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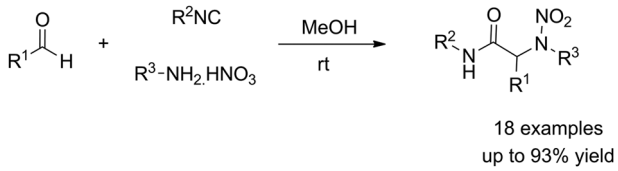

N–N bond formation in Ugi processes: from nitric acid to libraries of nitramines

Valentina Mercalli, Aude Nyadanu, Marie Cordier, Gian Cesare Tron,* Laurence Grimaud* and Laurent El Kaim*

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N–N bond formation in Ugi processes: from nitric acid to libraries of nitramines†

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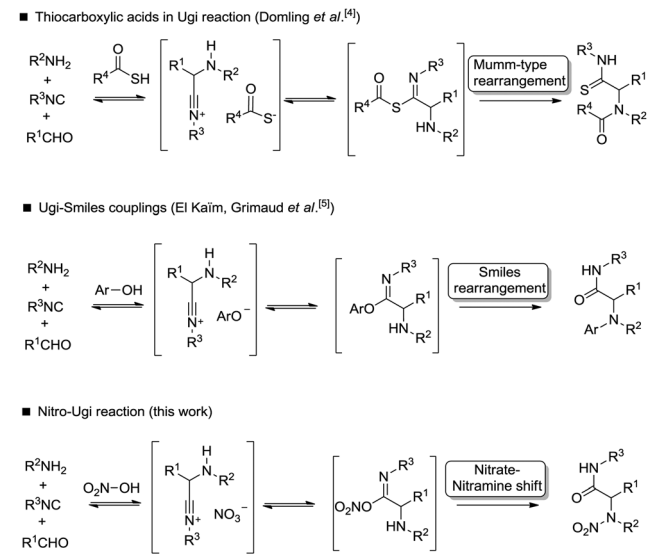
The Ugi reaction has drawn considerable attention over the years leading to numerous libraries of heterocycles and various extensions changing the nature of the components of the coupling. We report here the use of nitric acid as carboxylic acids surrogates, displaying the first aminative Ugi-type reaction leading to nitramines.

The success encountered by the use of the Passerini and Ugi reactions for the preparation of libraries of bioactive compounds has led to a renewal of isocyanide chemistry in the last two decades.[1] The potential of the Ugi reactions, in particular, has been widely explored through extensive modifications of the initial partners of the coupling. For most of these studies, the functional tolerance of the coupling allowed the addition of further reactive centers prone to cyclise after an initial Ugi reaction (the so-called Ugi post-condensations).[2] Extensions associated with modifications of the Ugi reaction mechanism are less documented due to a complex reaction cascade with each partner acting at the different stages of the mechanism. This is particularly the case of the acidic component which participates in the initial electrophilic activation of the imine but also plays a key role in the final formation of the Ugi adduct.[3] Thus, the replacement of the carboxylic acid has only been proposed with a reduced number of acids: thiocarboxylic acids still involving a Mumm rearrangement,[4] isocyanic and isothiocyanic acids leading to hydantoin derivatives[5] *via* a final cyclization, hydrazoic acid forming tetrazoles in an electrocyclization process,[6] electron-poor phenols with a final Smiles rearrangement,[7] and squaric acid[8] and hydroxy-tropolone[9] which behave similarly.

In most of these extensions, the initial amine partner is involved in a final N–C bond formation as observed in the *N*-acylation step of the Mumm rearrangement or the *N*-arylation of the Smiles rearrangement. Herein, we wish to report the use of nitric acid leading to the first N–N bond formation with the amine partner of the Ugi reaction (Scheme 1).

Strong mineral acids are known to trigger both Ugi and Passerini reactions but these acidic components have led to very few useful synthetic applications. Indeed, the strong activation of the carbonyl component is counterbalanced by the instability of the isocyanide in the presence of strong acids



Scheme 1 Acidic surrogates in Ugi reactions.

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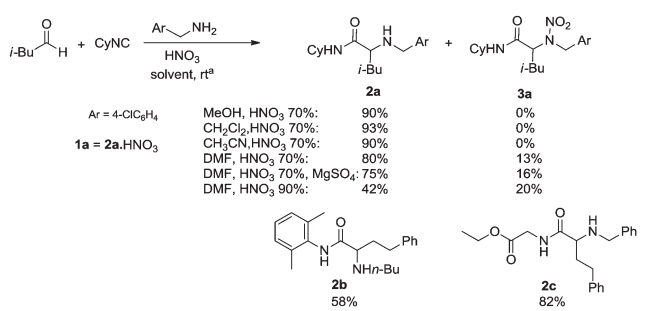
† Electronic supplementary information (ESI) available: Details of experimental procedures, ^{1}H NMR and ^{13}C NMR spectra for all unknown compounds. CCDC 1524126. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc10288c

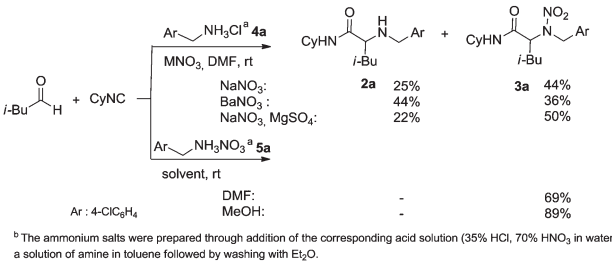
together with the weak nucleophilicity of the associated counter-anion. The latter point leads to important competitions in the attack of the intermediate nitrilium by the stabilized anion, the solvent, water or even the intermediate amines in the case of Ugi reactions.[10] Thus strong mineral acids (HCl, H_2SO_4, HNO_3 or H_3PO_4) have been reported in the Passerini reaction but require a large excess of the carbonyl derivative to form hydroxyamide derivatives in good yields.[11] Although their stoichiometric use in the Ugi reaction is not hampered by the high acidity of the medium, the few available reports are mostly limited to secondary amines[12] or present important competition with the Passerini reaction.[10] These difficulties together with the high synthetic potential of these acids towards undisclosed N–S, N–P or N–N Ugi adducts was challenging enough to re-evaluate some of these reactions. Nitric acid with its single hydroxy group appeared to be the best candidate for this study.

When equimolar amounts of *para*-chlorobenzyl amine, cyclohexyl isocyanide, isovaleraldehyde and nitric acid used as a 70% aqueous solution were mixed in methanol (0.3 M), we observed the formation of a white precipitate. After two hours, the precipitate could be either separated by filtration and washing with diethyl ether to afford the ammonium nitrate **1a** obtained in 90% isolated yield or the mixture could be directly treated by a sodium hydrogencarbonate solution to afford after extraction with diethyl ether the amine **2a** with the same yield (Scheme 2). Working in dichloromethane or acetonitrile instead of MeOH afforded **2a** in comparable yields. Other starting Ugi components afforded similar results when the reaction was performed in CH_2Cl_2 with 70% nitric acid; **2b** and **2c** were obtained after basic treatment without observing any precipitation in the medium in these cases (Scheme 2). Working in DMF was more rewarding as besides **2a** obtained in 75% yield, the expected nitramine **3a** could be isolated as a side product in a poor 13% yield. Adding magnesium sulfate to the mixture just gave a small increase and a more concentrated nitric acid (90%) allowed us to reach 20% (Scheme 2).

We next started to evaluate the use of nitrate salts together with various ammonium salts as the starting amine to optimize conditions with a lower amount of water in the solvent. Although sodium nitrate together with ammonium chloride **4a** allowed the improvement of the yields in DMF, the best results were obtained with ammonium nitrate **5a**,[13,14] which gave nitramine **3a** in 69% isolated yield (Scheme 3). An even



Scheme 2 Ugi-type reaction with nitric acid in various solvents.



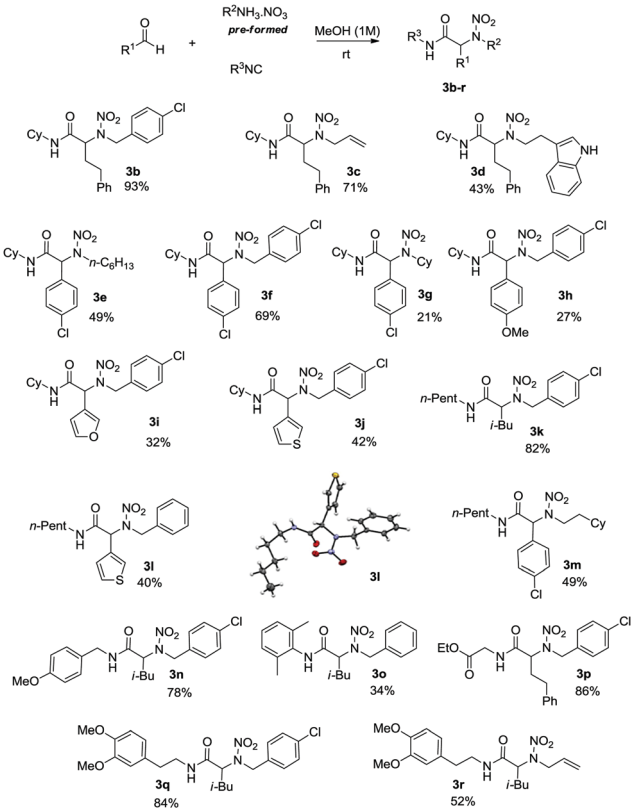
[b] The ammonium salts were prepared through addition of the corresponding acid solution (35% HCl, 70% HNO_3 in water) to a solution of amine in toluene followed by washing with Et_2O.

Scheme 3 Optimization using ammonium salts.

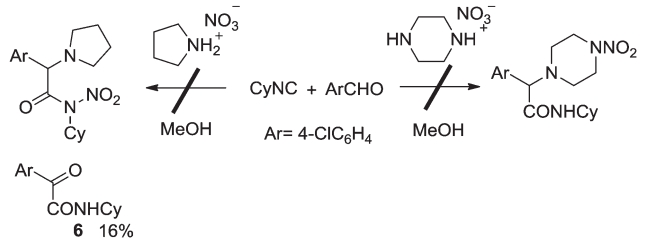
better 89% isolated yield was obtained when the same reaction was conducted in MeOH. The structure of **3a** was further confirmed through the nitration of amine **2a** under standard conditions (nitric acid and acetic anhydride).[15]

With this set of optimized conditions in hands, the scope of this new nitramine synthesis was further examined (Scheme 4).[16]

The reaction turned out to be efficient with both aliphatic (**3a–d**) and aromatic aldehydes (**3e–j**). The range of isocyanides successfully involved in this coupling is rather wide. Indeed, alkyl (**3a–m**, **3q–r**), benzyl (**3n**), aryl (**3o**) or isocyanoacetate (**3p**) derivatives gave the desired products in moderate to good yields. Surprisingly, no desired product could be isolated from the reaction of *tert*-butylisocyanide probably due to its particular acidic sensitivity. The isolation and X-ray analyses of compound **3l** further confirmed the structure of the products formed in this new nitric acid-promoted Ugi reaction.[17]



Scheme 4 Scope of the nitramine synthesis.



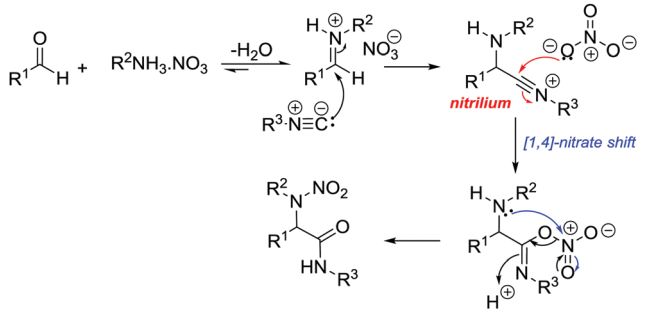
Scheme 5 Failed attempts with pyrrolidine and piperazine.

Concerning the amine partner in this coupling, the reaction proceeded smoothly with aliphatic (**3e**, **3m**), allylic (**3c**, **3r**) and benzylic (**3a–b**, **3n–q**) amines. However, no reaction was observed when using aniline, probably because of its lower nucleophilicity. Secondary amines such as pyrrolidine fail to afford the expected Ugi nitramide probably because of an unfavorable [1,3]-shift of the nitro group, the ketoamide **6** could just be isolated in low yield (Scheme 5). Similarly, no distal nitration could be observed with piperazine in contrast to the Ugi reaction with carboxylic acids (Scheme 5).[18]

By analogy with the mechanism of the classical Ugi reaction,[19] we can propose a plausible pathway involving the intermolecular trapping of the nitrilium by the nitrate anion. The resulting nitroimidate could further evolve through a [1,4]-shift of the nitro according to a Mumm-type transfer, to give the corresponding nitramine as depicted in Scheme 6.[20]

Nitramines are usually prepared through nitration of their related amine derivatives.[15] They are mostly known for their use as energetic materials and explosives[21] but also display some interesting applications as synthetic intermediates.[22] They can be easily reduced to hydrazine and nitrosamine derivatives.[23] Their biological activities have been mostly exploited in the agrochemical field with some promising herbicide and fungicide activities.[24]

To conclude, we have re-examined the use of strong mineral acids in isocyanide-based multicomponent reactions. The use of nitric acid was just reported once before as a catalyst in Passerini reactions with water as final nucleophilic trapping agents. The use of stoichiometric amount of acid in the absence of water ensures an efficient trapping of the intermediate nitrilium by the moderately nucleophilic nitrate anion followed by an intramolecular nitration. The extension of this approach to other families of strong acid (phosphonic and sulfonic acids) is under study in our research group as well as the potential applications of the newly obtained Ugi nitramines.



Scheme 6 Plausible mechanism for the nitramine formation.

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13 **Caution**: Though no explosion has been reported with ammonium nitrate prepared from primary amines, great care should be taken with small amines with one to three carbons due to the known sensibility of ammonium nitrate (NH_4NO_3).

14 All the ammonium nitrates displayed in this study were prepared through dropwise addition of HNO_3 70% (1 equiv.) to a solution of the amine (1 equiv.) in toluene (1 M). The reactions were stirred at room temperature for 30 minutes. The precipitates were filtrated off, washed with Et_2O, and used without further purifications. When no precipitate is formed, the crude ammonium nitrate can be dried by azeotropic removal of water with toluene, followed by evaporation of solvent under reduced pressure.
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17 The crystallographic data for compounds **3l** can be obtained free of charge under the reference CCDC 1524126 from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request_cif.
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