

The reaction of cyclohexyl isocyanide and dimethyl acetylenedicarboxylate with aldehydes: a novel synthesis of 2-aminofuran derivatives

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The 1:1 intermediate generated by the addition of cyclohexyl isocyanide to dimethyl acetylenedicarboxylate is trapped by aldehydes to yield 2-aminofuran derivatives in good yields.

The addition of nucleophilic carbenes such as isocyanides to dimethyl acetylenedicarboxylate has been investigated in detail.^{1–3} The initially formed 1:1 zwitterionic species undergo further reaction with DMAD and isocyanide in different molar proportions, ultimately leading to a variety of complex heterocyclic systems.^{4–9} This highly reactive intermediate **1** can manifest carbanion or carbene character or even resemble a cyclopropanone imine (Fig. 1).

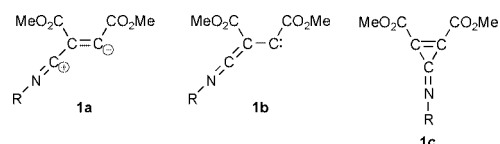
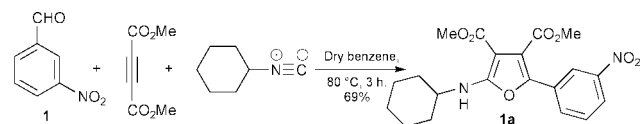


Fig. 1

In the context of our general interest in the synthesis of heterocyclic compounds by the reaction of dipolar species with carbonyl compounds,^{10,11} we were intrigued by the possibility of trapping the zwitterionic intermediate† derived from isocyanides and DMAD with aldehydes. It is noteworthy that previous attempts to trap **1** with various olefinic dipolarophiles have failed.⁶ The preliminary results of our investigations validating the usefulness of this process, leading to a novel aminofuran synthesis are presented here.

A mixture of 3-nitrobenzaldehyde and dimethyl acetylenedicarboxylate in dry benzene at 80 °C, when treated with cyclohexyl isocyanide afforded aminofuran **1a** in 69% yield (Scheme 1).‡



Scheme 1

In the ¹H NMR spectrum, the two carbomethoxy groups were observed at δ 3.79 and 3.94 as two singlets and the NH proton resonated at δ 6.70 supporting the IR absorption at 3367 cm⁻¹. The ¹³C signals for the two ester carbonyls were seen at δ 165.20 and 164.62.

Similar results were obtained with a number of other aldehydes and results are summarised in Table 1.§

A mechanistic rationale for the formation of the aminofurans is presented in Scheme 2.

In conclusion, we have found that the one pot reaction of isocyanides and DMAD with aldehydes leads to a facile synthesis of aminofuran derivatives. It should be mentioned that

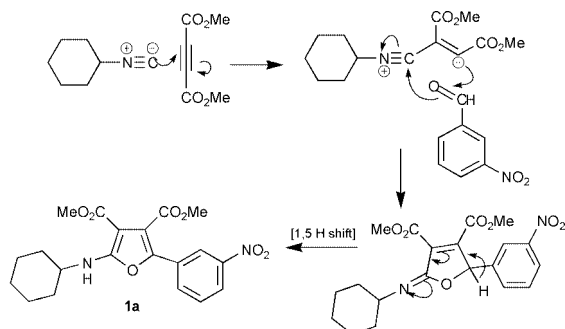
recently aminofurans have been found to undergo facile Diels–Alder reactions leading to hexahydroindolinones;¹² they also serve as useful intermediates in the synthesis of aromatic as well as aliphatic molecules.¹³ It is conceivable that the novel three component reaction described herein will be applicable to the synthesis of a variety of heterocycles; further studies are in progress.

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Table 1 Reaction of aldehydes with DMAD and cyclohexyl isocyanide

Entry	Aldehyde	t/h	Product	Yield(%) ^a
2		8		61
3		8		54
4		3		68
5		2		61
6		2.5		67
7		3		68

^aIsolated yield.



Scheme 2

Notes and references

† Earlier we reported on the addition of the zwitterion generated from triphenylphosphine and DMAD to quinones leading to novel γ -spiro-lactones.¹⁴

‡ *Experimental procedure and selected data for 1a*: a mixture of 3-nitrobenzaldehyde **1** (0.200 g, 1.32 mmol) and DMAD (0.207 g 1.45 mmol) in dry benzene (15 ml) was purged with argon at 80 °C. Cyclohexyl isocyanide¹⁵ (0.159 g, 1.45 mmol) was added to this mixture by syringe and refluxing was continued for a further 3 h. The solvent was then removed under vacuum and the residue on chromatographic separation on silica gel using hexane–ethyl acetate (85:15) gave aminofuran **1a** as a yellow solid (0.365 g, 69%); mp 122–123 °C (CH₂Cl₂–hexane) (Calc. for C₂₀H₂₂N₂O₇: C, 59.68; H, 5.51; N, 6.96. Found: C, 59.62; H, 5.47; N, 6.71%); ν_{\max} /cm⁻¹ 3367 (NH), 2943, 2849, 1726 (C=O), 1663 (C=O), 1620, 1532; δ_{H} (300 MHz, CDCl₃) 8.33 (s, 1H, ArH), 8.06 (d, 1H, *J* 8.05 Hz, ArH), 7.80 (d, 1H, *J* 7.71 Hz, ArH), 7.51 (t, 1H, ArH), 6.70 (d, 1H, *J* 7.80 Hz, NH), 3.94 (s, 3H,

OMe), 3.79 (s, 3H, OMe), 3.79 (m, 1H, CH), 2.07–1.39 (m, 10H, 5 × CH₂); δ_{C} (75 MHz; CDCl₃) 165.20 (C=O), 164.62 (C=O), 161.51, 148.79, 138.32, 130.95, 129.75, 129.71, 121.73, 119.21, 116.34, 88.23, 52.84, 51.70, 51.34, 33.59, 25.53, 24.58.

§ All new compounds were fully characterised.

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