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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 (Fig. 1).

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

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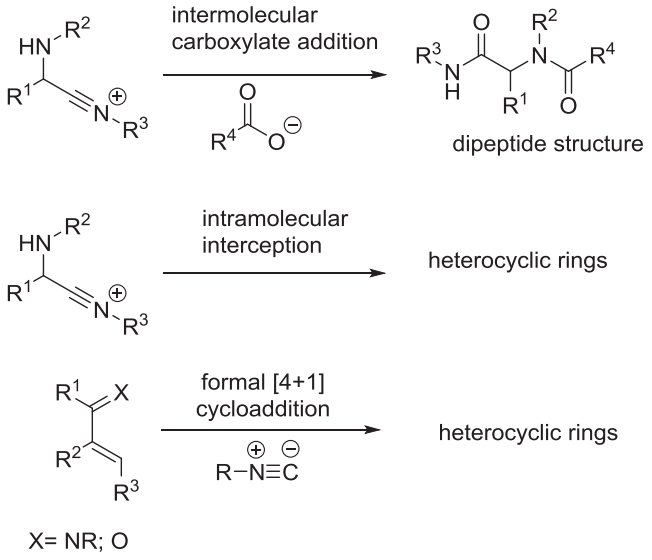
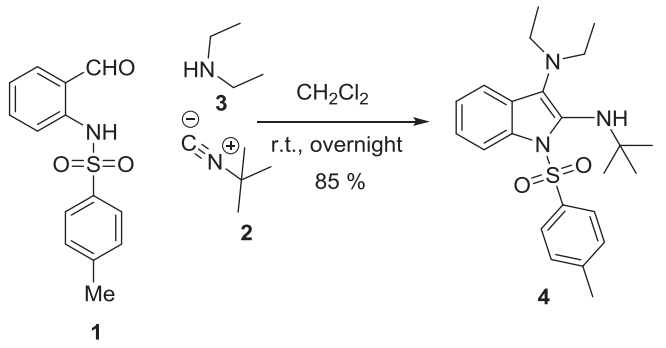


Fig. 1. Ugi reaction *vs* interrupted Ugi reactions.

internal nucleophile, intercepting the nitrilium ion to give 2,3-dialkyl diaminoindoles. With this in mind, when we tested



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

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.

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]

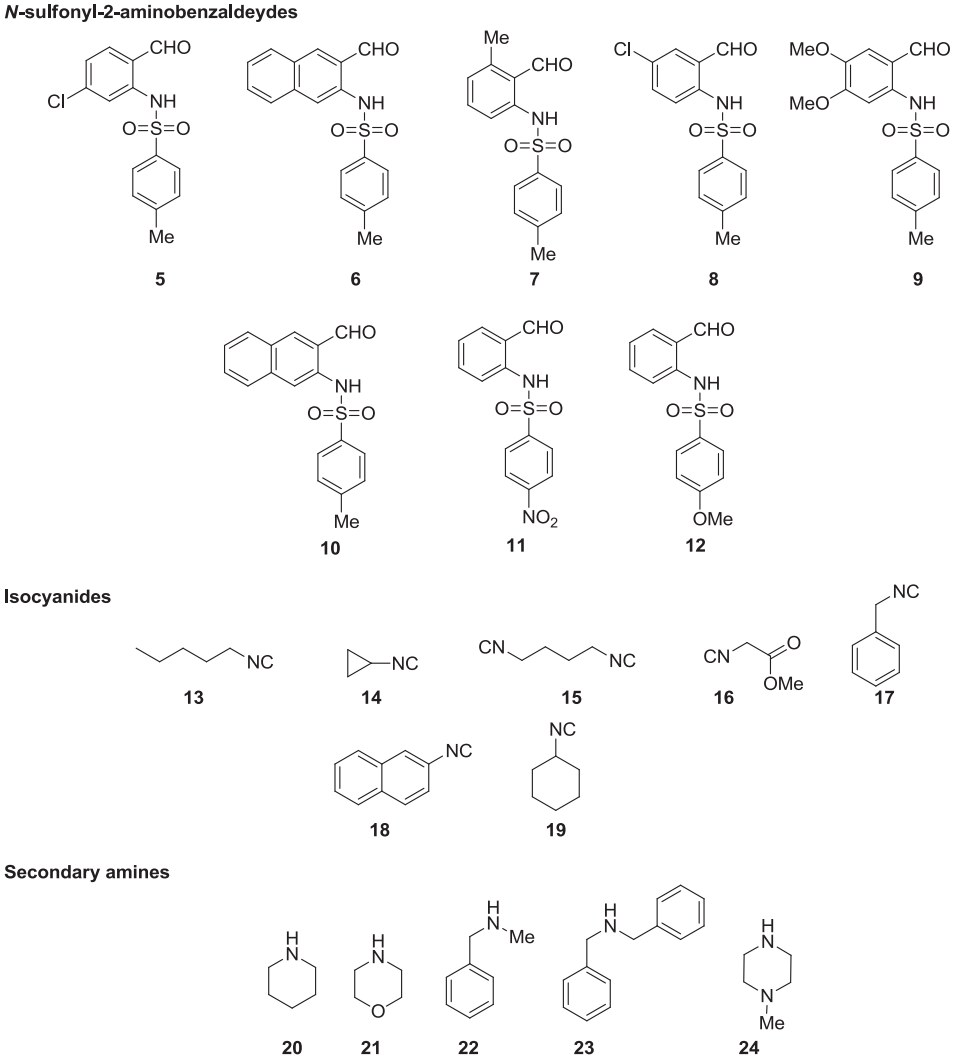


Fig. 2. Building blocks used.