Synthesis and dynamic ^{13}C NMR study of new system containing polarised carbon–carbon double bonds from reaction between cyclohexyl isocyanide and ethyl propiolate in the presence of *N, N′*-dimethylbarbituric acid

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The adduct produced in the reaction between cyclohexyl isocyanide and ethyl acetylenecarboxylate was trapped by *N, N′*-dimethylbarbituric acid. Dynamic NMR effects were observed in the NMR spectra of these compounds and were attributed to restricted rotation around the alkyl-nitrogen single bonds and the polarised carbon–carbon double bond.

Keywords: enaminones, *N*, *N′*-dimethylbarbituric acid, hindered rotation, three-component reactions, dynamic NMR

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the point of combinatorial chemistry.[1,2] Pyrimidine derivatives have been employed in a wide range of medicinal chemistry because of their diverse biological activities, such as antibacterial[3,4] anticonvulsant[5] antiflammatry[6-8] antitumor[9-11] and antifungal activities.[12]

We have recently described the synthesis and dynamic NMR study [13, 14] of 4*H*-pyrano[3,2-*d*]pyrimidine (**1**) and enaminone (**2**) derivatives from the reaction of alkyl isocyanides[15] with dimethyl acetylenedicarboxylate (DMAD) and *N*, *N′*-dimethylbarbituric acid (Fig. 1).

Here, we wish to report the reaction of cyclohexyl isocyanide with ethyl acetylenecarboxylate and *N*, *N′*-dimethylbarbituric acid (Fig. 2).

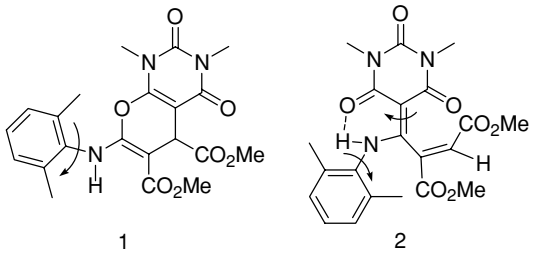

Fig. 1

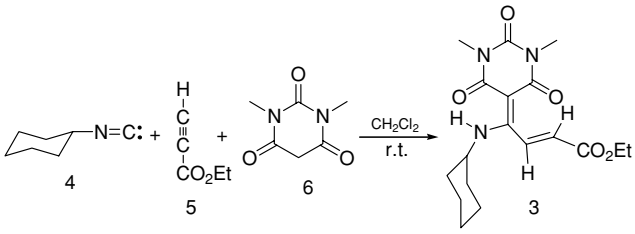

Fig. 2

Results and discussion

The reaction of cyclohexyl isocyanide **4** with electron-deficient acetylenic ester **5** in the presence of CH acids such as *N*, *N′*-dimethylbarbituric acid **6** proceeded at room temperature in dichloromethane and was completed after approximately 20 h. The structure of enaminone **3** were deduced from its elemental analysis and its IR, ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of **3** exhibits signals for the methyl group of the ester moiety (δ = 1.33 ppm), methylene groups of cyclohexyl (δ = 1.41–2.00 ppm), *N*-methyls (δ = 3.28 and 3.32 ppm),methine of cyclohexyl (δ =3.57 ppm), methylene of ester (δ = 4.30 ppm), vinylic protons at δ = 5.95 and 7.78 ppm and a broad peak for the NH group (δ =12.27 ppm). The complete data for compound **3** are given in the experimental section.

The ^{13}C NMR spectrum of **3** shows 16 sharp signals in agreement with the proposed structure. The presence of two separate signals for the *N*-Me groups in both the ^1H and ^{13}C NMR spectra of **3** can be explained in term of restricted rotation around the carbon–carbon double bond.

On the basis of the well established chemistry of isocyanides[15] it is reasonable to assume that **3** results from an initial addition of the cyclohexyl isocyanide to the acetylenic ester and subsequent protonation of 1:1 adduct by *N*, *N′*-dimethylbarbituric acid. Then the positively charged ion might be attacked by the enolate anion of the CH-acid which involves direct addition of the enolate anion to the positive ion, to produce the heterodiene **7**. This addition product undergoes an imine-to-enamine tautomerism to generate the enaminone system **3** (see Fig. 3).

The (*E*)-configuration of the carbon–carbon double bond in **3** is assigned tentatively and is based on the chemical shift and proton–proton coupling constant of the olefinic proton.[16–18] The ^{13}C NMR spectrum of **3** in $CDCl_3$ at 24.8 °C showed that the resonances arising from the *N*-Me groups are appreciably broadened in comparison with corresponding signals in the spectrum measured at 60 °C. The *N*-Me groups coalescence at 19 °C. From the coalescence of the *N*-Me groups resonances and using the expression $k = \pi\Delta\nu/\sqrt{2}$,[19] the first-order rate

Table 1 Selected carbon chemical shifts at 22.4 MHz, in ppm from Me_4Si and activation parameters (kJ mol^{-1}) for **3a**

Compound	Temp/°C	Resonance (N–*Me*)	Δν/Hz	k/s^{-1}	T_C/K	$\Delta G^{\neq}$/kJ mol^{-1}
3a	–50	27.77 27.44	7.46	16.57	292	64.5±2
	50	27.61				

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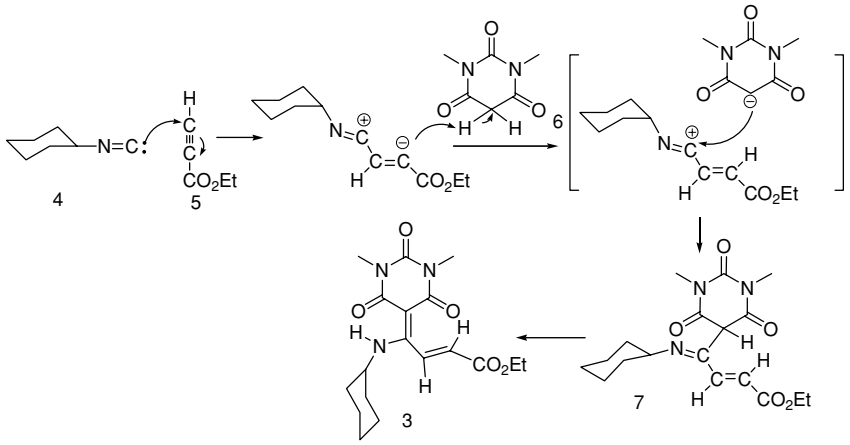

Fig. 3

constant (k=16.57 s^{-1}) for the carbon–carbon double bond rotation in **3** was calculated at 19 °C (see Table. 1).

Application of the absolute rate theory with a transmission coefficient of **3** gave a free-energy of activation ($\Delta G^{\neq}$) of 64.6±2 kJ mol^{-1}, where all known sources of errors were estimated and included.[20] The experimental data available were not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the error in $\Delta G^{\neq}$ as not large.[21] In conclusion, the three-component reaction of cyclohexyl isocyanide with electron-deficient acetylenic esters in the presence of CH-acids provides a simple synthesis of enaminones.

Experimental

Melting point and IR spectra were obtained on an Electrothermal 9100 apparatus and on a Shimadzu IR-460 spectrometer, respectively. Elemental analyses for C, H and N was performed using a Heraeus CHN-O-Rapid analyzer. The ^{1}H and ^{13}C NMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Cyclohexyl isocyanide, ethyl propiolate and *N, N'*-dimethylbarbituric acid were obtained from Fluka (Buchs, Switzerland) and used without further purification.

Preparation of ethyl (E)-4-cyclohexylamino-4-(1,3-dimethyl-2,4, 6-trioxohexahydropyrimidin-5-ylidene) but-2-enoate (**3**): To a magnetically stirred solution of *N, N'*-dimethylbarbituric acid (0.156 g, 1 mmol) and ethyl propiolate (0.1 g, 1mmol) in CH_2Cl_2 (6 ml) was added dropwise, a mixture of cyclohexyl isocyanide (0.11 g, 1 mmol) in CH_2Cl_2 (2 ml) at –10 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure, the solid residue was washed by cold diethyl ether (2×5 ml) and the product was obtained as pale yellow powder.

Pale yellow powder, m.p. 183–186 °C, yield: 0.27 g (75%). IR (KBr) (ν_{max}, cm^{-1}): 1711, 1687 and 1639 (C=O), 1608 (C=C). ^{1}H NMR (90 MHz, $CDCl_3$): δ_H 1.33 (3H, t, J=7.2 Hz, CH_3), 1.41–2.00 (10H, m. $5CH_2$), 3.28 and 3.32 (6H, 2 brs, $2NCH_3$), 3.57 (1H, m, N–CH), 4.30 (2H, q, J=7.2 Hz,), 5.95 (1H, d, J=14 Hz, CH), 7.78 (1H, d, J=14 Hz, CH), 12.27 (1H, brd, J=4.5 Hz, NH). ^{13}C NMR (22.6 MHz, $CDCl_3$): δ_C 14.05 (CH_3), 23.86 ($2CH_2$), 24.72 (CH_2), 24.48 and 27.81 ($2NCH_3$), 33.39 ($2CH_2$), 53.63 (N–CH), 61.32 (OCH_2), 89.99 (N–C=*C*), 122.28 and 138.24 (2CH), 151.32 (N–*C*=C), 162.23 (N–C=O), 164.88 (N–CO-N), 165.61 (N–C=O) and 166.55 (C=O, ester). Anal. Calcd for $C_{18}H_{25}N_3O_5$ (363.18): C, 59.5; H, 6.9; N, 11.6; found: C, 59.4; H, 7.3; N, 11.7%.

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