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On-water pyrrolidine-mediated domino synthesis of 2-iminoisatins

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The *on-water* reaction between 2-(sulfonylamino)-benzaldehydes, isocyanides and pyrrolidine is able to afford a library of poorly synthetically accessible 2-iminoisatins. The pyrrolidine exhibits for the first time the unique role of promoting a triple domino process, i.e. the formation of a *N*-alkyl-2,3-diaminoindole, the sulfonamide heterolytic *N*-S bond cleavage, and the hydrolysis of the resulting iminium ion, with loss of *p*-toluensulfonic acid. RP HPLC-DAD and UHPLC-HRMS real-time monitoring of the reaction provided experimental data that supports the reaction mechanism. The use of water as solvent under ultrasound catalysis, and the convergent nature of this approach, allow for the first time a green and sustainable synthesis of 2-iminoisatins.

Introduction

Synthetic or natural isatins are important privileged structures endowed with different biological activities¹. Despite the huge importance of this scaffold, 2-iminoisatins still lack a robust and general synthetic route. A SciFinder[®] survey yielded only seven different 2-iminoisatins and related structures, with a secondary amine in position 2- of the isatin moiety. Typically, they are prepared through condensation of indoxyl with nitrosobenzene², through the process of Sandmeyer³ or its modification, as also reported by Hope⁴, or through chlorination of isatin amide bond, and subsequent substitution with an amine⁵ (Fig. 1). However, these methodologies suffer from poor yields and scope, and harsh reaction conditions, such as the use of concentrated sulphuric acid. In most cases chlorinating agents are required with, or metal

catalysts such as copper chloride, or perbromide phosphonium catalysts or lead carbonate and cyanuric acid (used for the synthesis of hydrocyanocarbodiphenylimide **6**, Fig. 1). We reasoned that a new eco-friendly, straightforward, and wide scope methodology, capable of gaining access to this interesting class of compounds, would be welcomed.

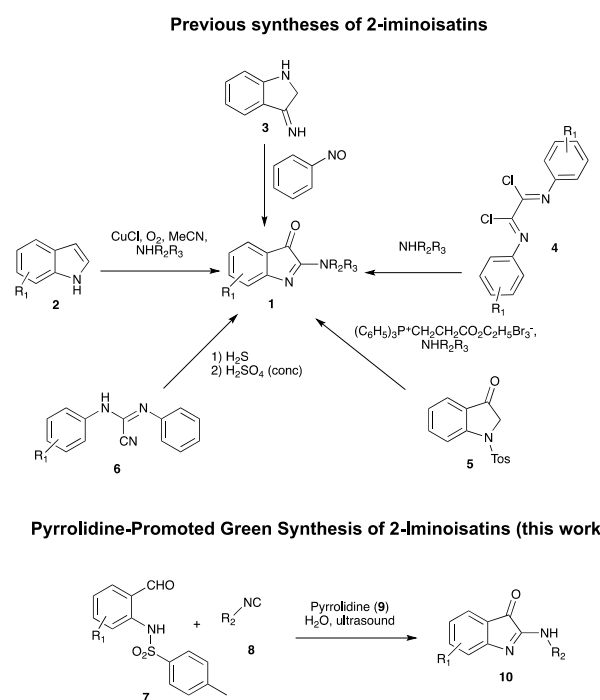


Fig. 1. Previous reported routes for the synthesis of 2-iminoisatins and strategy proposed herein.

Domino processes involving sequential chemical transformations are straightforward synthetic approaches to both drug-like heterocycles and molecular synthons being one-pot, atom economical and convergent reactions⁶. Recently, we reported the use of 2-(sulfonylamino)benzaldehydes as an amphoteric scaffold for the synthesis of functionalized *N*-alkyl-2,3-diaminoindoles⁷. The

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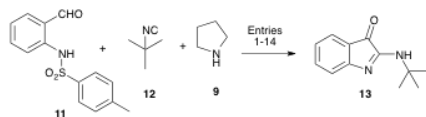
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cascade reaction of 2-(sulfonylamino)-benzaldehydes, isocyanides and secondary amines involves three consecutive transformations: 1) the formation of an iminium ion, 2) the attack of an isocyanide to the iminium ion forming a nitrilium ion intermediate, and 3) the intramolecular cyclization of the sulfonamide nitrogen into the nitrilium ion to give the *N*-alkyl-2,3-diaminoindols. During our investigation, we serendipitously discovered that the use of pyrrolidine as secondary amine led to a completely unexpected reaction pathway and the isolation of 2-iminoisatin derivatives **10** (Fig. 1).

Results and discussion

In order to figure out the optimal green reaction conditions (Table 1), we tested the reaction using different solvents, mixtures of water and methanol, temperatures (room temperature and 50°C), and also the use of microwave and ultrasound irradiation.



ENTRY	SOLVENT	TIME	TEMPERATURE	YIELD
1	DCM	5h	rt	47%
2	DCM	20h	rt	44%
3	MeOH	20h	rt	37%
4	H ₂ O	5h	rt	20%
5	H ₂ O	20h	rt	43%
6	H ₂ O/MeOH 1:1	5h	rt	45%
7	H ₂ O/MeOH 1:1	3h	rt Ultrasound	23%
8	H ₂ O	2h	rt Ultrasound	54%
9	H ₂ O	5 minutes	100° C MW	22%
10	H ₂ O	1h	50° C	3%
11 ^a	H ₂ O	20h	rt	47%
12 ^b	H ₂ O	20h	rt	47%
13	Neat	20h	rt	43%
14 ^c	H ₂ O	20h	rt	47%

Table 1. Optimization of reaction conditions [a) 1.2 equiv. of both pyrrolidine and isocyanide were used; b) a 1M concentration was used; c) the commercially pyrrolidine was redistilled].

For the test reaction we chose *N*-(2-formylphenyl)-4-methylbenzene-sulfonamide (**11**) and *tert*-butylisocyanide (**12**) as starting materials. Starting from 47% yield when the reaction was performed in dichloromethane (entry 1), we found that with use of water as the solvent the yield dropped to 20% comparing the same

reaction time (5 hours) (entry 4). After 20 hours the yield increased to 43% (entry 5). The use of methanol as organic co-solvent and water produced a 45% yield after 5 hours (entry 6). The use of higher temperatures, using water as solvent, was detrimental as yields were about 3% with conventional heating at 50°C, and about 22% after 5 minutes with microwave irradiation at 100°C, respectively. Finally, the most favourable conditions were obtained by performing the reaction *on-water*⁸, while irradiating with an ultrasound bath for two hours (54% yield). The molecular structure of (**13**) was confirmed by X-ray crystallographic analysis as shown in Fig. 2.

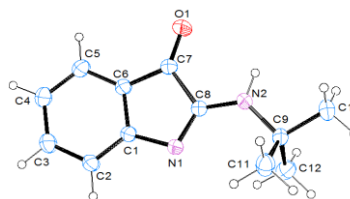


Fig. 2. ORTEP⁹ drawing of (**13**) with arbitrary atom numbering (ellipsoids are at 40% probability and H atoms are as spheres of arbitrary radii).

In order to establish if pyrrolidine (**9**) was unique in promoting such a transformation, we performed the reaction using different secondary amines (piperidine, diethylamine, morpholine), and in the presence of ammonium chloride (Table S1). In all these cases the 2,3-diaminoindoles were obtained as main products and, only in some cases, was a small percentage of (**13**) obtained. In the absence of a secondary amine, no reaction occurred, clearly suggesting the pivotal role played by the pyrrolidine (**9**). Furthermore, when *p*-tosyl-sulfonamide was replaced with a 4-nitrobenzene sulfonamide moiety, the yield dropped to 23%.

After the optimisation of the reaction conditions, we next explored the reaction scope. With this aim, we synthesized nine different 2-(sulfonylamino)benzaldehydes⁷ and selected five commercially available isocyanides, and their random combination gave derivatives **14-31**, as shown in Figure 3. When tertiary isocyanides were used, both electron-withdrawing and electron-donating groups were tolerated on the aromatic ring of 2-(sulfonylamino)benzaldehydes (**15-19**, **23-25**, and **28-31**), as well as a phenyl ring (**26** and **27**), while when primary and secondary isocyanides were employed, the corresponding products, albeit formed during the reaction, were not stable and were degraded during chromatographic purification. On the other hand, the presence of an additional fused aromatic ring was able to confer stability to products (**20**) and (**21**) even when primary and secondary isocyanides were used as starting materials, respectively. Aromatic isocyanides always gave slurry reaction mixtures and no traces of desired 2-iminoisatins could be detected.

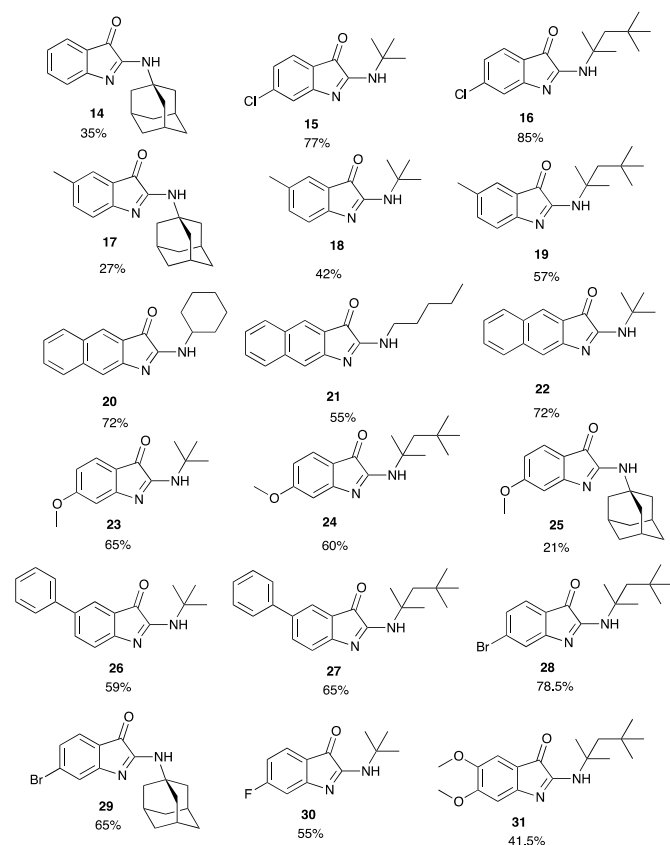
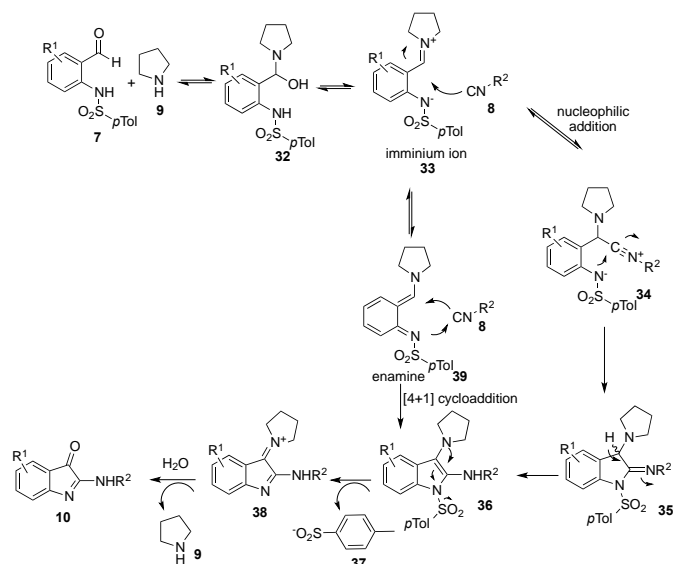


Fig. 3. Synthesised library of 2-iminoisatins 14–31.

Intrigued by the mechanism of this unprecedented reaction, we set out to investigate this transformation in detail. According to Scheme 1, we speculated that the reaction proceeds through an early condensation of aldehyde **7** with pyrrolidine (**9**) to give the hemiaminal **32**, which loses a molecule of water to form the iminium ion **33** with the concomitant formation of the sulfonamide anion. The iminium ion **33** is then attacked by the isocyanide **8** to give a nitrilium ion **34**. The sulfonamide anion then intramolecularly intercepts the latter to give the intermediate **35**. A 1,3-*H* shift readily affords the adduct **36**. Alternatively, the isocyanide carbon could also react as a carbene with the enamine tautomer **39** in a formal [4+1] cyclization giving, after a tautomeric shift, derivative **36**. When secondary amines other than pyrrolidine are used, the corresponding 2,3-diaminoindoles are stable as such, while pyrrolidine is able to promote a sulfonamide heterolytic *N*-*S* bond cleavage leading to the iminium ion **38**, with loss of *p*-toluenesulfonic acid (**37**). The former readily hydrolyses to give the 2-iminoisatin **10**. The *p*-toluenesulfonic acid (**37**) forms an ion pair with pyrrolidine (**9**) and this is probably the reason why pyrrolidine is needed in stoichiometric amounts, as the reaction performed with 0.2 equivalents only gave a 11% yield of (**13**) (Table 1). The reaction apparently proceeds therefore in a triple domino process: the formation of a *N*-alkyl-2,3-diaminoindol, a sulfonamide heterolytic *N*-*S* bond cleavage and an iminium ion hydrolysis. The unique role of pyrrolidine as organocatalyst is related to the particular reactivity of the nitrogen and has been well documented¹⁰.



Scheme 1. Proposed reaction mechanism for the formation of 2-iminoisatins **10**.

In order to demonstrate this working hypothesis, we undertook real-time monitoring of the test reaction between (**11**), (**12**) and (**9**) (Table 1) by RP HPLC-DAD and UHPLC-HRMS. The reaction was monitored after 2 minutes, 90 minutes, 3, 5 and 7 hours (Fig. 4). After two minutes only starting material (**11**) was detected, however after 90 minutes a new peak corresponding to the *N*-alkyl-2,3-diaminoindol (**40**) appeared (identity confirmed via UHPLC-HRMS analysis, see Supplementary Information). After three hours, 2-iminoisatin (**13**) and *p*-toluenesulfonic acid (**37**) were clearly detectable, confirming that the formation of **13** is associated with formation of (**37**) (for more details see Supporting Information)¹¹.

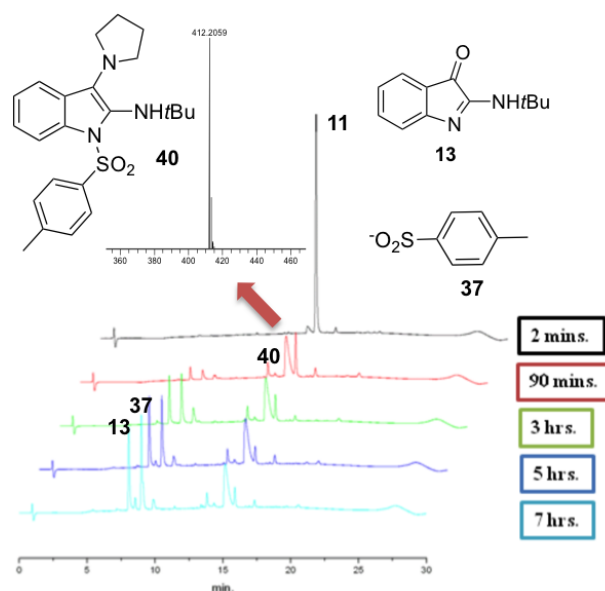


Fig. 4. RP HPLC-DAD real-time monitoring of the reaction and UHPLC-HRMS of **40** (HRMS calculated for $C_{23}H_{30}N_3O_2S^+$: 412.2054).

Conclusions

In summary, we report for the first time a green, one-pot synthesis of 2-iminoisatins starting from readily available reagents. The reaction is performed using water as solvent, and no chlorinating agents, nor metal catalysts or strong and corrosive acids, are required. This newly discovered transformation relies on an organocatalytic cascade reaction, where pyrrolidine is shown for the first time to promote a triple domino process leading to the formation of the 2-iminoisatins. HPLC-DAD and UHPLC-HRMS real-time monitoring of the reaction provided experimental data to support the proposed reaction mechanism, which evolves through an unprecedented sulfonamide fragmentation. The reaction was demonstrated to be general in scope, and respectful of green chemistry principles as the benign solvent, water, has been chosen and the reaction conditions further optimized by means of sonocatalysis. This newly reported synthetic approach represents a stepping-stone towards the awareness of the huge potential of domino processes to achieve the ideals of green chemistry philosophy¹².

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from University of Naples Federico II and University of Piemonte Orientale, Novara, is acknowledged. M. G. acknowledges AIRC (MFAG 18793). We are grateful to the Drug Control Centre at King's College London for access to UHPLC-HMRS instrumentation.

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- The test reaction monitored through HPLC-DAD and UHPLC-HRMS experiments was performed in DCM at 0.3 M concentration instead of 0.5 M. The higher dilution was likely responsible for a slower reaction, since at 7 hours a small amount of starting material **11** could be still detected. Furthermore, intermediate **34** decreased as the aza-Grob fragmentation proceeds, but increases with the progress of the MCRs among **11**, **12** and **9**: this dynamic equilibrium results in a pretty constant peak for **34** at various time points of the reaction, as shown in Figure 4.
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