A simple synthesis of enaminones from reaction between isocyanides and cyclic 1,3-dicarbonyl compounds

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Polarised olfinic systems are synthesised from the reaction between alkyl or aryl isocyanides and cyclic 1, 3-dicarbonyl compounds such as thiobarbituric acid, 5,5-dimethylcyclohexane-1,3-dione and cyclopentane-1,3-dione in good yield.

Keywords: enaminones, isocyanides, pyrimidinones, 1,3-dicarbonyl compounds, pull–push olefins

The most usual reactivity observed in isocyanides is reaction of the functional group with acidic reactants.[1-4] A general feature of isocyanide reactions is the formation of α,α-addition reaction products: *i.e.* two new bonds are formed to the terminal isocyanide carbon atom.[5-11] Typical examples are the reaction of isocyanide with protonic acids.[1,2] We report here that CH-acids such as cyclopentane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione (dimedone) and thiobarbituric acid react with alkyl or aryl isocyanides **1** producing 1 : 1 adducts. This two-component reaction produces the enaminones **3a**–**g**. Enaminones are a group of organic compounds containing the conjugated system N–C=C-C=O formed between a primary amine and 1,3-dicarbonyl compound. It may act as a pro-drug, releasing a primary amine that may be an actual drug,[12-14] *via* proton-catalysed hydrolysis. Enaminones[15] have recently been recognised by several co-workers as compounds of interesting pharmacological activities.[16,17] Enaminones are of interest as synthetic intermediates for the preparation of a large number of heterocyclic compounds such as aziridines and pyrroles.[18,29]

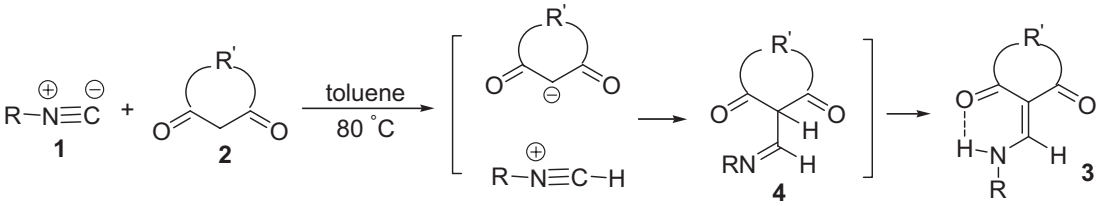
Previous reports of the preparation of enaminones analogous to those reported here have involved fusing the CH acid analogue with formanilide or its derivatives,[30,31] and the three-component condensation of dimethylbarbituric acid, trimethyl orthoformate, and aniline.[32] In this work, we reported a facile synthesis for enaminones.

Results and discussion

Synthesis compounds may be formulated as having been derived from initial α,α-addition of CH-acids to the isocyanide and subsequent proton transfer reaction to produce the polarised olefinic systems **3a**–**g**. The reactions proceed in fairly high yields.

All the products **3** are stable crystalline solids whose structures are fully supported by elemental analyses and IR, ^{1}H, ^{13}C NMR and mass spectral data. The mass spectra of these 1 : 1 adduct displayed molecular ion peaks at the appropriate *m/z* values.

The ^{1}H NMR spectrum of 2-(benzylaminomethylene)-3,3-dimethylcyclohexane-1,3-dione **3a** exhibited three sharp singlets, readily recognisable as arising from the C*Me*$_2$ (δ 1.06) and two C*H*$_2$ (δ 2.34 and 2.37) protons, along with a multiplet (δ 7.23–7.48) for the aromatic protons. *H*N–C*H*$_2$ moiety showed an AX$_2$ spin system (δ_{NH} 11.36, δ_{CH2} 4.57 ^3J = 6.1) and *H*C–NH moiety showed an AX spin system (δ_{CH} 8.25, δ_{NH} 11.38 ^3J = 13.4). The ^{13}C NMR spectrum showed 13 distinct resonances consistent with the structure **3a**. Partial assignments of these resonances are given in the experimental section. The structural assignments of compounds **3a**–**g** made on the basis of their ^{1}H and ^{13}C NMR spectra which are supported by their IR spectra. Of special interest are the strong carbonyl absorption bands at 1705–1662 cm^{-1} for all



3	R	R'	Yield (%)
a	benzyl	-CH_2-C(Me)$_2$-CH_2-	95
b	*tert*-butyl	-CH_2-C(Me)$_2$-CH_2-	90
c	cyclohexyl	-CH_2-C(Me)$_2$-CH_2-	92
d	cyclohexyl	-CH_2-CH_2-	95
e	cyclohexyl	-NH-CS- NH-	75
f	*tert*-butyl	-NH-CS- NH-	80
g	2,6-dimethylphenyl	-NH-CS- NH-	85

Scheme 1

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compounds and a fairly broad NH peak at about 3440 cm^{-1} for amino groups (see experimental).

We have not established the mechanism of the reaction between isocyanides and 1,3-dicarbonyl compound, however, a possible explanation is illustrated in Scheme 1. On the basis of the well established chemistry of isocyanides,[1-4] it is reasonable to assume that compound **3** results from initial protonation of the isocyanide carbon atom by the CH-acid. The positively charged ion is then attacked by the enolate anion of the CH-acid to produce the α,α-addition product **4**. Such addition product tautomerises under reaction conditions to produce the enaminone **3** (see Scheme 1).

In summary, the reaction between alkyl or aryl isocyanides and 1,3-dicarbonyl compounds provides a simple one-pot entry into the synthesis of poly functional enaminone derivatives of potential synthetic interest.

Experimental

Thiobarbituric acid, dimedone and cyclopentane-1,3-dione, *tert*-butyl, cyclohexyl, benzyl and 2,6-dimethylphenyl isocyanides were purchased from Merck and Fluka, respectively, and used without further purification. Melting points were taken on an Electrothermal 9100 apparatus and IR spectra of all compounds were run on a Shimadzu IR-470 spectrometer. The ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 and 75.5 MHz, respectively. Elemental analyses for C, H and N using a Heraeus CHN–O–Rapid analyser. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionisation potential of 70 eV.

General procedure (*exemplified by* **3a**)
To a magnetically stirred solution of 5,5-dimethylcyclohexane-1,3-dione (1 mmol) in toluene 10 ml was added, dropwise a solution of benzyl isocyanide (1 mmol) in toluene 3 ml at –5°C over 10 min. The reaction mixture then kept for 48 hours at 80°C. The solvent was removed under reduced pressure and the solid residue was washed with cold diethyl ether (2 × 5 ml).

2-(Benzylaminomethylene)-5,5-dimethylcyclohexane-1,3-dione (**3a**): Light brown powder; yield (95%), m.p. 118–120°C, IR (KBr) (υ_{max}, cm^{-1}): 3407 (N–H), 1665 (C=O) and 1583 (C=C). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.05 (6 H, s, 2 CH_3), 2.34, 2.37 (4 H, 2 s, 2 CH_2), 4.57 (2 H, d, ^3J = 6.1 Hz, CH_2), 7.23–7.48 (5 H, m, C_6H_5), 8.25 (1 H, d, ^3J = 13.4 Hz, C*H*–NH), 11.36 (1 H, br, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 27.53 (2 *C*H_3), 30.15 (*C*Me_2), 50.04 and 50.37 (2 *C*H_2), 53.16 (*C*H_2NH), 106.67 (CO–*C*–CO), 126.53 (2 *C*H), 127.48 (*C*H), 128.11 (2 *C*H), 134.27 (C_{ipso}), 157.31(N–*C*H), 195.34 and 198.31 (2 C=O). MS (*m/z*, %): 258 (M^+ + 1, 20), 257 (M^+, 100), 242 (8), 240 (13), 214 (3), 173 (20), 166 (27), 91 (88), 55 (14). Anal. Calcd for $C_{16}H_{19}NO_2$ (257.14): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.81; H, 7.45; N, 5.60.

2-(tert-Butylaminomethylene)-5,5-dimethylcyclohexane-1,3-dione (**3b**): Light orange powder; yield (90%), m.p. 73–75°C, IR (KBr) (υ_{max}, cm^{-1}): 3415 (N–H), 1663 (C=O) and 1467 (C=C). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.10 (6 H, s, 2 CH_3), 1.42 (9 H, s, CMe_3), 2.38 (4 H, 2 s, 2 CH_2), 8.25 (1 H, d, ^3J = 14.5 Hz, C*H*–NH), 11.55 (1 H, br, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 28.25 (CMe_3), 30.94 (*C*Me_2), 54.13 and 57.30 (2 *C*H_2), 67.97 (*C*–NH), 103 (CO–*C*–CO), 157.25 (N–*C*H), 191.22 and 203.68 (2 C=O). MS (*m/z*, %): 223 (M^+, 14), 208 (12), 193 (13), 166 (38), 140 (11), 83 (100), 58 (86), 57 (50). Anal. Calcd for $C_{13}H_{21}NO_2$ (223.16): C, 69.92; H, 9.48; N, 6.27. Found: C, 70.08; H, 9.53; N, 6.32.

2-(Cyclohexylaminomethylene)-5,5-dimethylcyclohexane-1,3-dione (**3c**): Pale white powder; yield (92%), m.p. 175–177°C, IR (KBr) (υ_{max}, cm^{-1}): 3415 (N–H), 1665 (C=O) and 1581 (C=C). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.07 (6 H, s, 2 CH_3), 1.12–2.00 (10 H, m, 5 CH_2), 2.36 (4 H, s, 2 CH_2), 3.31 (1 H, m, C*H*–N), 8.20 (1 H, d, ^3J = 14.3 Hz, *H*C–NH), 11.22 (1 H, br, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 24.26, 24.93 and 28.23 (3 *C*H_2 of cyclohexyl), 28.55 (2 *C*H_3), 31.19 and 33.38 (2 *C*H_2 cyclohexyl), 31.19 (*C*Me_2), 51.01 and 51.37 (2 *C*H_2), 58.85 (*C*HNH), 107.15 (CO–*C*–CO), 156.33 (*C*H–NH), 196.29 and 198.97 (2 C=O). MS (*m/z*, %): 250 (M^+ + 1, 18), 249 (M^+, 100), 234 (13), 220 (8), 194 (7), 97 (79), 55 (73). Anal. Calcd for $C_{15}H_{23}NO_2$ (249.17): C, 72.25; H, 9.30; N, 5.62. Found: C, 72.32; H, 9.28; N, 5.69.

2-(Cyclohexylaminomethylene)cyclopentane-1,3-dione (**3d**): Pale brown powder, yield (95%), m.p. 125–127°C, IR (KBr) (υ_{max}, cm^{-1}): 3414 (N–H), 1617 and 1697 (C=O), 1476(C=C). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.27–2.02 (10 H, m, 5 CH_2), 2.23 (4 H, s, 2 CH_2); 3.33 (1 H, m, C*H*N); 7.80 (1 H, d, ^3J = 14.3 Hz, *H*C–NH), 10.35 (1 H, br, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 24.23, 24.82, 33.15, 33.17, 33.18 (5 *C*H_2), 33.70 (2 *C*H_2), 58.74 (*C*HNH), 107.41(CO–*C*–CO), 152.63 (*C*H–N), 202.29 and 205.89 (2 C=O). MS (*m/z*, %): 208 (M^+ + 1, 13), 207 (M^+, 100), 192 (14), 178 (12), 164 (16). Anal. Calcd for $C_{12}H_{17}NO_2$ (207.13): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.67; H, 8.32; N, 6.82.

2-(Cyclohexylaminomethylene)thiobarbituric acid (**3e**): Light orange powder, yield (75%), m.p. 317–319°C, IR (KBr) (υ_{max}, cm^{-1}): 3418 (N–H), 3217 (2N–H), 1703 and 1648 (C=O), 1598 (C=C) and 1120 (C=S). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.20–2.20 (10 H, m, 5 CH_2), 3.50 (1 H, m, C*H*–NH), 8.22 (1 H, d, ^3J = 14.9 Hz, *H*C–NH), 8.77 (2 H, br, N*H*), 10.31 (1 H, br, N*H*). MS (*m/z*, %): 253 (M^+, 90), 210 (30), 157 (16), 111 (14), 97 (69), 55 (100). Anal. Calcd for $C_{11}H_{15}N_3O_2S$ (253.10): C, 52.15; H, 5.97; N, 16.59. Found: C, 52.24; H, 6.03; N, 16.57.

2-(tert-Butylaminomethylene)thiobarbituric acid (**3f**): Yelow powder, yield (80%), decomposed 238–240°C, IR (KBr) (υ_{max}, cm^{-1}): 3419 (N–H), 3109 (2 N–H), 1675 and 1682 (C=O), 1625(C=C) and 1150 (C=S). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.50 (9 H, s, CMe_3), 8.25 (1 H, d, ^2J = 15.1 Hz, *H*C–NH), 8.85 (2 H, br, N*H*), 10.60 (1 H, br, N*H*). MS (*m/z*, %): 227 (M^+, 3), 144 (100), 116 (48), 84 (9), 69 (47), 59 (54), 44 (16). Anal. Calcd for $C_9H_{13}N_3O_2S$ (227.07): C, 47.56; H, 5.77; N, 18.49. Found: C, 47.65; H, 5.68; N, 18.58.

2-(2,6-dimethyphenylaminomethylene)thiobarbituric acid (**3g**): Pale white powder, yield (85%), decomposed 157–159°C, IR (KBr) (υ_{max}, cm^{-1}): 3421 (N–H), 3108 (2 N–H), 1669 and 1680 (C=O), 1625 (C=C) and 1150 (C=S). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 2.29 and 2.33 (6 H, s, 2 CH_3-C); 7.10–7.23 (3 H, m, C_6H_3), 8.11 (1 H, d, ^2J = 14.25 Hz, C*H*N), 8.44 (2 H, br, N*H*), 10.43 (1 H, br, N*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 17.88 and 18.10 (6 H, 2 s, ArMe_2), 82.31 (CO–*C*–CO), 126.56, 127.47, 128.62, 131.9 and 134.67 (5 C, C_6H_3), 158.35 (*C*H–NH), 161.69 (C–NH and C=S), 174.76 and 179.77 (2 C=O). MS (*m/z*, %): 275 (M^+, 1), 144 (100), 116 (61), 84 (8), 69 (58), 59 (73), 44 (20). Anal. Calcd for $C_{13}H_{13}N_3O_2S$ (275.07): C, 56.71; H, 4.76; N, 15.26. Found: C, 56.78; H, 4.58; N, 15.33.

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