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Revision of Outcome and Mechanism of a New Multicomponent Reaction

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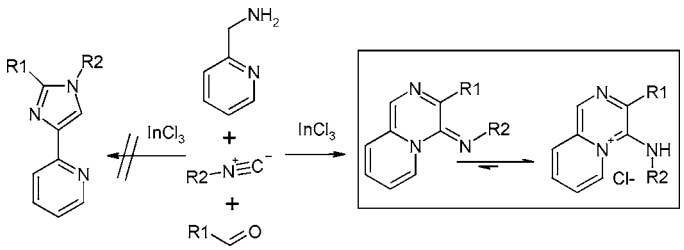
ABSTRACT



A recently reported multicomponent reaction (MCR) produces pyrido[1,2-*a*]pyrazines and not the previously described 1*H*-imidazol-4-yl-pyridines. This different structure is proposed on the basis of a new mechanism of formation and the spectroscopic data.

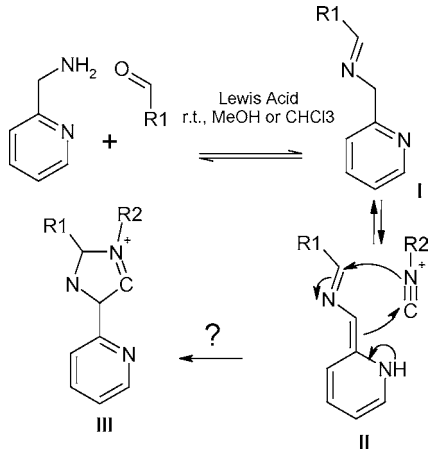
Our group is deeply involved in the discovery and development of new MCRs due to their great potential for the rapid construction of new chemically complex entities and for the facile synthesis of arrays of compounds in a combinatorial chemistry fashion.

Preparation of *1H-imidazol-4-yl-pyridines* has been recently published[1] via a new and very elegant isocyanide-based MCR. This work immediately attracted our attention due to the great importance of substituted imidazoles and the difficulty of synthesis using a conventional multistep sequence. A careful study of this work, however, revealed several points that made us doubt the structure initially proposed.

First, the result of imidazole formation is rationalized on the basis of a mechanism (Scheme 1) that relies upon the isocyanide displaying rare chemical behavior. The authors propose the formation of the substituted imidazole on the basis of comparison with van Leusen's[2] previously reported TosMIC chemistry, but in our opinion there is not much similarity with the unusual 1,3-dipolar cycloaddition proposed here (Scheme 1).

This MCR is also compared with the preparation of pyridylpyrroles[3] from *o*- and *p*-picolinamines. However, on the basis of this mechanism, one would predict that *p*-picolinamines should react as well as *o*-picolinamines (as in

Scheme 1. Previously Proposed Mechanism for the Formation of Substituted Imidazoles



(1) Illgen, K.; Nerdinger, S.; Behnke, D.; Friedrich, C. *Org. Lett.* **2005**, *7* (1), 39.

(2) (a) Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153. (b) Sisko, J.; Kassick, A. J.; Mellinger, M.; Fian, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516. (c) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529.

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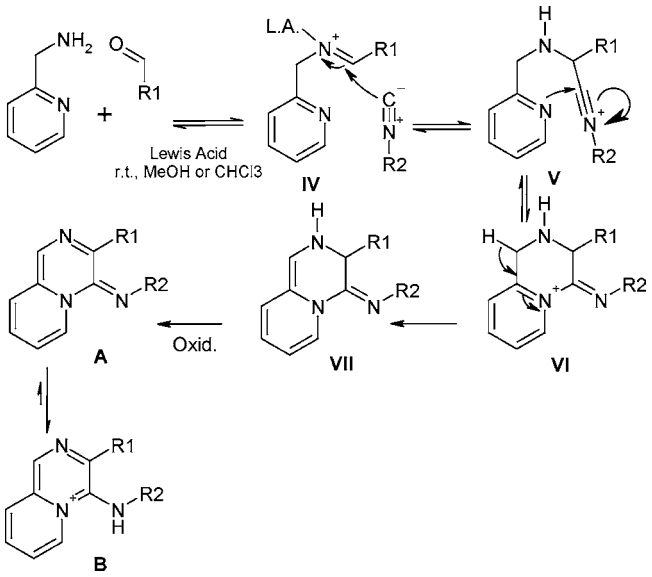
the cited work). Since only *o*-picolinamines are suitable substrates for this MCR, this made us regard the participation of the *o*-nitrogen of the pyridine in the reaction mechanism as absolutely necessary.

There are no literature precedents for such substituted imidazoles, and their physical properties therefore cannot be compared. The published structure determination was accomplished by NMR and MS; however, we think that there is not enough proof of the imidazole framework formation, and the spectroscopic data provided are also consistent with structure **A**. This new proposed structure can be rationalized on the basis of a mechanism reported by Bienaymé[4] and Weber[5] (Scheme 2).

Scheme 2. New Proposed Mechanism and Outcome



We propose a different scenario. In a first step, imine intermediate **IV** of *o*-picolinamine is activated with Lewis acid to allow nucleophilic attack of isocyanide forming intermediate **V**.

The pyridine nitrogen then reacts with the carbon electrophile to yield intermediate **VI**. Note that only when a nitrogen is placed in the ortho position will this intermediate be formed (explaining why *p*-picolinamines do not react). Oxidation provides final product **A**, which would be shifted to **B** in a protic medium.

To confirm these new structures and the mechanism proposed, compound **1** was prepared following the same procedure[6] described by Illgen et al. and fully characterized through a combination of one- and two-dimensional NMR experiments, including ^{1}H, ^{13}C, COSY, $^{1}H-^{13}C$ HSQC, $^{1}H-^{13}C$ HMBC, $^{1}H-^{15}N$ HMBC, and NOESY experiments.

The ^{1}H spectrum of this compound in wet $CDCl_3$ matches that reported in the previous paper, confirming that the same compound was obtained (see Supporting Information). Interestingly, the spectrum recorded in dry $CDCl_3$ shows an additional peak at 10.99 ppm that corresponds to an exchangeable proton, indicating that the protonated compound was isolated. This signal is coupled to the benzylic protons at position 12, which is only consistent with structure **1**. This behavior for compounds similar to **1** has already been described in the literature.[7] Valuable structural information can be obtained from a HMBC experiment, which provides long-range $^{1}H-^{13}C$ or long-range $^{1}H-^{15}N$ correlations over two or three bonds, allowing connectivities to be traced across quaternary carbons in order to piece together otherwise uncorrelated molecular fragments. Thus, a $^{1}H-^{13}C$ HMBC spectrum of the compound shows a correlation from H1 to C8, which is only in agreement with **1**, since these atoms are only within a four-bond distance in **5**. The correct structure can also be deduced from the analysis of a $^{1}H-^{15}N$ HMBC spectrum (Figure 1). The correlations from H8

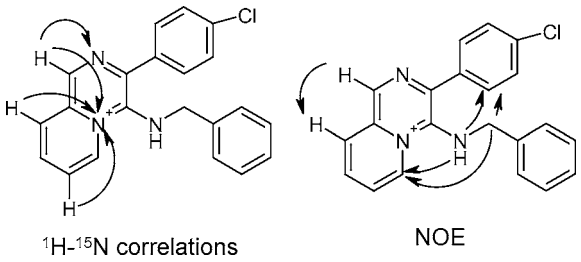
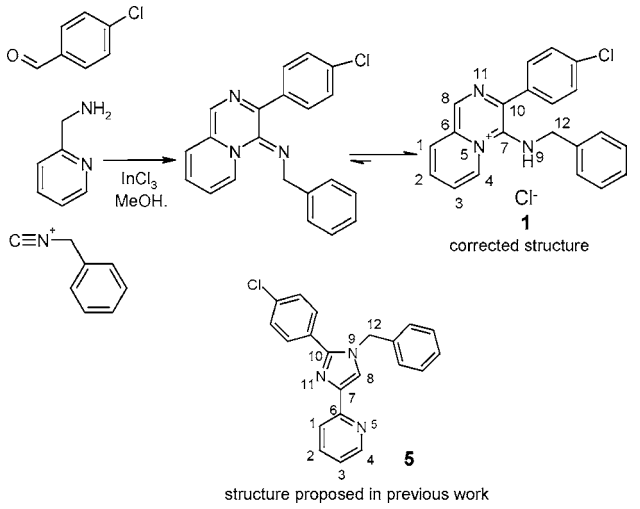


Figure 1.

to a nitrogen at 337.8 ppm and from H1 and H3 to a nitrogen at 203.3 ppm led to the identification of N11 and N5, respectively. The key observation is that H8 also shows a long-range correlation to the nitrogen at 203.3 ppm, which is only in agreement with structure **1**.

Scheme 3. Preparation of Compound **1**[a]

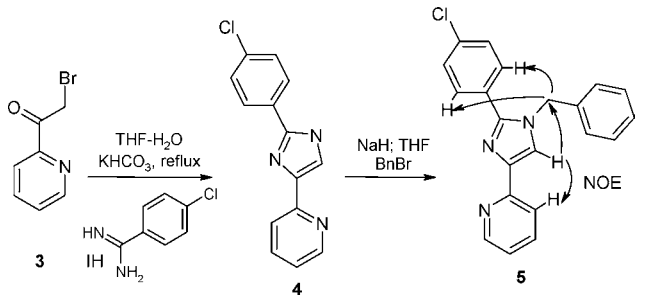


[a] Yield: 56% purity by LCMS at 300 nm, 26% isolated compound.

(3) Klappa, J. J.; Rich, A. E.; McNeill, K. *Org. Lett.* **2002**, *4*, 435.
(4) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234.
(5) (a) Lack, O.; Weber, L. *Chimia* **1996**, *50*, 445. (b) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *3*, 366.

Finally, 2-[1-benzyl-2-(4-chloro-phenyl)-1*H*-imidazol-4-yl]-pyridine **5** was prepared (Scheme 4) here using an

Scheme 4. Preparation of Compound **5**



unambiguous, multistep route following reported literature.[8] Comparison of this NMR spectrum with that supplied in the previous paper clearly indicates they are different compounds.

A full NMR characterization of **5** was carried out, and the resonance assignments can be found in Supporting Information. The position of the benzyl group was determined through a one-dimensional NOESY experiment: selective inversion of the benzylic protons produced a NOE to the imidazole H8 and to the aromatic protons meta to the chlorine atom, indicating that the benzyl group is linked to N9. As anticipated, the ^{1}H spectrum recorded for **5** is different from that of **1**.

In summary, we have disclosed the corrected structure for a novel multicomponent reaction and proposed a mechanistic pathway for its formation. The structure has been assigned on the basis of spectroscopic data. One imidazole derivative proposed previously has been synthesized in a multistep sequence, and its spectroscopic properties have been compared with those reported in that previous work. A set of several compounds has been synthesized in our laboratory confirming the reproducibility of this reaction with several aldehydes and isocyanides, and we are currently investigating the scope of this novel MCR. These results will be communicated in due time.

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

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(6) **Preparation of Compound 1.** *o*-Picolinamine (2 mmol) and 4-chlorobenzaldehyde (2 mmol) were dissolved in 6 mL of methanol at room temperature. $InCl_3$ (1 mmol) and benzylisocyanide (2 mmol) were added after 5 min. The reaction was allowed to stir at rt overnight and checked by LCMS. Solvent was evaporated using a stream of N_2, and product was either purified directly on a HLB Oasis cartridge (H_2O/MeOH in a gradient of 5% to 50%) or filtered through silicagel and then purified by reverse phase to yield pure product according to TLC (DCM/MeOH 95:5) and LCMS (>95% pure). The experiment was repetead twice, to confirm its reproducibility, using two different isocyanides and aldehydes.

(7) (a) Heinrich, W.; Schmidt, A. *J. Org. Chem.* **1993**, *58*, 6976. (b) Llamas-Saiz, A.; Foces-Foces, C.; Martínez, A.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 923. (c) Bradsher, C. K.; Sherer, J. P. *J. Org. Chem.* **1967**, *32* (3), 733. (d) Brandenburg, J.; Beckert, R.; Fehling, P. *J. Prakt. Chem.* **1996**, *338*, 430.

(8) (a) Bryan, L.; Chiu, K.-F.; Hank, R.; Murry, J.; Roth, J.; Tobiassen, H. *Org. Process Res. Dev.* **2002**, *6*, 682. (b) Takalo, H.; Mukkala, V. Pat. Appl. WO 93/11433. (c) Salimbeni, A.; Paleari, F.; Mizrahi, J.; Scolastico, C. Pat. Appl. WO 94/03449