

Aminoisocyanides in Multicomponent Reactions (MCRs): A Facile Synthesis of Substituted 3(5*H*)-Pyrrolin-2-ones via a Dimroth-type Rearrangement

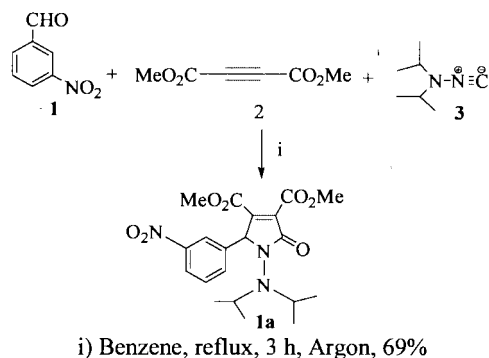
Vijay Nair,* Joseph Swaroop Mathen, A. Unni Vinod, and R. Luxmi Varma
Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum 695 019, India

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The 1,3-dipolar species generated from diisopropylaminoisocyanide and dimethyl acetylenedicarboxylate (DMAD) is trapped with aldehydes affording substituted 3(5*H*)-pyrrolin-2-ones presumably *via* a Dimroth-type rearrangement of the initially formed furanone hydrazones in good yields.

The recognition of the versatility of Ugi and Passerini reactions from the vantage point of synthesizing novel bioactive molecules has led to renewed interest in isocyanides.^{1–3} Although much is known about the chemistry of isocyanides, most of the available information is derived from the reactions of *C*-isocyanides; the *N*-isocyanides^{4–6} have remained largely unexplored, particularly in the context of multicomponent reactions (MCRs). In view of our recent interest in devising novel MCRs involving isocyanides, for the construction of heterocycles,^{7,8} we were curious about the outcome of such reactions using *N*-isocyanides. Therefore, we investigated the reaction of the zwitterionic intermediate generated from diisopropylaminoisocyanide and DMAD with aldehydes and the preliminary results form the subject matter of this letter.

In the first instance, we carried out the reaction of diisopropylaminoisocyanide⁵ and DMAD with 3-nitrobenzaldehyde in refluxing benzene under an inert atmosphere which afforded the substituted 3(5*H*)-pyrrolin-2-one derivative **1a**⁹ in 69% yield (Scheme 1). Presumably the product materializes by the Dimroth-type rearrangement¹⁰ of the initially formed furanone hydrazone.



Scheme 1.

The structure of the product was assigned on the basis of spectroscopic data. In the IR spectrum, the carbomethoxy group resonated at 1735 cm⁻¹ and the lactam carbonyl was observed at 1682 cm⁻¹. In the ¹H NMR spectrum, the methoxy protons resonated at δ 3.81 and δ 3.96. In the ¹³C NMR spectrum, the signals observed at δ 165.21 and 164.61 have been assigned to two ester carbonyls and the one at δ 163.93 is attributed to the lactam carbonyl group. All other signals were in good agreement with the assigned structure.

The spectroscopic data, however, cannot effectively distinguish between the primary adduct **1a'** and the Dimroth rearranged product **1a** (Figure 1). The structure of the adduct was established by ¹H–¹⁵N HMBC and NOE experiments on **1a**. In the ¹H NMR, H-5 and H-8 signals were observed at δ 7.32 (singlet) and δ 1.09 (doublet) respectively while the signal due to N-6 appeared at δ 132 in ¹⁵N NMR. In the HMBC experiment, N-6 couples with both H-5 and H-8 (³J_{H–N} = 100 Hz, ³J_{H–N} = 10 Hz respectively) (Figure 2). Also strong ¹H–¹H NOE was observed between H-5 and H-7 further confirming the identity of the product.

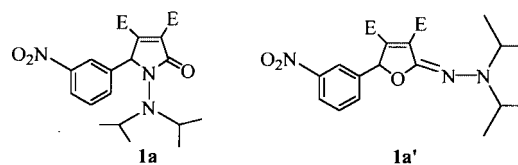


Figure 1.

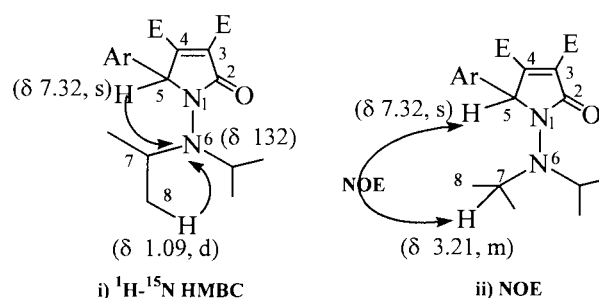


Figure 2: Selected data from NMR analysis of **1a**.

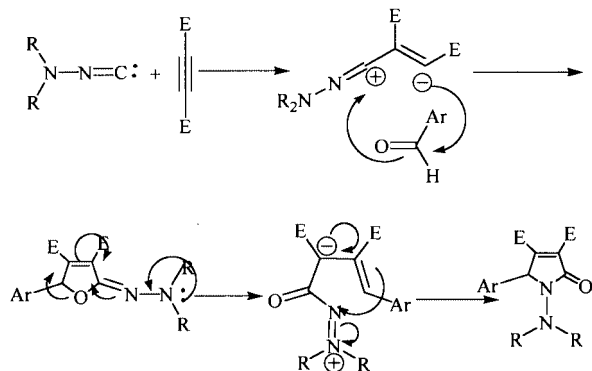
The reaction has been found to be general with other aldehydes and the results are summarized in Table 1.¹¹

Table 1.

Sl. No.		Time /h		Yield /%
1	R ₁ =R ₂ =H; R ₃ =NO ₂	3	R ₁ =R ₂ =H; R ₃ =NO ₂	65
2	R ₂ =R ₃ =H; R ₁ =NO ₂	3	R ₂ =R ₃ =H; R ₁ =NO ₂	68
3	R ₁ =R ₂ =H; R ₃ =Cl	2	R ₁ =R ₂ =H; R ₃ =Cl	55
4	R ₂ =R ₃ =H; R ₁ =Cl	2.5	R ₂ =R ₃ =H; R ₁ =Cl	57
5	R ₁ =R ₂ =H; R ₃ =Me	3	R ₁ =R ₂ =H; R ₃ =Me	52
6	R ₂ =R ₃ =H; R ₁ =Me	3	R ₂ =R ₃ =H; R ₁ =Me	54
7	R ₁ =R ₂ =H; R ₃ =CF ₃	3.5	R ₁ =R ₂ =H; R ₃ =CF ₃	79

^aIsolated yield, E = CO₂Me.

A rationalization for the formation of the 3(5*H*)-pyrrolin-2-one is given in Scheme 2. The initially formed furanone hydrazone undergoes a Dimroth-type rearrangement to give the pyrrolinone.



Scheme 2.

In conclusion, we have found that aminoisocyanide participates in a facile MCR with DMAD and aldehydes leading to an efficient synthesis of 3,4,5-trisubstituted-3(5*H*)-pyrrolin-2-ones.

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References and Notes

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- 9 Experimental procedure and data for **1a**: To a well-stirred solution of 3-nitrobenzaldehyde (0.030 g, 0.2 mmol) and DMAD (0.031 g, 0.027 mL, 0.22 mmol, 1.1 equiv) in refluxing benzene (1 mL) under an atmosphere of argon was added diisopropylaminoisocyanide (0.037 g, 0.3 mmol, 1.5 equiv). The solution was refluxed for 3 h. Then the reaction mixture was subjected to chromatography on Chromatotron[®] and the product was separated with 5% EtOAc in hexane as the eluent in 69% yield. Yellow solid. Mp. 115–117 °C. IR(CCl₄) ν_{max} , cm⁻¹: 2976, 1735, 1682, 1613, 1529, 1465, 1354, 1249, 1222, 1096. ^1H NMR (CDCl₃, 300 MHz) δ 1.09 (d, J = 6.18 Hz, 12 H); 3.21 (m, 2H); 3.81 (s, 3H); 3.96 (s, 3H); 7.32 (s, 1H); 7.52 (t, J = 7.92 Hz, 1H); 7.86 (d, J = 7.62 Hz, 1H); 8.06 (d, J = 7.75 Hz, 1H); 8.38 (s, 1H). ^{13}C NMR (CDCl₃, 75 MHz) δ 19.00, 51.45, 52.85, 87.82, 115.72, 119.43, 121.87, 129.7, 130.05, 130.83, 138.92, 148.61, 163.93, 164.61, 165.21. Anal. Calcd for C₂₀H₂₅N₃O₇: C, 57.28; H, 5.97; N, 10.02. Found: C, 57.39; H, 5.99; N, 10.10.
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- 11 All new compounds have been fully characterized.