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-toluenesulfonic 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-(sulfonyl amino)benzaldehydes as an amphoteric scaffold for the synthesis of functionalized N-alkyl-2,3-diaminoindoles2. The
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-iminosatin 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.

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®, 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.

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-iminosatin derivatives could be detected.

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

![Table 1](image-url)
The unique role of pyrrolidine as organocatalyst is
presented for the first time. The iminium ion
reaction, involving pyrrolidine and toluensulfonic
acid, proceeds through 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 documented.

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-toluensulfonic acid (37) were clearly detectable,
confirming that the formation of (13) is associated with
formation of (37) (for more details see Supporting Information).

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

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

Intrigued by the mechanism of this unprecedented reaction, we set
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 8, 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-
toluensulfonic acid (37). The former readily hydrolyses to give the 2-
iminoisatin 10. The p-toluensulfonic 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 documented.
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 respect 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 philosophy.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

11. 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 could be still detected. Furthermore, intermediate 34 was detected as the aza-Groeb fragmentation products, 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.