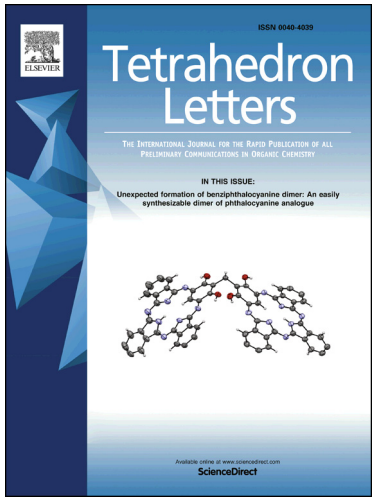

Amphoteric 2-(Sulfonylamino)Benzaldehydes, Secondary Amines and Isocyanides in the Multicomponent Synthesis of Elusive *N*-Alkyl-2,3-diaminoindoles.

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ABSTRACT

A novel interrupted Ugi reaction between *ortho*-sulfonylaminated aryl aldehydes, secondary amines, and isocyanides affords in good to high yields *N*-alkyl-2,3-diaminoindoles, providing access to a so far unexplored area of the indole chemical space. With only one single chemical operation, this novel reaction affords a broad gamma of substituted 2,3-diaminoindoles with five points of diversity. The success of this novel multicomponent transformation lies in presence of the amphoteric sulfonylamino group, which sequentially acts as a Brønsted acids and as a nucleophile the lack of need for additional catalysts and the high atom economy, with the loss of only one molecule of water, renders this approach a very effective one.

Nowadays, multicomponent reactions (MCRs)[1] are considered precious transformations both for organic and medicinal chemists thanks to their intrinsic convergent nature, atom economy and efficiency. MCRs telescope the access to complex biologically active scaffolds, as exemplified by the four-component Ugi reaction.[2] This reaction, discovered in 1959, has served as a basis for the development of related transformations that have substantially expanded its scope and the area of the chemical space it can target.[3] The discovery of novel Ugi-related reactions capitalizes on the use of functionalized starting reagents. These can intercept intramolecularly the ephemeral nitrilium ion generated by the reaction between an aldehyde, an amine and an isocyanide, eluding termination by carboxylate attack. Alternatively, functionalized reagents can exploit the carbenic nature of isocyanide and engage it in formal [4+1] cycloadditions.[4] In all these cases, the net result is the switch from a dipeptide structure to a drug-like heterocycle compound (Figure 1).

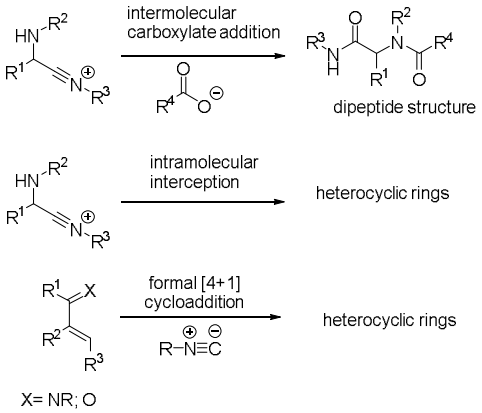
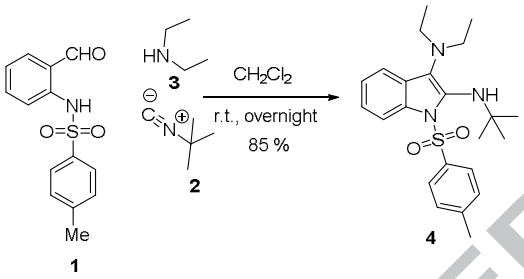


Figure 1. Ugi reaction *vs* interrupted Ugi reactions.

These transformations are referred to as interrupted Ugi reactions, a name coined by Sorensen in 2009.[5]

The final formation of a heterocycle replaces the amide-generating Mumm rearrangement of the classic Ugi reaction as a driving force for the reaction.

Although the first example of an intramolecular interception of a nitrilium ion can be traced back to 1969,[6] the most famous and versatile example of an Ugi interrupted reaction remains the Groebke–Blackburn–Bienaymé multicomponent reaction, where a 2-aminopyridine reacts with an isocyanide and an aldehyde in the presence of a catalytic amount of protic or Lewis acids to give fused 3-aminoimidazoles.[7] Subsequently, other transformations, which can be considered interrupted Ugi reactions, emerged from the literature.[8] In our opinion, however, this attractive subclass of Ugi isocyanide chemistry is still an underexplored territory, which can still lead to the identification of novel multicomponent transformations. For this reason, we became interested in the study of novel interrupted Ugi reactions, and, in particular, we envisioned the possibility to synthesize elusive *N*-alkyl-2,3-diaminoindoles,[9] starting from an amphoteric sulfonyl amino arylaldehyde, a secondary amine, and an isocyanide according to Scheme 1. In this case, the carbonyl component bears an aromatic electrophilic aldehyde and a sulfonamide at the *ortho* position, which could act as internal nucleophile, intercepting the nitrilium ion to give 2,3-dialkyl diaminoindoles. With this in mind, when we tested this reaction using 2-[(4-tolylsulfonyl)amino]benzaldehyde **1**, *tert*-butyl isocyanide **2** and diethylamine **3** mixed in dry dichloromethane at room temperature overnight, we were pleased to observe the formation of a single new spot, which revealed to be the desired *N*-alkyl-2,3-diaminoindoles **4,** obtained in 85 % yield.



Scheme 1. Three-component-four-center reaction between 2-tolylsulfonylamino benzaldeyde, *tert*-butylisocyanide and diethylamine.

It is important to note that despite the massive presence of indole nucleus in biologically active compounds, 2,3-diaminoindoles derivatives are still a rare class of compounds, probably due to the lack of a straightforward synthetic approach.[10]

Taking advantage of this novel interrupted Ugi multicomponent reaction, a library of *N*-alkyl-2,3-diaminoindoles has been prepared with the aim to investigate scope and generality. Different *ortho*-sulfonylaminated aryl aldehydes (**1**, **5**-**12**) were readily prepared by the corresponding commercially available anthranilic acids in three easy steps following literature reported procedures.[11] Distinctive isocyanides (**2**, **13**-**19**) and secondary amines (**3**, **20**-**24**) were also chosen in order to give a clear picture of this novel multicomponent transformation (Figure 2).

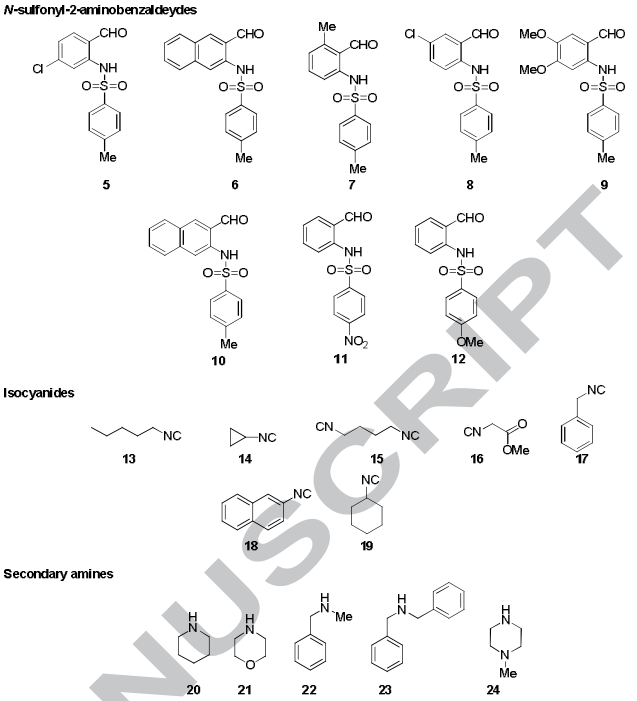


Figure 2. Building blocks used.

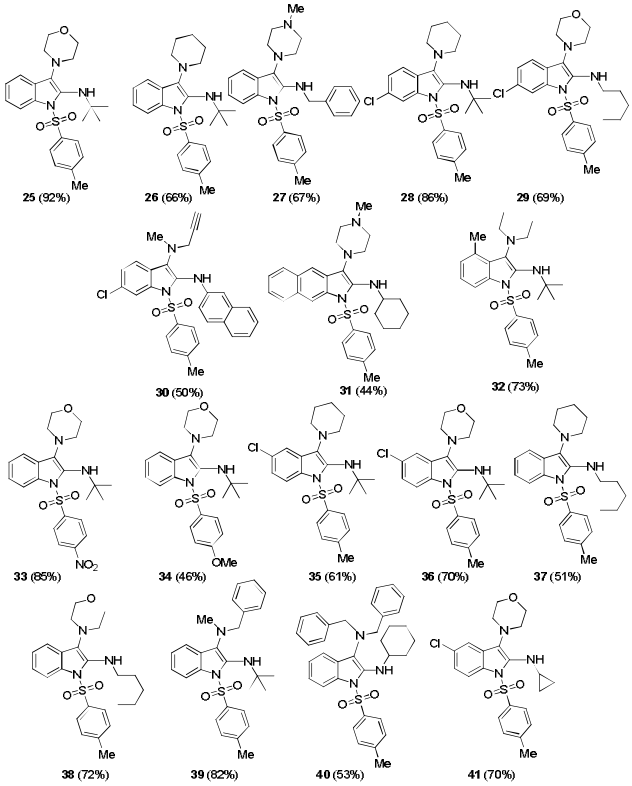


Figure 3. Synthesized compounds.

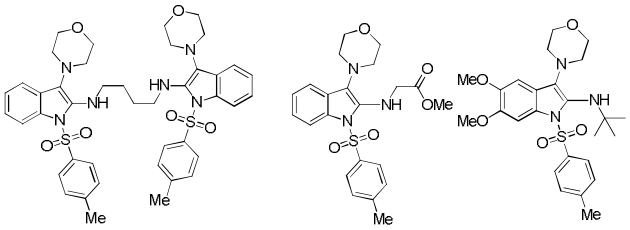


Figure 3. Synthesized compounds (continue).

As shown in Figure 3, we synthesized twenty-one (**25**-**44**) variously decorated *N*-alkyl-2,3-diaminoindoles with a yield range of 27-92 %. In particular, we observed that the reaction was complete overnight (ca. 16 h) when either electron withdrawing substituents or no substituents were present on the aromatic rings of *ortho*-sulfonylaminated aryl aldehydes, while in the presence of electron donating groups the reactions was slower requiring 48-72h to be completed. Increasing the temperature as well as changing the solvent was detrimental for the success of this transformation. Interestingly, when an electron-withdrawing group was present on the benzenesulfonamide ring (**11**) the reaction was very fast (2 h) while, on the contrary, in the presence of an electron-donating group (**12**) the reaction was sluggish requiring again 48-72 h to go to completion. We can speculate that the change in acidity of the sulfonamide group can dramatically influence the velocity of formation of the iminium ion.

N-alkyl-2,3-diaminoindole derivatives appear to be stable on chromatographic conditions and they can be crystalized in methanol without sign of decomposition. In Figure 4, we report the X-ray crystal structure of compound **32** (see supporting information for a full discussion).

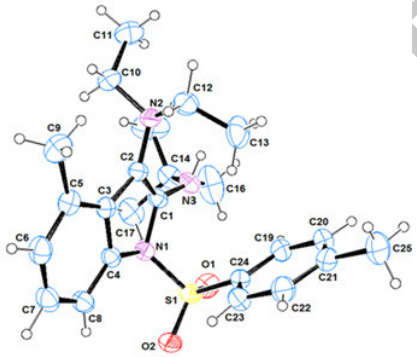
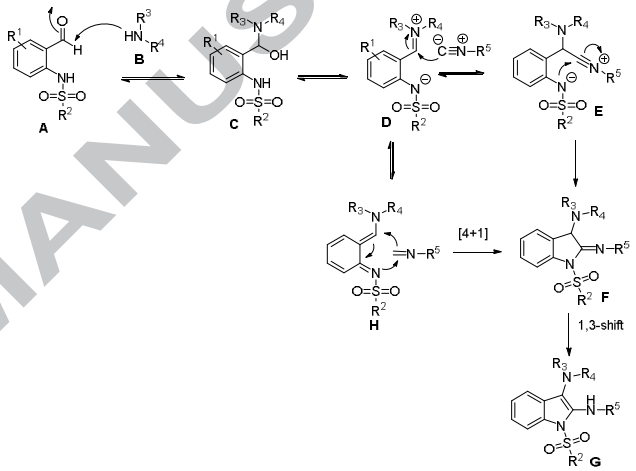


Figure 4. ORTEP view of **32** and the relative arbitrary atom numbering scheme (thermal ellipsoids at 40% probability).

Before proposing a mechanism for this reaction, we carried out some more different experiments. We evaluated whether in the presence of an aliphatic primary amine (e.g. phenylethylamine) and an aromatic amine (e.g. aniline) we could obtain the same results. In this case anyway we were not able to observe the formation of the desired products, but only the formation of the imine intermediates, which were isolated in 75 and 69 % yield, respectively. It is possible to rationalize these results by considering the lesser acidity of *N*-sulfonyl-2-aminobenzaldeydes compared with that of a carboxylic acid (pKa 7.9 *vs* 5.0),[12] which cannot protonate and activate the imino group. On the other hand, when secondary amines are used, the subsequent iminium ion is already a much better electrophile with respect to the imine formed by primary aliphatic amines and anilines. Additionally, when we replaced the *N*-sulfonyl-2-aminobenzaldeydes with the 2-aminobenzaldeyde we observed the formation of a plethora of spots even with secondary amines.[13] This means that the sulfonamide moiety is the key group for the success of this multicomponent transformation driving the reaction toward the formation of a single final product. Indeed, its weak acidity can still favor the protonation of the hemiaminal, facilitating the formation of the iminium ion with the simultaneous formation of the sulfonamide anion, nucleophilic enough to intercept the transient nitrilium ion. We therefore propose the following mechanism: the oxo- function **A** and the amine **B** condense to form the hemiaminal form **C**, which loses a molecule of water to form the iminium ion **D** with the concomitant formation of the sulfonamide anion. Now, two different reaction mechanisms are possible: the iminium ion could be directly attacked by the isocyanide to form a nitrilium ion **E** which is in turn attacked by the sulfonamide nitrogen to give the cyclic intermediate **F**, which rearranges to form a substituted 2,3-dialkyl diaminoindole **G** upon a 1,3-*H* shift. Alternatively, the isocyanide carbon could also react according to its carbenic nature with the enamine tautomer **H** in a [4+1] cyclization giving, after a tautomeric shift, the desired *N*-alkyl-2,3-diaminoindole (Scheme 2).



Scheme 2. The proposed reaction mechanism

In conclusion, we reported a novel three component-four-center reaction which allows, for the first time, the synthesis of until now elusive *N*-alkyl-2,3-diaminoindole derivatives where both amino groups are substituted. The reaction requires ambient temperature simple mixing equimolar amount of sulfonyl amino arylaldehyde, a secondary amine, and an isocyanide in dichloromethane. This newly discovered reaction is in perfect agreement with the fundamentals of multicomponent reactions, exhibiting an extraordinary atom economy (only one molecule of water is lost during the process) and a high bond forming efficiency, since two new C-N bonds and one C-C bond are formed in the one-pot process. The sensible choice of the sulfonamide group gives the right balance between acidity, needed to promote the formation of the iminium ion, and nitrogen nucleophilicity, necessary to intercept the nitrilium ion. We hope that this work can draw new interest towards the interrupted Ugi reactions, which have the potential to be powerful tools to gain access to unexplored regions of the chemical space not easily accessible by the two-component chemistry.

Acknowledgments

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Supplementary Material

Experimental procedure, spectroscopic data, copies of ^{1}H and ^{13}C spectra (PDF).

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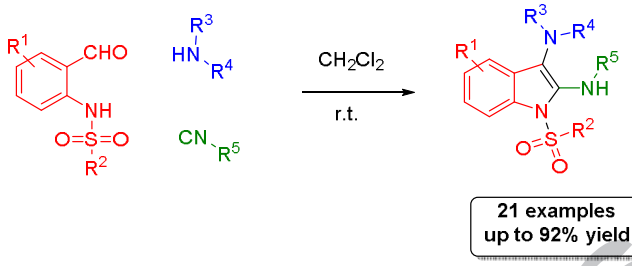

- One pot synthesis of *N*-alkyl 2,3-diaminoindoles
- The sulphonamide group intercepts the nascent nitrilium ion
- No transition metals required