ORGANIC
LETTERS

2013
Vol. 15, No. 22
5902–5905

Isocyanide-Mediated Multicomponent Synthesis of *C*-Oximinoamidines

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Received October 24, 2013

ABSTRACT

By capitalizing on the different reactivity of nitrile *N*-oxides with isocyanides and amine, α-oximinoamidines, a so far elusive class of compounds, have been synthesized in a straightforward way by reacting isocyanides, *syn*-chlorooximes, and amines in a multicomponent fashion.

The identification of novel domino multicomponent reactions[1] (MCRs) is a hard and challenging task for organic chemists but it can be extremely rewarding; it is possible to gain access with simplicity to chemical frameworks which are unknown or would be otherwise difficult to achieve.[2] Because of their unique reactive nature, isocyanides are a versatile class of chemical compounds and have been used as pivotal reagents in multicomponent reactions,[3] thanks to the their well-known ability to react with various electrophilic partners to form the so-called α-adduct[4] (Figure 1).

A major challenge in the search for novel isocyanide-mediated MCRs is to select suitable electrophilic partners capable of generating adducts sufficiently reactive to continue the reaction. In this case, a third player, until that moment an inert spectator, can react in an irreversible manner with them, eventually leading to a domino multicomponent reaction.

Recently, we unveiled the role of *syn*-chlorooximes (also named hydroximoyl chlorides) as suitable partners for isocyanides, and we discovered a novel multicomponent reaction by adding a carboxylic acid to the isocyanide-*syn*-chlorooxime mixture to give *syn*-α-oximinoamides in a stereospecific manner.[5]

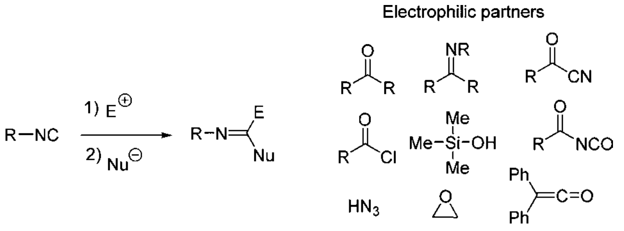

Figure 1. Selected examples of electrophilic partners for isocyanides.

To rationalize the course of this reaction, we suggested the formation of an α-adduct between the *syn*-chlorooxime and the isocyanide, ruling out the participation of a nitrile *N*-oxide species, since, in an independent experiment, among *syn*-phenylchlorooxime (**1**), phenylacetic acid (**2**), and triethylamine (**3**), the formation of the nitrile *N*-oxide dimerization products diphenylfuroxan (**4**) and/or 3,6-dipheyl-1,4,2,5-dioxadiazine (**5**) was not detected.[6] Later, we realized that the formation of these dimerization

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(1) Three- or four-component reactions can be divided in three main groups: domino, sequential, and consecutive multicomponent reacions. See: Müller, J. J. *Top. Heterocycl. Chem* **2010**, *25*, 25–94.

(2) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005 and references cited therein.

(3) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135.

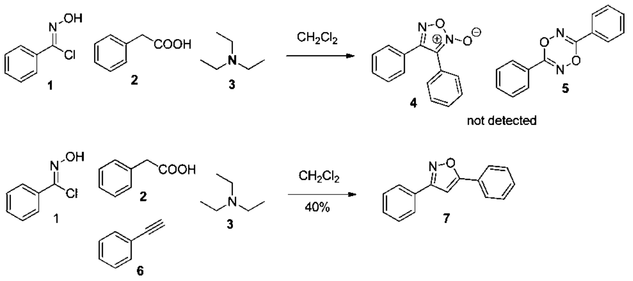
(4) (a) Saegusa, T.; Ito, Y. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp 65–92. (b) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707–2752.

(5) Pirali, T.; Mossetti, R.; Galli, S.; Tron, G. C. *Org. Lett.* **2011**, *13*, 3734–3737.

10.1021/ol403062m

products is actually not as easy as we thought[6] and cannot be considered as a marker for the involvement of nitrile *N*-oxides. Indeed, when we carried out the reaction in the presence of phenylacetylene (**4**), the corresponding isooxazole (**7**) was obtained in 40% yields, pointing out that, even under these buffered conditions (TEA, carboxylic acid), nitrile *N*-oxides can, indeed, be generated (Scheme 1).

Scheme 1. Experiments To Demonstrate the Direct Involvement of the nitrile *N*-Oxide Species



Having showed the ability of isocyanides to directly react with the nitrile *N*-oxides,[7] we hypothesized we could introduce a novel level of complexity by using an amine as a third component. In principle, in this case several scenarios are possible as reactions between chlorooximes and amines, via nitrile *N*-oxide, are well-known in literature for giving amidoximes.[8] This fact could increase the chaos in the round-bottomed flask aborting the multicomponent reaction pathway (Figure 2).

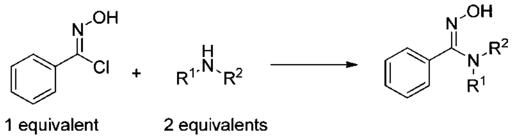
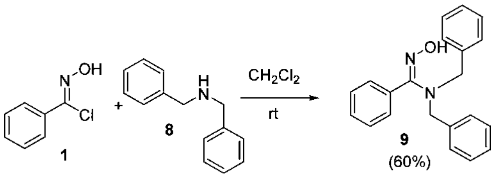


Figure 2. Possible scenario in the reaction between *syn*-chlorooximes and amines.

However, initial experiments revealed that the reaction between 1 equiv of *syn*-phenylchlorooxime (**1**) and 2 equiv of *N*,*N*-dibenzylamine (**8**) was sluggish and not clean, requiring at least 10 h to go to completeness to give **9** in 60% yield (Scheme 2).

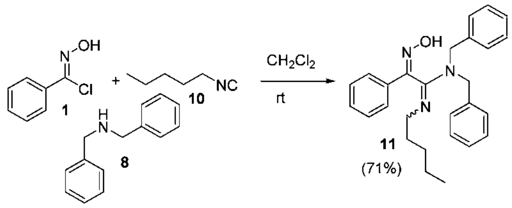
On the other hand, when pentyl isocyanide (**10**) was reacted with the *syn*-phenylchlorooxime (**1**) in dichloromethane at room temperature, after 6 h, the TLC analysis revealed a complex mixture.

Scheme 2. Synthesis of Amidoxime **9**



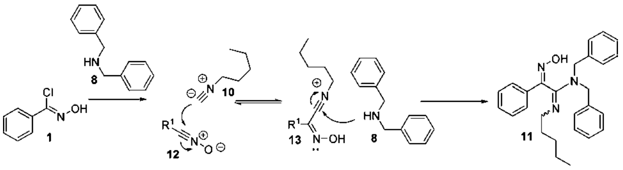
However, this disappointing scenario dramatically changed when in the third experiment an amine (2 equiv) was present in the flask. Indeed, we could observe, after 3 h, the neat formation of a novel product (**11**) which incorporated all of the reactants. Spectroscopic analyses determined the formation of an α-oximinoamidine in 71% yield, a novel chemical moiety never reported before to the best of our knowledge (Scheme 3).

Scheme 3. Three-Component Synthesis of *C*-Oximinoamidines



The proposed mechanism for this new multicomponent transformation is depicted in Scheme 4. The *syn*-phenylchlorooxime (**1**) reacts with a base (**8**), forming the corresponding nitrile *N*-oxide (**12**), rapidly intercepted by pentylisocyanide (**10**) to give a nitrilium ion intermediate (**13**), eventually stereospecifically trapped by the amine,[9] to afford the final product (**14**).

Scheme 4. Proposed Mechanism for the Three-Component Reaction



Unlike those of most amidines,[10] the ^1H and ^{13}C spectra of the final adducts recorded at 80 °C reveal, in most cases,

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(6) For an example of compound formed by dimerization of benzonitrile *N*-oxide according to the reaction conditions, see: Marinone Albini, F.; De Franco, R.; Bandiera, T.; Grunanger, P.; Caramella, P. *Gazz. Chim. Ital.* **1990**, *120*, 1–6.

(7) Only a two-component reaction between isocyanides and nitrile *N*-oxides to give isocyanates and nitriles has been disclosed to date. See: Vita Finzi, P.; Arbasino, M. *Tetrahedron Lett.* **1965**, *6*, 4645–4646.

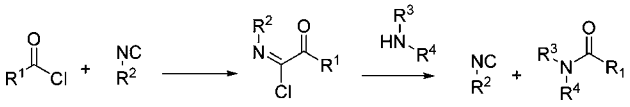
(8) (a) Johnson, J. E.; Carvallo, C.; Dolliver, D. D.; Sanchez, N.; Garza, V.; Cansexo, D. C.; Eggleton, G. L.; Fronczek, F. R. *Aust. J. Chem.* **2007**, *60*, 685–690. (b) Kunz, R. K.; Rumfelt, S.; Chen, N.; Zhang, D.; Tasker, A. S.; Bürli, R.; Hungate, R.; Yu, V.; Nguyen, Y.; Whittington, D. A.; Meagher, K. L.; Plant, M.; Tudor, Y.; Schrag, M.; Xu, Y.; Ng, G. Y.; Essa Hu, E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5115–5117. (c) Thipyapong, K.; Uehara, T.; Tooyama, Y.; Braband, H.; Alberto, R.; Arano, Y. *Inorg. Chem.* **2011**, *50*, 992–998. (d) Exner, O.; Motekov, N. *Collect. Czech. Chem. Commun.* **1982**, *47*, 814–827.

(9) It has been well established by Professor Hegarty that nitriulium species react with nucleophiles is a stereospecific way with the entering nucleophile and the lone pair trans from each other. See: Hegarty, A. F. *Acc. Chem. Res.* **1980**, *13*, 448–454.

the lack of geometrical isomerism pointing to a fast equilibrium between the two geometrical isomers.

Remarkably, the use of *syn*-chlorooximes makes it possible to overcome the lack of reactivity of the isocyanide–Nef adduct[11] with amines, owing to a higher reactivity of the carbonyl.[12,13] The *syn*-chlorooximes can therefore be considered *excellent surrogates* for acyl chlorides in the reaction with isocyanides (Scheme 5).

Scheme 5. Isocyanide Nef Reaction and Reaction between Imidoyl Chlorides and Amines



This novel multicomponent reaction was next examined. Different *syn*-chlorooximes (**1**, **14**–**18**), isocyanides (**10**, **19**–**22**), and amines (**8**, **23**–**29**) were chosen (Figure 3). *syn*-Chlorooximes were readily prepared by reacting oximes with *N*-chlorosuccinimide in DMF.[14] When R is an aryl group, *syn*-chlorooximes can be purified by column chromatography and stored at 4 °C over a long period of time without noticeable decomposition. On the other hand, aliphatic hydroximoyl chlorides are unstable and should be directly used. *E*/*Z* isomerism of the starting oximes is not relevant to the reaction outcome,[15] as it gets lost during the chlorination step, in accordance with previous reports.[16] Furthermore, precedent works indicated that only the *Z* geometrical isomer of hydroximoyl chloride is formed during the reaction.[17]

As shown in Figure 4, the reaction is quite general. Yields vary from 80% to 26%; this result depends on the purification step, since these compounds are extremely polar. The reaction was tolerant to primary, secondary and tertiary isocyanides, but failed with aromatic isocyanides. Indeed, reaction of phenylchlorooxime (**1**) with phenylisocyanide (**22**) and morpholine (**26**) only gave the adduct between the chlorooxime and the morpholine in 61% yield. This result is not surprising in the light of the reduced nucleophilicity of aromatic isocyanides.[18] Both primary and secondary amines were good partners for the reaction, and even aniline reacted, although in low yield. The presence of electron-withdrawing or electron-donating groups on the phenyl ring of arylchlorooximes does not seem to alter the course of the reaction.

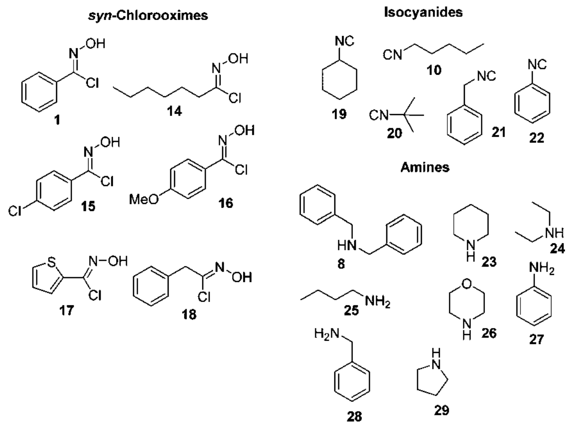


Figure 3. Building blocks.

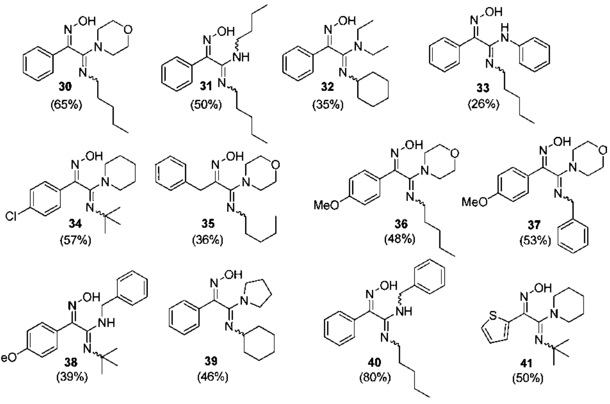


Figure 4. Synthesized *C*-oximinoamidines.

The structure and the stereochemistry of **30** was unambiguously established by a single-crystal X-ray diffraction analysis.

Figure 5 shows the molecular structure of **30**, disordered at C14 and C16 of the morpholine moiety. The two alternate conformations of the ring show a site occupancy of 75% and 25% for the *a* labeled atoms, respectively. Both imino groups show a *Z*-conformation in the solid

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(10) (a) Neilson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: New York, 1991; Vol. 2. (b) Komber, H.; Limbach, H. H.; Böhme, F.; Kunert, C. *J. Am. Chem. Soc.* **2002**, *124*, 11955–11963.

(11) Nef, J. U. *Justus Liebigs Ann. Chem.* **1892**, *270*, 267–335.

(12) (A) Ugi, I.; Beck, F.; Fetzer, U. *Ber.* **1962**, *95*, 126–135. (b) El Kaïm, L.; Grimaud, L.; Wagschal, S. *Synlett* **2009**, 1315–1317.

(13) *C*-Acylamidines have never been synthesized starting from α-keto imidoyl chlorides and amines.

(14) All the *syn*-chlorooximes were prepared according to this procedure: Liu, K. C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916–3918.

(15) All the oximes used are known compounds, and their stereochemistry was confirmed by comparison of their melting points, ^{1}H and ^{13}C NMR.

(16) Kanemasa, S.; Matsuda, H.; Kamimura, A.; Kakimani, T. *Tetrahedron* **2000**, *56*, 1057–1064.

(17) (a) Hegarty, A. F.; Mullane, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 995–1001. (b) Jeong, H. J.; Park, Y. D.; Park, H. Y.; Jeong, Y.; Jeong, T. S.; Lee, W, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5576–5579. (c) DeClercq, P. J.; Germain, G.; Van Meerssche, M. *Acta Cryst B* **1975**, *31*, 2894–2895.

(18) Mironov, M. A. General Aspects of Isocyanide Reactivity. In *Isocyanide Chemistry*; Nenajdenko, V. G., Ed.; Wiley-VCH: Weinheim, 2012; pp 35–73.

(19) Only three multistep methods for the synthesis of symmetrical *C*-acylamidines have been reported. See: (a) Seyferth, D.; Hui, R. C. *J. Org. Chem.* **1985**, *50*, 1985–1987. (b) Corriu, R. J. P.; Lanneau, G. F.; Perrot-Petta, M. *Synthesis* **1991**, 954–958. (c) Zhang, C.; Zhang, L.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 1293–1300.

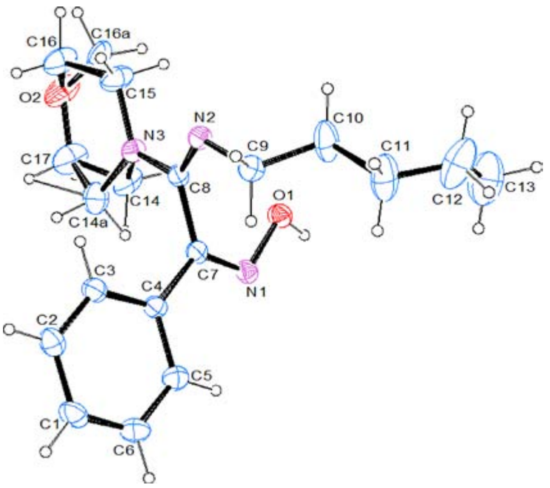

Figure 5. ORTEP[19] view of **30** and the relative arbitrary atom-numbering scheme (thermal ellipsoids at 40% probability).

state. The two rings are almost perpendicularly oriented, as shown by the N3−C8−C7−C4 are linked through strong hydrogen bond interactions between O1−H1a···N2, forming chains running in the *a* axis direction.

As described above, *C*-oximinoamidine are a novel class of previously unreported compounds, which could be used as starting materials for further elaborations taking advantage of the presence of the oxime.

In conclusion, we developed a novel multicomponent reaction that generates to α-oximinoamidines, a class of previously unreported compounds whose reactivity deserves further investigation.[19] An additional important advantage of this reaction is the synthesis of oximes of known configuration (*Z*). Furthermore, we pointed out the ease of reactivity between isocyanides and nitrile *N*-oxide species paving the way for the discovery of novel multicomponent transformations. Considerations of atom economy and practicability compensate for the moderate yields observed in some cases.

Acknowledgment. Financial support from Università del Piemonte Orientale is gratefully acknowledged. V.M. acknowledges a grant for the Lagrange Project−Crt Foundation.

Supporting Information Available. Experimental procedures and characterization data for all new compounds synthesized. X-ray data for **30** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.