Synthesis of Aminocarbonyl *N*-Acylhydrazones by a Three-Component Reaction of Isocyanides, Hydrazonoyl Chlorides, and Carboxylic Acids

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S *Supporting Information*

ABSTRACT: A novel one-pot multicomponent synthesis of α-amino-carbonyl *N*-acylhydrazones starting from readily available hydrazonoyl chlorides, isocyanides, and carboxylic acids is reported. The strategy exploits the ability of the carboxylic acid as a third component to suppress all competing reactions between nitrile imines and isocyanides, channeling the course of the reaction toward the formation of this novel class of compounds.
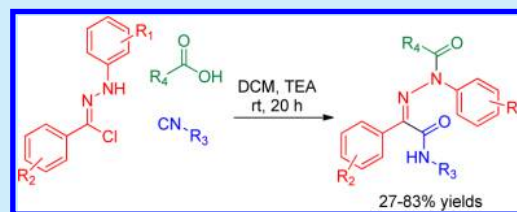
Pioneering work on the reactions between nitrile imines and isocyanides by Professor Moderhack has shown that, according to the experimental conditions and the steric and electronic nature of the isocyanides and hydrazonoyl chlorides used, at least four competing reactions can take place (Scheme 1).[1] This simple two-component reaction affords four different

Scheme 1. Products of the Reaction between Nitrile Imines and Isocyanides
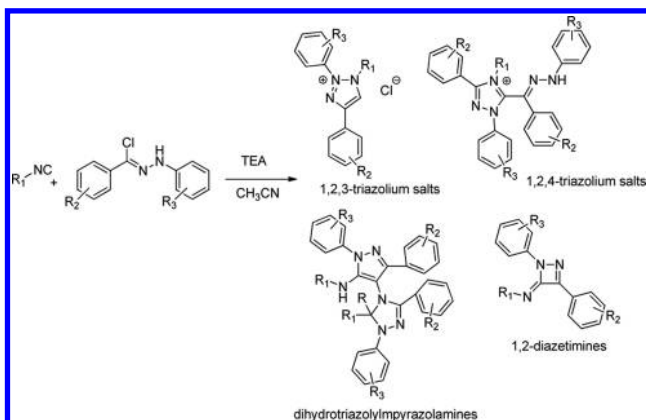
products, usually with modest yields: 1,2,3- and 1,2,4-triazolium salts, dihydrotriazolyl pyrazolamines, and the unstable 1,2-diazetimines. While the diversity of obtainable products has to be considered a bonus of this chemistry, the impossibility of limiting the course of the reaction to a single product, or controlling the ratio of the various adducts, under the

conditions and with the reagents used drastically reduces the generality of these transformations. This chaotic result is due to the formation of a reactive nitrilium intermediate (from the isocyanide attack to the nitrile imine) which can follow different paths, none being preferred over the others. Aware of this situation, we wondered whether the presence of a third component[2] could change the anarchic situation typical of the two-component reaction between nitrile imines and isocyanides and render the method more suitable for the creation of libraries of compounds useful from a medicinal chemistry point of view. We therefore tested the three-component reaction (3-CR) between a hydrazonoyl chloride (**1**), cyclohexylisocyanide (**2**), and benzoic acid (**3**) as the third component, in dichloromethane (0.2 M) at room temperature overnight, and with 2 equiv of triethylamine (one needed to generate the nitrile imine, and the other to form the carboxylate). We were pleased to observe the formation of the multicomponent adduct α-aminocarbonyl *N*-acylhydrazone **4** in 37% yield, along with the adduct **5** in 42% yield deriving from a two-component reaction between the hydrazonoyl chloride **1** and the carboxylic acid **3** (Scheme 2).

To explain the formation of these two products the following mechanistic scenario is proposed. The hydrazonoyl chloride **1**, under basic conditions, forms the ephemeral nitrilimine species **6**[3] bearing an electrophilic carbon suitable for the isocyanide attack. At this point, the generated nitrilium ion **7** would be ready to undergo the transformations reported by Moderack.

**Scheme 2. Three-Component Reaction between a Hydrazonoyl Chloride (1), Cyclohexylisocyanide (2), and Benzoic Acid (3)**
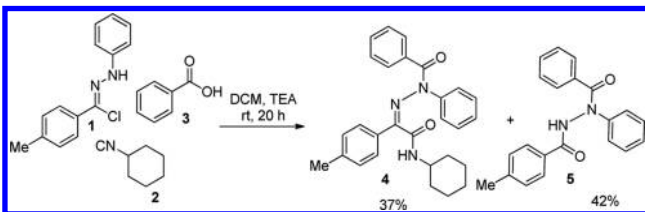
Instead the presence of the carboxylate ion prevents the other reaction pathways by generating, in a stereoselective way,[4] the iminoanhydride intermediate **8**, which affords the desired product by undergoing a Mumm type rearrangement thanks to the properly positioned hydrazine nitrogen atom (Scheme 3).

Scheme 3. Proposed Mechanism for the Three-Component Reaction
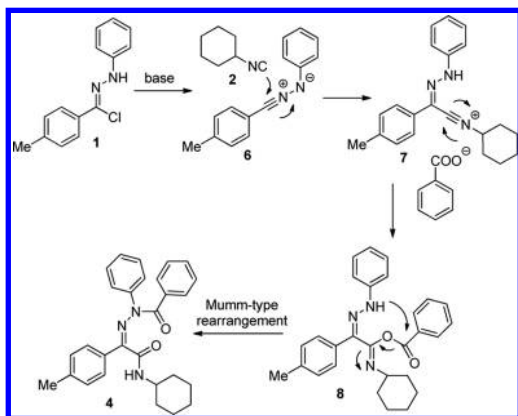
Additionally, nitrile imines are highly reactive species which can react directly with carboxylic acids[5] and undergo an acyl migration to generate the byproduct compound **5**. It is important to highlight that we did not observe any of the compounds described by Moderack, proving that the use of the carboxylate as a third component suppresses all the competing reactions between nitrile imines and isocyanides. Stimulated by this early result and with the goal to suppress/reduce the formation of the product **5**, we decided to screen the reaction conditions in order to improve the **4:5** ratio and increase the yield of α-aminocarbonyl N-acylhydrazones. The results are shown in Table 1 (see Supporting Information).

To our delight, solvent-free reaction conditions with equimolar amounts of hydrazonoyl chloride, isocyanide, and carboxylic acid, and 2 equiv of TEA gave the α-aminocarbonyl N-acylhydrazone **4** in 52% yield and compound **5** in 18% yield, increasing the desired/undesired product ratio. With these optimized conditions in hand, we planned to explore the scope and the limitations of this novel multicomponent process by randomly combining one of six hydrazonoyl chlorides (**1, 9–13**) with one of five isocyanides (**2, 14–17**) and one of ten carboxylic acids (**18–27**) (Figure 1).

The starting hydrazonoyl chlorides (**1, 9–13**) were readily synthesized in two steps with quite good yields (43–77%) (see Supporting Information). A library of 14 α-aminocarbonyl N-acylhydrazones was thus generated (**28–40**, Figure 2), with yields ranging from 83% to 27%, indicating the generality and the versatility of the process. In particular we observed that the
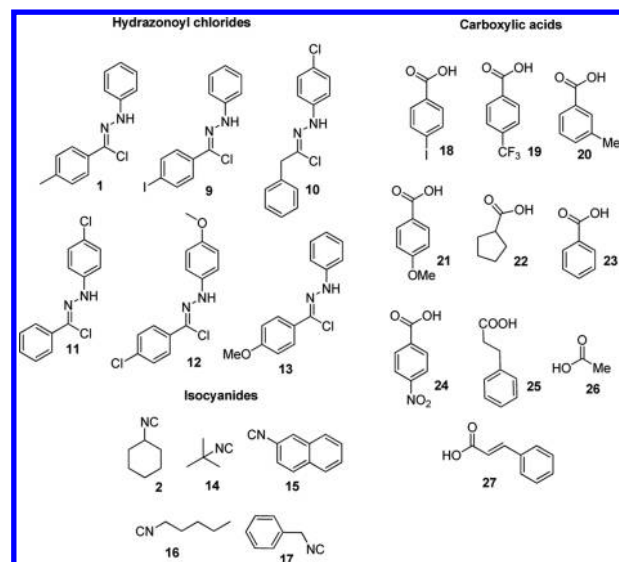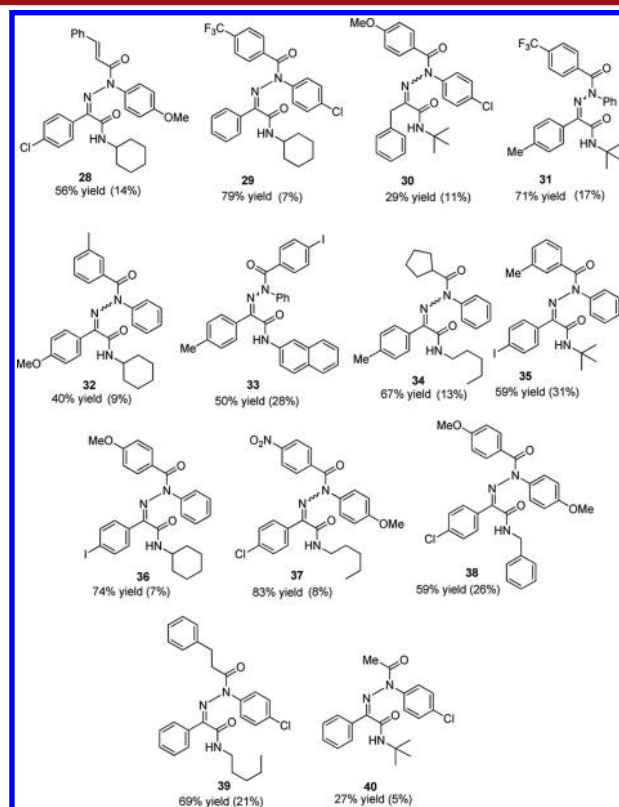

Figure 1. Building blocks used.

Figure 2. Synthesized α-aminocarbonyl N-acylhydrazones. Yields in parentheses refer to the competing reaction between nitrile imines and carboxylic acids.

reaction proceeded well when the carboxylic acids were solid. When they were liquid (e.g., cyclopentancarboxylic acid) the formation of the undesired product was preponderant (86% yield). In this case prior salification to afford a solid was used with success affording the desired 3-CR product in 67% yield. Although the reaction stereoselectively generates the Z isomer, we observed that these acylhydrazones are not always geometrically stable and, on standing, some of them undergo an isomerization process to afford a mix of E and Z isomers (see Supporting Information for more details). In order to

provide a detailed structure assignment of the proposed structures, a single crystal X-ray diffraction analysis on derivative **4** has been carried out. The established solid state structure is represented in Figure 3, together with the relative arbitrary atom-numbering scheme.
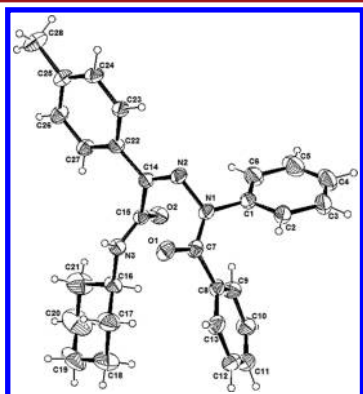

Figure 3. ORTEP[6] view of **4** and the relative arbitrary atom-numbering scheme (thermal ellipsoids at 40% probability).

It is noteworthy that we could only find in the literature *one example* of α-aminocarbonyl N-acylhydrazone, produced by a two-step reaction involving hydrazonoyl chloride **1**, cyclohexyl-isocyanide **2**, and sodium acetate (Scheme 4).[1b] This reaction is

**Scheme 4. Only Two-Step Synthesis of α-Aminocarbonyl N-Acylhydrazones Reported to Date**
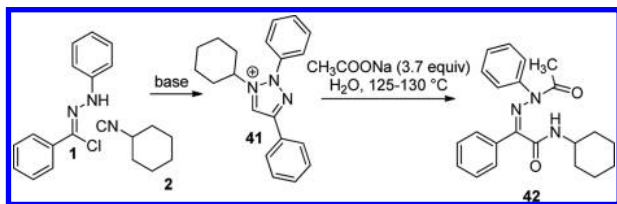
however *conceptually different* from the one reported here, as it involves first the attack of isocyanide **2** to the hydrazonoyl chloride **1** to form a 1,2,3-triazolium salt **41**, followed by a challenging purification step consisting of several recrystallizations. The purified intermediate then undergoes a ring opening reaction with 3.7 equiv of sodium acetate at 125−130 °C to give the α-aminocarbonyl N-acylhydrazones **42** in 33% yields (overall yield after a further purification step). Therefore, such a two-component reaction is not deemed suitable for the fast and efficient synthesis of libraries of α-aminocarbonyl N-acylhydrazone due to the low yield of product, the formation of several byproducts, and the need for several purification steps.

In order to widen the scope of this novel 3-CR and to further explore the reactivity of the nitrilimine nitrogen atom toward a Mumm-type rearrangement we decided to react nitrilimine **1**, *tert*-butylisocyanide **14**, and 2-hydroxymethylbenzoic acid **43**. The use of the substituted benzoic acid has been already reported by us[7] for the synthesis of unsymmetrical bis(β-aminoamides). The presence of a hydroxymethyl function at the *ortho* position of benzoic acid engenders an alternative reaction path leading to the formation of phthalide and a formal addition of water to the final compound. It should be noted that water itself would not be nucleophilic enough to intercept the nascent nitrilium ion.

To our satisfaction the reaction was clean, and we observed a marked increase in yield in the presence of solvent. Whereas the desired α-aminocarbonylhydrazone **44** was produced in 67% yield in the presence of CH_2Cl_2 (Scheme 5), under neat

Scheme 5. Multicomponent Synthesis of α-Aminocarbonylhydrazone Using the Sacrificial Acid 43
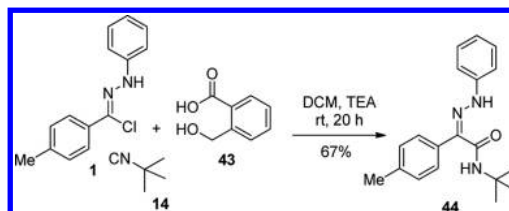
conditions the yield was only 18%. A possible reaction mechanism accounting for the formation of **47** is depicted in Scheme 6. Here the α-adduct **45** could in principle follow two

Scheme 6. Possible Paths of 3-CR with "Sacrificial Acid"
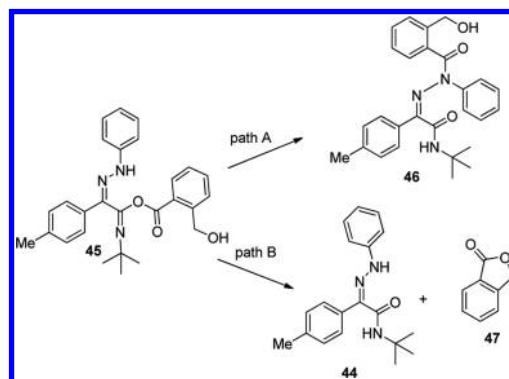
different reaction pathways: path A, which via a Mumm-type rearrangement gives a six-membered transition state leading to compound **46**, and path B, which following the intramolecular attack of the hydroxyl function on the iminoanhydride gives the adduct **44** (via a five-membered transition state) and phtalide **47**. Since only **44** is obtained we speculate that the formation of the five-membered intermediate has a lower activation energy than in the six-membered case.[8]

To further prove the generality of such a mechanism and the selectivity toward path B, the synthesis of a small collection of α-aminocarbonylhydrazones was attempted. In all cases the α-aminocarbonylhydrazone (**48−52**) was the only reaction product and medium-high yields were obtained (Figure 4).

Some of them undergo a rapid isomerization (see Supporting Information). It is important to highlight that the "sacrificial acid" **43** is not able to accomplish the formal addition of water when an Ugi-type reaction with a primary amine is attempted, due to the higher nucleophilicity of the secondary amine formed in situ, which leads to Mumm rearrangement.

We were therefore enthusiastic in discovering the possibility, in our new 3-CR, to tune the reactivity of the nitrilimine nitrogen atom. Additionally the presence of the NH group in the final adduct **44** enables further derivatization, opening up the way to a variety of post-MCR modifications and thus enlarging the scope of the reaction.

In conclusion, starting from an erratic two-component reaction between nitrile imines and isocyanides, we discovered a novel 3-CR between nitrile imines, isocyanides, and carboxylic
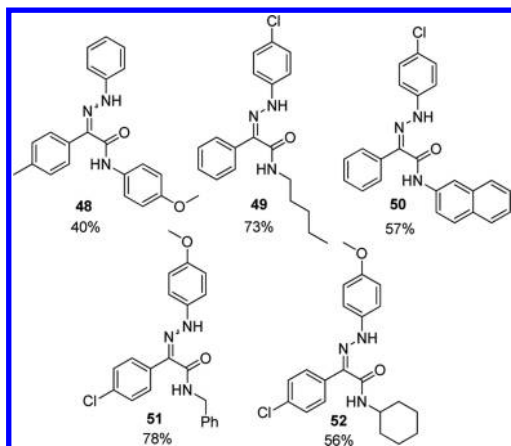
Figure 4. α-Aminocarbonyl N-acylhydrazones synthesized.

acids and applied it to the synthesis of the first reported library of α-aminocarbonyl N-acylhydrazones and some related α-aminocarbonylhydrazones. The compounds obtained could also be seen as aza-homologues of the Ugi scaffold. Indeed, although obtained in a completely different way, the novel 3-CR molecular scaffold shows the atom connectivity NCCNNC and an evident peptidomimetic nature similar to the four-component Ugi scaffold with a NCCNC connectivity. Additionally, the different chemical functionalities present (hydrazone, amide, and acyl groups) enable a potentially large number of post-transformation reactions, similar to the Ugi adducts.[9] Finally, we reckon that other 1,3 dipolar species lay dormant, since their multicomponent reaction with isocyanides have not yet been investigated and they are ready to be successfully used for the discovery of novel multicomponent reactions.[10]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds synthesized. Cif file of **4** (CCDC number: 1025235). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Moderhack, D.; Lorke, M. *Heterocycles* **1987**, *26*, 1751−1754. (b) Moderhack, D. *Liebigs Ann. Chem.* **1989**, 1271−1274. (c) Moderhack, D.; Lorke, M.; Ernst, L.; Schomburg, D. *Chem. Ber.* **1994**, *127*, 1633−1639. (d) Moderhack, D.; Daoud, A.; Ernst, L.; Jones, P. G. *J. Prakt. Chem.* **2000**, *342*, 707−710. (e) Moderhack, D.; Daoud, A.; Jones, P. G. *Monatsh. Chem.* **2002**, *133*, 1165−1175. (f) Moderhack, D.; Daoud, A. *J. Heterocycl. Chem.* **2003**, *40*, 625−637.

(2) (a) Pirali, T.; Mossetti, R.; Galli, S.; Tron, G. C. *Org. Lett.* **2011**, *13*, 3734−3737. (b) Mercalli, V.; Meneghetti, F.; Tron, G. C. *Org. Lett.* **2013**, *15*, 5902−5905.

(3) (a) Huisgen, R.; Seidel, M.; Wallbillich, G.; Knupfer, H. *Tetrahedron* **1962**, *17*, 3−29. (b) Bégué, D.; Qiao, G. G. H.; Wentrup, C. *J. Am. Chem. Soc.* **2012**, *134*, 5339−5350.

(4) Hegarthy, A. F. *Acc. Chem. Res.* **1980**, *13*, 448−454.

(5) Shawali, A. S.; Osman, A. *Tetrahedron* **1971**, *27*, 2517−2528.

(6) (a) Farrugia, L. J. *ORTEP-3 for Windows*; University of Glasgow: Scotland, 1997. (b) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.

(7) La Spisa, F.; Feo, A.; Mossetti, R.; Tron, G. C. *Org. Lett.* **2012**, *14*, 6044−6047.

(8) For examples in the Smiles rearrangment a five-membered transition state is favoured over a six-membered transition state: Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273−412.

(9) Banfi, L.; Basso, A.; Riva, R. In *Synthesis of heterocycles via multicomponent reactions I*; Orru, R. V. A., Ruijter, E., Eds.; Springer-Verlag: Berlin, 2010; pp 1−39.

(10) (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565−598. (b) Moderhack, D. *Synthesis* **1985**, 1083−1096. (c) *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*; Padwa, A., Pearson, W. H., Eds.; Wiley & Son: New York, 2002.