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Reaction between Alkyl Isocyanides and Dimethyl Acetylenedicarboxylate in Presence of *N,N′*-Dimethylbarbituric Acid. A Convenient Route to Highly Functionalized 4*H*-Pyrano[3,2-*d*]pyrimidine Derivatives†

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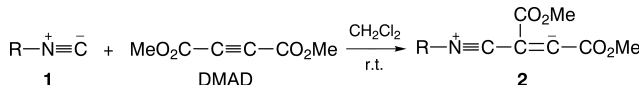
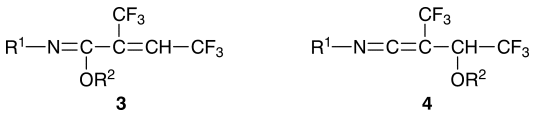
The highly reactive 1:1 intermediate produced in the reaction between alkyl isocyanides and dimethyl acetylenedicarboxylate is trapped by *N,N′*-dimethylbarbituric acid to yield 4*H*-pyrano[3,2-*d*]pyrimidine derivatives in fairly high yields.

The reaction of isocyanides **1** with carbon-centered triple bonds tends to occur in a stepwise manner through a zwitterionic intermediate the ultimate fate of which appears to be dictated by the nature of the original triple-bonded substrate.[1–4] In the case of electron-deficient acetylenic esters, such as dimethyl acetylenedicarboxylate (DMAD), it is reasonable to assume the prior formation of a 1:1 intermediate **2** which possesses predominantly carbanionic character.

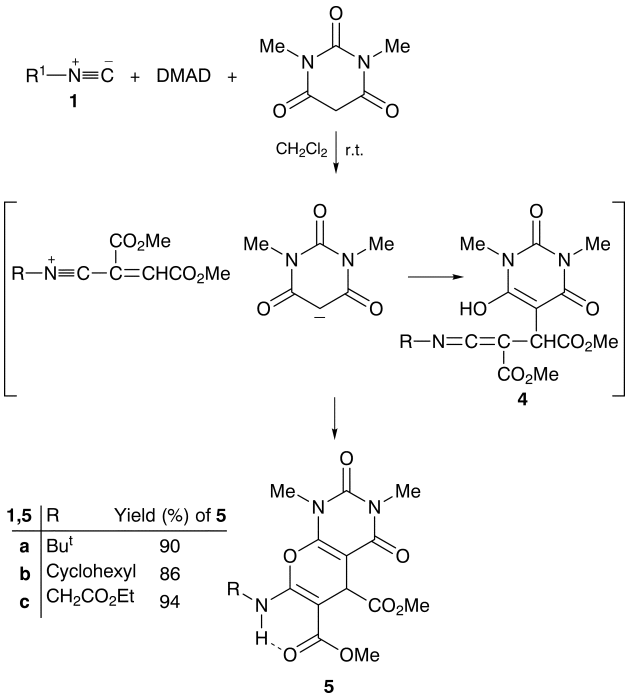


In order to confirm the presence of the highly reactive intermediate **2**, the reaction was carried out in various olefins as solvent, but produced the same products as obtained in the absence of olefin.[5] However, the existence of the 1:1 intermediate was indicated by the isolation of two different 1:1:1 adducts, *viz*. an amino ester **3** and a ketenimine **4**, from the reaction mixture of an isocyanide with hexafluorobut-2-yne in the presence of an alcohol.[5]



The work reported here was undertaken in order to study the possibility of trapping the reactive 1:1 intermediate **2** using a strong CH acid such as *N,N′*-dimethylbarbituric acid. Thus, alkyl isocyanides **1** and DAMD in the presence of *N,N′*-dimethylbarbituric acid undergo a smooth 1:1:1 addition reaction in dichloromethane at room temperature to produce the hitherto unknown 4*H*-pyrano[3,2-*d*]-pyrimidines **5a**–**c**. On the basis of the well established chemistry of isocyanides[1–4] it is reasonable to assume that compounds **5** result from initial addition of the alkyl isocyanides to the acetylenic ester and concomitant protonation of the 1:1 adduct by *N,N′*-dimethylbarbituric acid. Then, the positively charged ion is attacked by the enolate anion of the CH acid to form ketenimines **4**. Such addition products apparently isomerize, under the reaction conditions, to produce the fused heterocyclic system **5** (see Scheme 1).

Structure **5** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, ^{13}C NMR and mass spectral data. IR was used to distinguish it from the primary product, the ketenimine derivative **4**. The mass spectra of 4*H*-pyrano[3,2-*d*]pyrimidine **5a**–**c** are similar, as



1,5	R	Yield (%) of 5
a	Bu^t	90
b	Cyclohexyl	86
c	CH_2CO_2Et	94

Scheme 1

expected, and confirm their molecular weights. Initial fragmentations involve loss of the side chains and scission of the 4*H*-pyrano ring system.

The ^{1}H NMR spectrum of compound **5a** exhibited six single sharp lines, readily recognizable as arising from *tert*-butyl (δ 1.52), *N*-methyl (δ 3.40 and 3.58), methoxy (δ 3.78 and 3.82) and methine (δ 4.62) protons, along with a fairly broad band for the NH group at δ 9.0, indicating extensive intramolecular hydrogen bond formation with the vicinal carbonyl group.[6] The ^{13}C NMR spectrum showed fifteen distinct resonances consistent with the 4*H*-pyrano[3,2-*d*]-pyrimidine structure. Partial assignments of these resonances are given in Table 1. The ^{1}H and ^{13}C NMR spectra of **5b** and **5c** are similar to those of **5a**, except for the isocyanide residues, which displayed characteristic resonances with appropriate chemical shifts (see Table 1).

The structural assignments of compounds **5a**–**c** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the strong carbonyl absorption bands at 1688–1730 cm^{-1} for all compounds and a fairly broad NH peak at about 3216–3255 cm^{-1} for alkylamino groups (see Experimental section).

In summary, the reaction of alkyl isocyanides with electron-deficient acetylenic esters, such as DMAD, in the presence of *N,N′*-dimethylbarbituric acid provides a simple

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Table 1 Proton and carbon-13 NMR data for compounds **5a–c**

Compound	δ ($CDCl_3$–Me_4Si)	
5a	^1H	1.52 (9 H, s, CMe_3), 3.40 and 3.58 (6 H, 2 s, 2 NMe), 3.78 and 3.82 (6 H, 2 s, 2 OMe), 4.62 (1 H, s, CH), 9.0 (1 H, br s, N—H···O═C)
	^{13}C	27.27 and 29.75 (2 NMe), 29.89 (CMe_3), 34.98 (CH), 50.82 and 51.92 (2 OCH_3), 52.32 ($^{13}CMe_3$), 73.50 and 87.83 (2 ^{13}C═C—O), 149.77 and 151.11 (2 C═^{13}C—O), 158.52, 160.60, 168.83 and 173.39 (4 C═O)
5b	^1H	1.1–2.1 (10 H, m, 5 CH_2), 3.27 (1 H, m, CHN), 3.35 and 3.48 (6 H, 2 s, 2 NMe), 3.70 and 3.80 (6 H, 2 s, 2 OMe), 4.60 (1 H, s, CH), 8.7 (1 H, br d, $^3J_{HH}$ 7.0 Hz, N—H···O═C)
	^{13}C	24.36, 24.39, 25.33, 33.42 and 33.72 (5 CH_2), 28.26 and 29.08 (2 NMe), 35.59 (CH), 50.90 (N—CH), 51.27 and 52.49 (2 OMe), 73.05 and 88.36 (2 ^{13}C═C—O), 150.30 and 151.56 (2 C═^{13}C—O), 157.87, 161.17, 169.15 and 173.96 (4 C═O)
5c	^1H	1.32 (3 H, t, $^3J_{HH}$ 7.2, CH_3), 3.35 and 3.43 (6 H, 2 s, 2 NMe), 3.72 and 3.78 (6 H, 2 s, 2 OMe), 4.12 (2 H, complex ABX system, NCH_2), 4.26 (2 H, q, $^3J_{HH}$ 7.2, OCH_2), 4.64 (1 H, s, CH), 8.9 (1 H, br t, $^3J_{HH}$ 6 Hz, N—H···O═C)
	^{13}C	14.23 (CH_3), 28.38 and 29.03 (2 NMe), 35.63 (CH), 43.29 (NCH_2), 51.59 and 52.65 (2 OMe), 61.94 (OCH_2), 75.68 and 88.49 (2 ^{13}C═C—O), 150.26, 151.36 (2 C═^{13}C—O), 157.79, 161.09, 168.84, 168.88 and 173.59 (5 C═O)

one-pot entry into the synthesis of polyfunctional 4*H*-pyrano[3,2-*d*]pyrimidines of potential synthetic interest. Further investigations of the present method will be required to establish its utility and scope.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer, ^1H and ^{13}C NMR spectra with a JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively, and mass spectra on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides **1**, dimethyl acetylenedicarboxylate and *N,N′*-dimethylbarbituric acid were obtained from Fluka (Buchs, Switzerland) and used without further purification.

The preparation of *dimethyl* 7-tert-*butylamino*-1,3-*dimethyl*-2,4-*dioxo*-4H-*pyrano*[3,2-d]*pyrimidine*-5,6-*dicarboxylate* **5a** is described as an example. To a magnetically stirred solution of *N,N′*-dimethylbarbituric acid (0.156 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in CH_2Cl_2 (6 ml) was added, dropwise, a mixture of *tert*-butyl isocyanide (0.083 g, 1 mmol) in CH_2Cl_2 (2 ml) at −10 °C over 10 min. The mixture was allowed to warm to room temperature and stand for a week. The solvent was removed under reduced pressure and the solid residue washed with cold diethyl ether (2 × 3 ml) and the product **5a** was obtained as a pale yellow powder, yield 0.34 g (90%). IR (KBr): $\tilde{\nu}_{max}/cm^{-1}$ 3216 (N—H); 1693, 1720 (C═O) MS (*m/z*, %): 383 ($M^+ + 1$, 10); 323 ($M^+ - CO_2Me$, 85), 266 ($M^+ - C_6H_{11}O_2$, 100), 234 ($M^+ - C_8H_{19}O_2$, 80), 177 ($M^+ - C_{10}H_{20}O_4$, 37); 57 ($M^+C_{13}H_{14}O_7N_3$, 77) (Found: C, 53.3; H, 6.0; N, 11.0. $C_{17}H_{23}N_3O_7$ requires C, 53.54; H, 6.03; N, 11.02%).

Selected data for **5b**: pale yellow powder, mp 208–209 °C, yield 0.35 g (86%); IR (KBr) $\tilde{\nu}_{max}/cm^{-1}$ 3240 (N—H), 1720, 1688 (C═O); MS (*m/z*, %) 309 ($M^+ + 1$, 7), 349 ($M^+ - CO_2Me$, 90), 266 ($M^+ - C_8H_{13}O_2$, 47), 234 ($M^+ - C_{10}H_{21}O_2$, 100), 177 ($M^+ - C_{12}H_{22}O_4$, 43) (Found: C, 56.0; H, 6.1; N, 10.4. $C_{19}H_{25}N_3O_7$ requires C, 56.0; H, 6.14; N, 10.3%).

Selected data for **5c**: pale yellow powder, mp 210–211 °C, yield 0.38 g (94%); IR (KBr) $\tilde{\nu}_{max}/cm^{-1}$ 3255 (N—H), 1730, 1698 (C═O); MS (*m/z*, %) 413 ($M^+ + 1$, 8), 353 ($M^+ - CO_2Me$, 100), 341 ($M^+ - C_3H_3O_2$, 23), 235 ($M^+ - C_8H_{16}O_4$, 25), 66 ($M^+ - C_{14}H_{21}O_9N_2$, 28) (Found: C, 49.5; H, 5.1; N, 10.3. $C_{17}H_{21}O_9$ requires C, 49.63; H, 5.11; N, 10.22%).

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References

1 I. Ugi, *Isonitrile Chemistry*, Academic Press, London, 1971.
2 I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 810.
3 H. M. Walborsky and M. P. Persiasamy, in *The Chemistry of Functional Groups, Supplement C*, ed. S. Patai and Z. Rappopors, Wiley, New York, 1983, ch. 20, pp. 835–887.
4 S. Marcaccini and T. Torroba, *Org. Prep. Proced. Int.*, 1993, **25**, 141.
5 T. R. Oakes and D. J. Donovan, *J. Org. Chem.*, 1973, **38**, 1319.
6 R. Huisgen, K. Herbig, A. Siegl and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.