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An interrupted Ugi reaction enables the preparation of substituted indoxyls and aminoindoles

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Dedicated with admiration to Professor Justin Dubois, recipient of the Tetrahedron Young Investigator Award

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ABSTRACT

In a variation of the classical Ugi reaction, an acid-promoted reaction between imines and isocyanides forms both 3-aminoindoles and substituted indoxyls. A recently reported triflyl phosphoramide is shown to be critical to obtain high yields under mild conditions.

1. Introduction

The nitrilium ion has been studied since the earliest days of organic chemistry, although the preparation of a stable nitrilium salt was not reported until 1955 by Klages and Meerwein.[1] As a result of this longstanding interest, a variety of powerful transformations are based on nitrilium chemistry. These reactions typically feature the attack of a heteroatom- or carbon-based nucleophile at the electrophilic carbon of a nitrilium ion.[2] They differ, however, in the mechanisms by which the nitrilium ion is produced. In the Beckmann rearrangement, a nitrilium species is generated by migration of a carbon–carbon bond (see Ref. 3). The Houben–Hoesch cyclization[4] (or Hoesch reaction[5]) utilizes protonated or alkylated nitriles to generate aryl ketones, and is a relative of the Friedel–Crafts reaction. The Ritter reaction relies on the addition of water to a nitrilium ion generated by the reaction between a nitrile and a carbocation as a general method for the aminoacylation of carbocations.[6] A closely related variant, the Pinner reaction, involves the reaction between protonated nitriles and alcohols to generate imidate esters.[7] The Bischler–Napieralski reaction is another common transformation that relies on dehydration of an amide or removal of the halide from an imidoyl halide to generate the putative nitrilium ion.[8] A mild generation of nitrilium ions is also at the heart of some powerful multicomponent couplings in organic synthesis; mechanistically, the addition of an isocyanide to an oxocarbenium or iminium ion to generate a reactive nitrilium intermediate is a central step of the Passerini and Ugi reactions, respectively.[9] These multicomponent reactions are of particular interest due to their wide functional group tolerance and ability to rapidly generate chemical diversity. In many cases, multiple carbon–carbon bonds, carbon–heteroatom bonds, and a stereogenic center are formed in a single operation. New variations of these nitrilium-centered reactions are of interest to the general field of chemical synthesis as they often prove useful for the rapid construction of complex, biologically active molecules.

2. Results and discussion

In the course of planning a synthesis of a structurally complex natural product, we were intrigued by the possibility that a nitrilium ion generated by the addition of an isocyanide to an iminium ion might be intercepted by an electron-rich arene. Such a variation on the classical Ugi reaction would result in the formation of an additional carbon–carbon bond, and, in the case of an intramolecular reaction, a new heterocyclic ring. This interrupted Ugi reaction would combine mechanistic elements of both the Ugi and the Houben–Hoesch reactions. Prior studies on the Houben–Hoesch reaction have established that the reaction between

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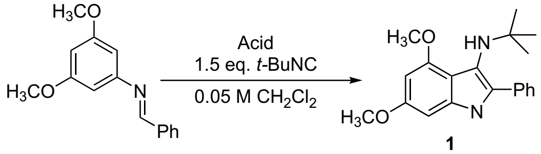
a protonated nitrile and an electron-rich arene can be quite efficient. Livinghouse[10] and Townsend[11] have also established that electron-rich arenes react with acylated isocyanides or alkylated nitriles to form hydroquinoline derivatives and benzophenones, respectively. Other related transformations have been reported as well.[5,12–14] While these reaction manifolds have proven useful, a general strategy focused on generation of the reactive nitrilium intermediate by addition of an isocyanide to an activated imine, followed by intramolecular trapping with a pendant arene could give direct access to different structural classes of useful heterocyclic products.

In practice, such a transformation might be accomplished by replacing the carboxylic acid component of the Ugi reaction with a Lewis acid or strong Brønsted acid and employing an aniline as the amine component. In the absence of a nucleophilic counterion in the reaction mixture, the α-amino nitrilium ion would be free to react selectively with the pendant nucleophilic π system. In the case of aldimines, the resultant cyclized imines could tautomerize to form 3-aminoindoles. The analogous ketimine-derived intermediates could lead to the production of indoxyls after hydrolysis of the initially formed bicyclic imine (Fig. 1). A previous report has shown that it is feasible to generate 3-aminoindoles through this type of cyclization. Two substrates were reported and the reaction was shown to require several days with concentrated strong acid and/or at high temperature (100 °C): yields ranged from 27 to 68%.[15] We felt that a milder procedure, which also extended the reaction scope to indoxyls would be of general interest. Our first attempt to study the reaction focused on the condensation of benzaldehyde, 3,5-dimethoxyaniline, and *tert*-butyl isocyanide (Table 1).

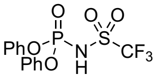
As has been observed in other studies of the Ugi reaction, we found that an imine synthesis by precondensation of aniline and carbonyl components markedly improved the chemical yield of 3-aminoindole **1** and minimized the formation of undesired side products. A variety of Brønsted and Lewis acids were screened (Table 1). Moderate yields were observed with mineral acids such as hydrochloric acid (entry 2), although no reaction was observed with solid supported sulfonic acids such as Amberlyst-15 (entry 3). Other acids such as *p*-toluenesulfonic acid, camphorsulfonic acid, or carboxylic acids such as trifluoroacetic or pivalic acid all provided only moderate yields of compound **1** (not shown). Some improvement was noted with stronger acids such as $HBF_4 \cdot OEt_2$ or triflic acid (entries 4 and 6–7). Although Lewis acids such as scandium(III) triflate also catalyzed the reaction (entry 9), yields were generally superior with Brønsted acids. The most notable increase in yield was observed with the use of acid **2**, a recently reported triflyl phosphoramide.[16] Acid **2** appears to provide a strong Brønsted acid with a non-nucleophilic counterion, and is surprisingly mild. Under optimized conditions, aminoindole **1** was prepared in 2 h at rt in 96% yield.

Table 1
Screen of acids for the interrupted Ugi reaction



1

Entry	Acid	Equiv	Yield (%)
1	None	N.A.	NR
2	HCl	1.0	50
3	Amberlyst-15	1.0	NR
4	$HBF_4 \cdot OEt_2$	1.0	86
5	Tf_2NH	1.1	46
6	TfOH	1.1	62
7	TfOH	0.3	42
8	**2**	**1.1**	**96**
9	$Sc(OTf)_3$	0.1	34



2

We examined the substrate scope of the reaction by studying a variety of arenes, aldehydes, and isocyanides (Table 2). In general, aldimines were prepared by condensation in toluene in the presence of molecular sieves and used without purification. The reaction was found to be tolerant of a number of substrates. Imines derived from a variety of substituted benzaldehydes (Table 2, entries 1–4) as well as ethyl glyoxalate (entries 9–17) performed well in the reaction. Branched and linear aliphatic aldimines were also shown to provide aminoindoles (entries 5 and 6). Substituted alkyl and electron-rich aryl isocyanides such as *p*-methoxyphenyl

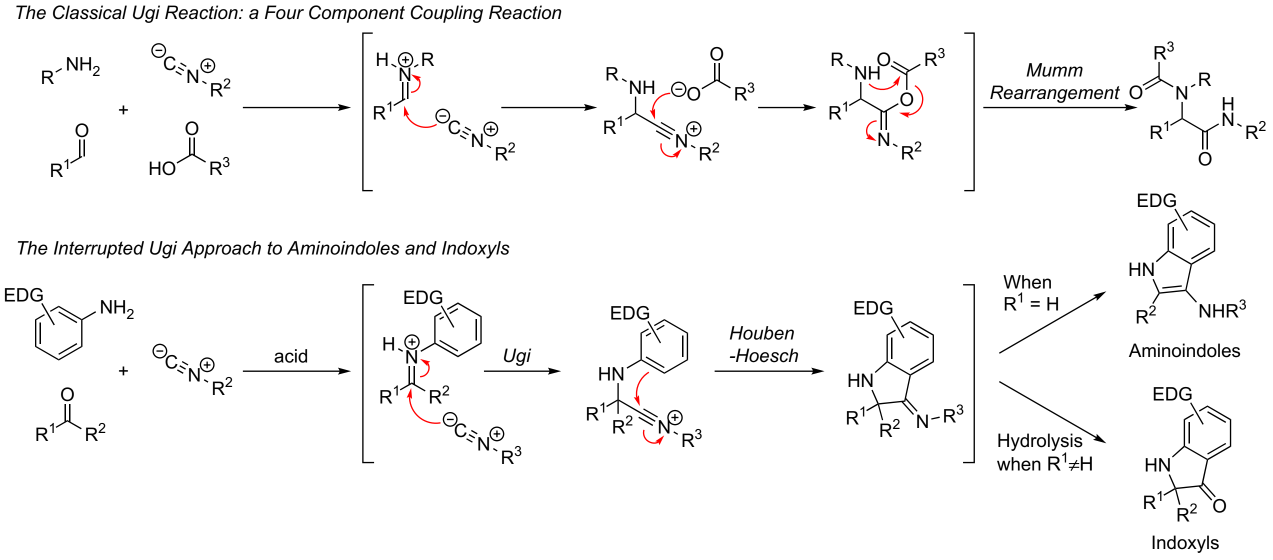


Figure 1. Ugi-type reactions.