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A Novel Three-Component One-Pot Synthesis of 1*H*-Imidazol-4-yl-pyridines

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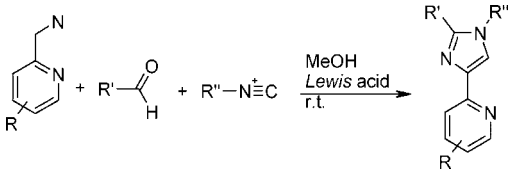
ABSTRACT



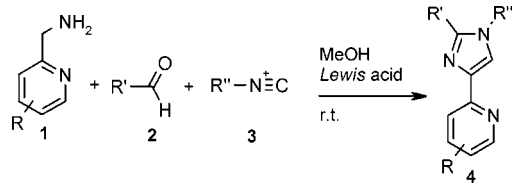
A novel three-component, one-pot condensation yielding 1*H*-imidazol-4-yl-pyridines from aldehydes, *o*-picolylamines, and isocyanides is described. The scope and limitations of the reaction have been investigated.

Combinatorial chemistry is being increasingly applied for the discovery of novel biologically active compounds. In this context multicomponent reactions (MCRs) are a powerful tool in the modern drug discovery process in terms of lead finding and lead optimization,[1−6] but the range of easily accessible and functionalized small heterocycles is rather limited. The development of new, rapid, and robust routes toward focused libraries of such heterocycles is therefore of great importance.

The imidazole scaffold is often found in biologically relevant compounds. Substituted imidazoles have received significant attention as a result of their diverse medical uses.[7] Only a few general methodologies exist for the assembly of substituted imidazoles.[8] Elegant approaches based on van Leusen's TosMIC chemistry have been reported.[9]

Through our attempts to prepare substituted imidazoles as pharmacologically relevant scaffolds, we have discovered a new multicomponent reaction (MCR) yielding 1*H*-imidazol-4-yl-pyridines **4** (Scheme 1).

Scheme 1. General Reaction



Stirring a solution of substituted *o*-picolylamines **1**, aldehydes **2**, isocyanides **3**, and acetic acid or Lewis acids in methanol at 25 °C for 16 h resulted in the conversion to 1*H*-imidazol-4-yl-pyridines **4**. Analysis of the reaction mixtures by LC−MS showed only moderate transformation rates. Therefore the role of the Lewis acid was explored on

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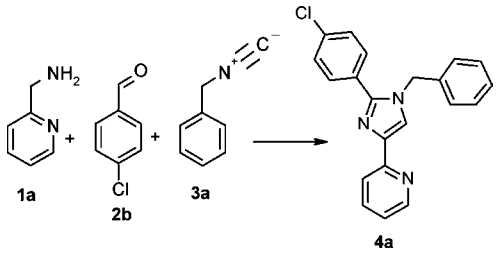
one example (Table **1**). It turned out that 50 mol % $InCl_3$ and methanol as solvent gave the best conversion rates to 1*H*-imidazol-4-yl-pyridine **4a** according to HPLC analysis.

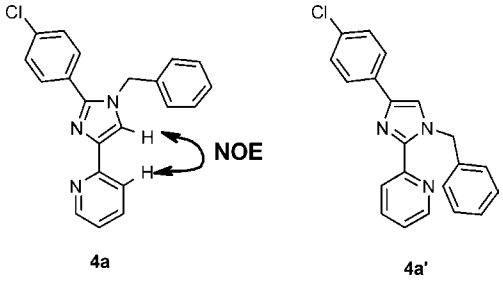
Table 1. Reaction Conditions



entry	condition	yield (LC, 220 nm)
1	20 mol % $InCl_3$, MeOH	20%
2	50 mol % $InCl_3$, MeOH	65%
3	equiv *p*-TsOH, MeOH	28%
4	20 mol % $Yb(OTf)_3$, MeOH	19%
5	2 equiv AcOH, MeOH	25%
6	10 mol % $Yb(OTf)_3$, $CHCl_3$	39%
7	20 mol % $Yb(OTf)_3$, $CHCl_3$	57%
8	50 mol % $InCl_3$, $CHCl_3$	43%
9	equiv *p*-TsOH, $CHCl_3$	44%

This reaction can be regarded as a special case of the Ugi reaction.[10] To verify which of the possible isomers, **4a** or **4a′**, was formed during this reaction, NOE studies were undertaken. An NOE was found between the hydrogens of **4a** described in Scheme 2 (see Supporting Information).

Scheme 2



Although no definitive mechanistic pathway can be delineated for the reaction at the present time, the following rationalization may be advanced to account for the formation of the product. The initial event may be considered as nucleophilic attack on the isocyanide carbon by the carbon atom in α position to the pyridine. Further loss of a proton in the proposed mechanism leads to a species **6A**, which under subsequent aromatization during workup can conceivably deliver the desired imidazole **4** (Scheme 3). It is proposed that the nucleophilicity of the (2-pyridyl)methyl carbon arises from the enamine tautomer **6** (Scheme 3). This hypothesis is bolstered by another reaction of *o*-picolylamine that came to our attention: its condensation with 1,3-diones leads to substituted 2-pyridylpyrroles[11] and in the order of

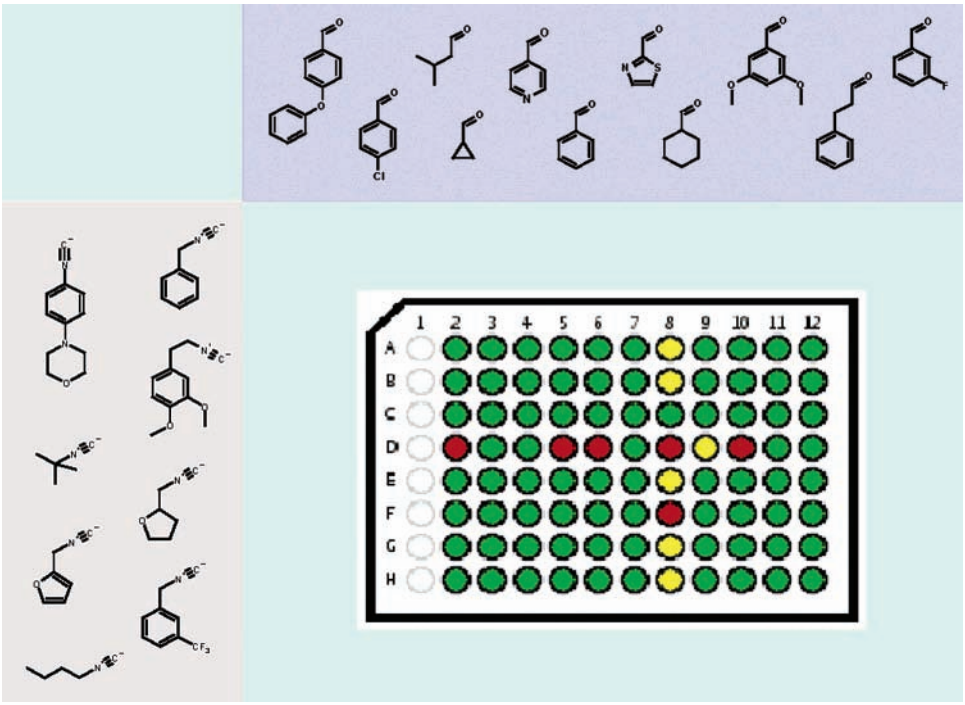
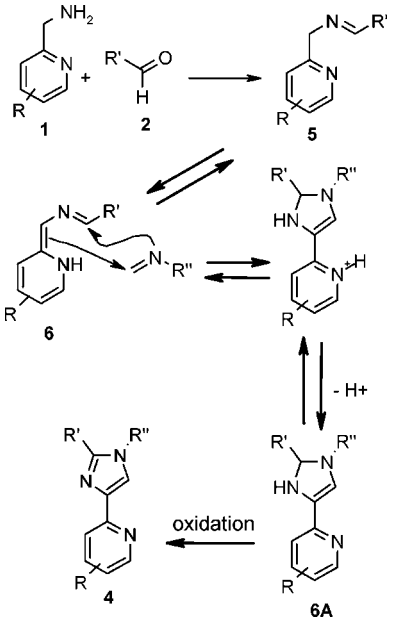


Figure 1. LC−MS overview of formed products in MeOH using 50 mol % $InCl_3$. LC analytics: MeOH/H_2O gradient mode, Chromolith Flash column. MS analytics: positive ESI. Color-coding: intensity of EIC (extracted ion count) of desired product compared to the intensity of EIC of a 0.1 mM solution of the isolated **4a** (green = >20%, yellow = 5−20%, red = <5%)

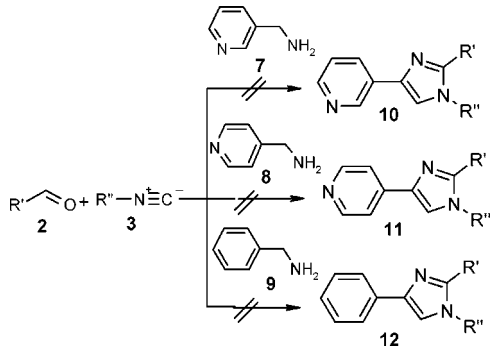
Scheme 3. Proposed Mechanism



the mechanism proposed by van Leusen[9a] for the synthesis of imidazoles from isocyanides.

Closely to the work described by Klappa et al.,[11] we investigated further pyridyl-methylamine derivatives: 3- and 4-pyridylmethylamine **7** and **8** and benzylamine **9** do not participate in this reaction under the same conditions (Scheme 4). The formation of the products **10**−**12** was not observed.

Scheme 4



On the basis of our initial observation, preliminary studies focused on determination of scope and limitation of this reaction were investigated. In Table 2 are shown selected examples of the described compound class synthesized by the general procedure and purified via preparative HPLC.[12] The reaction afforded the desired products in moderate to good yields (15−55%) as dark colored powders (Table 2).

To investigate the application of this reaction for high throughput plate synthesis, a representative set of aldehydes

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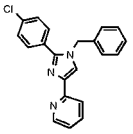
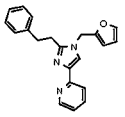
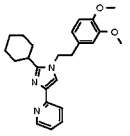
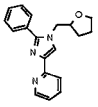
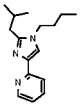
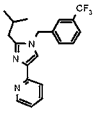
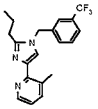
Table 2. Structures and Yields of Some Representative Examples of 1*H*-Imidazol-4-yl-pyridines **4**

entry	compound	yield (%)[a]
4a		34
4b		27
4c		55
4d		17
4c		49
4f		23
4g		39
4h		43

[a] Isolated yields

2a−**k** and isocyanides **3a**−**h** were used together with *o*-picolylamine **1a**. The reaction conditions mentioned above were transferred to plate synthesis. In a typical procedure equimolar amounts of the three starting materials **1**, **2**, **3** and 50 mol % $InCl_3$ are mixed together in MeOH and react at room temperature overnight.[13] The plate layout and the observed results are shown in Figure 1. Each reaction mixture was analyzed by LC−MS. The formation of the product is color-coded. The green-colored wells represent the ones where the product was well detected. No formation of the product was observed in the red-labeled wells. In the yellow-

(12) **General Procedure for a Representative Example.** A 1 mmol portion of *o*-picolylamine and 1 mmol of aldehyde is dissolved in 3 mL of methanol at room temperature. Next 50 mol % of $InCl_3$ and 1 mmol of isocyanide are added after 5 min. The reaction mixture is allowed to stir for 16 h at room temperature. After evaporation of the solvent the residue is filtrated through a silica gel pad using MeOH/$CHCl_3$ as solvent to remove the polar impurities. The resulting semipure product is purified via preparatory HPLC after evaporation of the solvent.

labeled wells the formation of the desired product was detected only moderately.

The reaction was found to be tolerate a range of R groups with different steric and electronic demands, including aliphatic groups and aromatic rings involving electronic-donating and electron-withdrawing groups (Figure 1). Only bulky isocyanides such as *tert*-butylisocyanide (row D) show some limitations, as well as heterocyclic aldehydes, e.g., 2-thiazolylcarbaldehyde (column 8). In the most cases the 1*H*-imidazol-4-yl-pyridines were formed (Figure 1).

(13) The reactions were conducted in 96-well plates, and the experimental procedure of the plate was as follows. To 50 μL of a 0.1 M ($n = 5$ μmol) solution of amine in methanol are dispensed 50 μL of a 0.1 M ($n = 5$ μmol) solution of aldehyde in methanol. The 25 μL of a 0.1 M ($n = 2.5$ μmol) $InCl_3$ solution in methanol and 50 μL of a 0.1 M ($n = 5$ μmol) isocyanide solution in methanol are added. The plate is shaken overnight at room temperature. The solvent is removed under reduced pressure. To analyze the plate by fast LC−MS the residue was dissolved in 1:1 methanol/water to give a 1 mM solution.

In summary, we have discovered a novel three-component reaction yielding 1*H*-imidazol-4-yl-pyridines **4** in a one-pot procedure. NMR data of representative examples prove the formation of this compound class. This novel reaction can be regarded as a new method for the preparation of pharmaceutically relevant highly substituted imidazoles. An efficient synthesis for the parallel preparation under mild and robust conditions was explored. The further determination of scope and limitations is still under investigation.

Acknowledgment. We gratefully appreciate Robert Eckl and Dr. Walfrido Antuch for NMR support.

Supporting Information Available: Representative experimental procedure and characterization data (^{1}H and ^{13}C NMR) for selected products. This material is available free of charge via the Internet at http://pubs.acs.org.

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