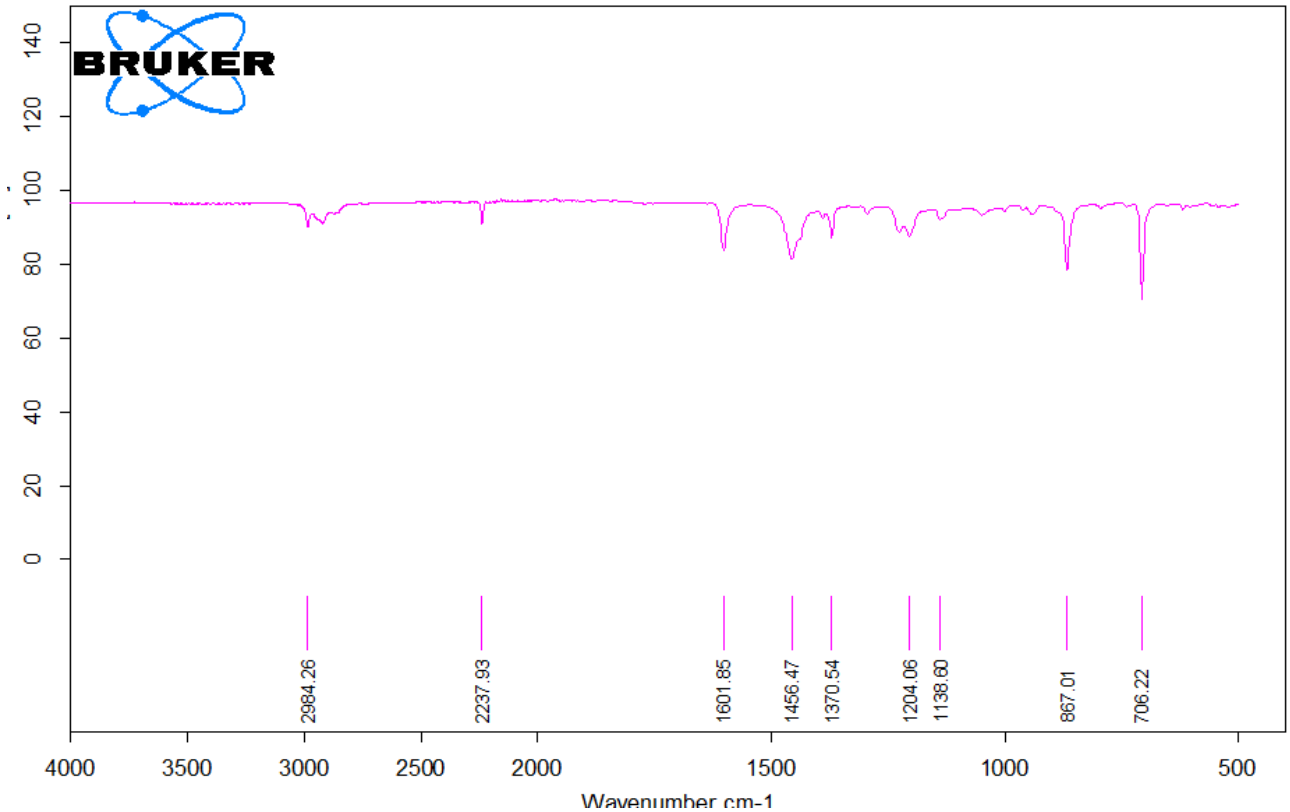


Figure 80 : *FT-IR obtained from the batch synthesis of 2,2'-(5-bromomethyl-1,3-phenylene)di(2-methyl propionitrile)* ***41***.