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Cyanamide in isocyanide-based MCRs

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Dedicated to Ivar Ugi

Abstract—Cyanamide reacts with enamines and isocyanides in the presence of Lewis acids to give the hitherto unknown scaffold 2-amino-(*N*-cyano)-amidines. Preliminary scope and limitation of this novel reaction is described.

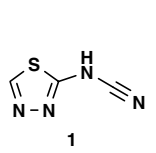
1. Introduction

Multicomponent processes are at a premium for the achievement of high levels of *diversity* and *brevity*, as they allow three or more simple and flexible building blocks to be combined in practical, one-pot operations. Due to their inherent *simple experimental procedures* and their one-pot character they are perfectly suited for *automated synthesis*. MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. The structure of the reaction product is easily diversified by systematic variation of each input. Moreover, the starting materials are either commercially available or easily prepared. Unlike the usual stepwise formation of individual bonds in the target molecule, the utmost attribute of MCRs is the inherent formation of several bonds in one operation without isolating the intermediates, changing the reaction conditions, or adding further reagents. It is obvious that the adoption of such strategies would allow minimization of both waste production and expenditure of human labor. Just pooling their collections of corresponding starting materials forms the products.[1]

The α-addition of nucleophiles and electrophiles onto the carbon of isocyanides followed by a rearrangement is generally known as the Ugi reaction.[2] More than 100 different scaffolds have been described in the past, based upon the U-MCR and a subsequent reaction.

Herein, we would like to report for the first time on the reaction of cyanamide in isocyanide-based MCRs yielding highly substituted *N*-cyanoamidines.[3]

N-Cyanoamidines are isosteric to α-aminoacids, show interesting biological activities and occur in several drugs and natural products. Thus Amitivir **1** show antiviral activity. Pinacidil **2** and similar compounds show anti-diabetes activity.[4]



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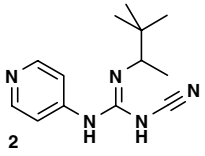

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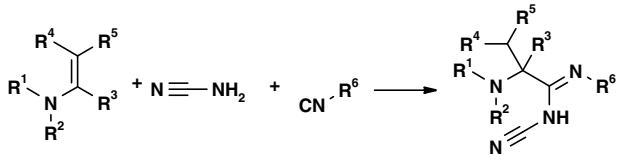
In the course of our investigations on new acid components (nucleophiles) in isocyanide-based MCRs we decided to look into the hitherto unknown reactivity of cyanamide (Scheme 1).



Scheme 1. The multicomponent reaction of cyanamide, isocyanides, and either enamines or Schiff bases yield α-amino-*N*-cyanoamidines.

Keywords: MCR; Ugi reaction; Cyanamide; Isocyanide; Combinatorial chemistry.

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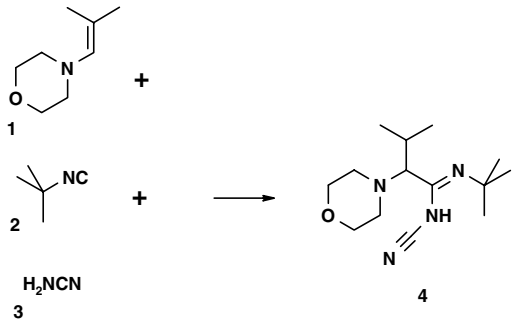
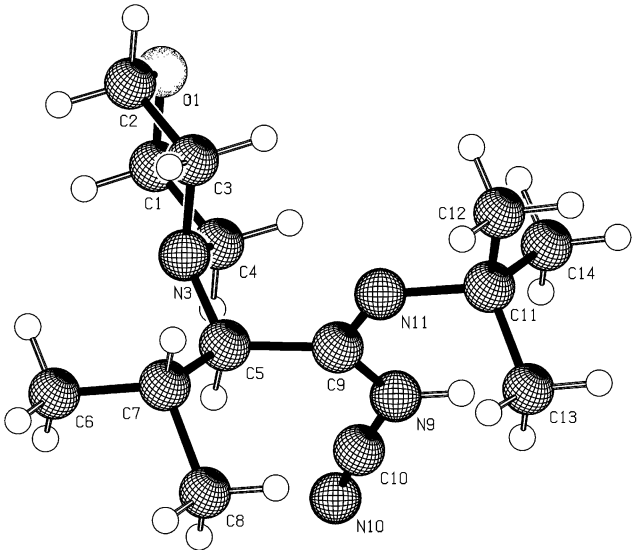


Scheme 2. Three-component reaction of cyanamide, an enamine, and an isocyanide.

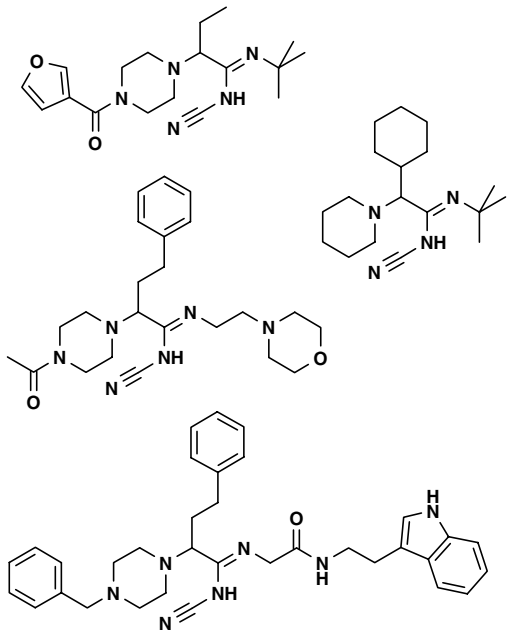
Thus, reacting cyanamide in a classical Ugi protocol, the three components enamine **1**, *tert*-butylisocyanide **2** and cyanamide **3** in 1 M concentration in methanol, at room temperature yielded **4** after chromatography in 65% yield (Scheme 2).[5]

For the unambiguous structural proof of the proposed unusual Ugi product a single crystal X-ray structure analysis of the product **4** was performed (Scheme 3).[6]

Subsequent studies have demonstrated the generality of this reaction. As part of our program to discover novel bioactive compounds we produced arrays of substituted α-amino-*N*-cyanoamidines by this novel MCR. These reactions were performed on a 0.02 mmol scale in a parallel format. Representative products are shown in Scheme 4.



Scheme 3. Pluton drawing of α-*N*-cyanoamidine **4** in the solid state. Selected bond length [Å] and angles [°]: O1–C1 1.423(11), O1–C2 1.407(9), N3–C3 1.441(7), N3–C4 1.433(8), N3–C5 1.452(7), N9–C9 1.307(6), N9–C10 1.321(6), N10–C10 1.138(7), N11–C9 1.340(6), N11–C11 1.479(8); C1–O1–C2 109.6(6), C3–N3–C4 109.2(5), C3–N3–C5 118.9(4), C4–N3–C5 112.5(5), C9–N9–C10 122.2(5), C9–N11–C11 126.1(4).



Scheme 4. Representative examples of a library of 2-amino-(*N*-cyano)-amidines.

2. Conclusion

In this letter, we describe a new MCR of cyanamide, isocyanides, and enamines yielding the medicinally important scaffold α-amino-*N*-cyanoamidines. With final products containing three points of potential diversity and a facile and rapid protocol, access to thousands of diverse analogs of this physiologically important core is feasible. Further investigations in our laboratories are directed toward a solid phase variation of this reaction.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.032.

References and notes

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5. The following procedure was followed for the preparation of **4**: 1 mmol of each *tert*-butylisocyanide, cyanamide, and the precondensed enamine from morpholine and isobutyric aldehyde are stirred in 1 ml of methanol at 20 °C for 24 h. The solvent is evaporated and the residue is purified by silica gel chromatography (ethylacetate/hexane 1:1) to yield 173 mg of an off white powder (65%); MW $C_{14}H_{26}N_4O$ = 266.4; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.9 (d, 3H); 1.1 (d, 3H); 1.4 (s, 9H); 2.2 (m, 2H); 2.4 (m, 1H); 2.5 (m, 1H); 3.4 (d, 1H); 3.7 (m, 3H); 6.4 (s, br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4; 19.4; 27.3; 28.2; 51.3; 53.2; 66.9; 72.3; 116.8; 170.2. GC–MS (MAT 8200, CI-Mode, isobutene) = 267.1.
6. Experimental and analytical data are available in the Supplementary data.