Preparation and Novel Cycloaddition Reactions of 7-Dimethylamino-1*H*-azepin-3(2*H*)-one

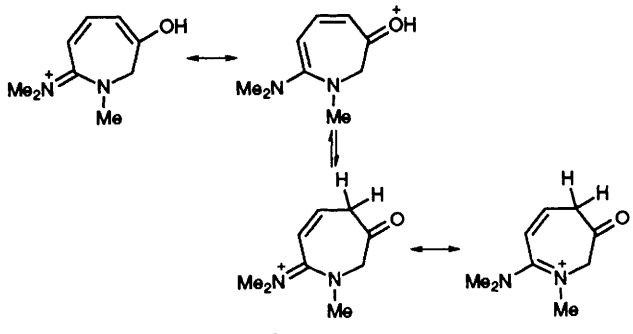
Elise Cartmell, James E. Mayo, Hamish McNab* and Ian H. Sadler

Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, UK EH9 3JJ

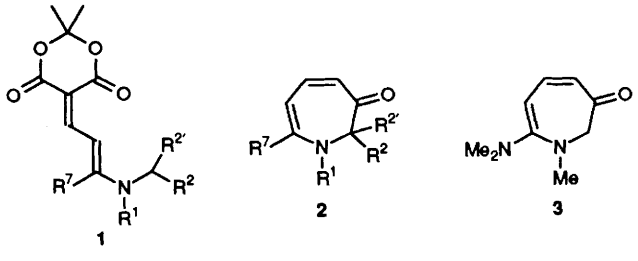
A convenient preparation of the functionalised azepinone **3** is reported: this compound reacts with acid to give a stable mixture of *O*- and *C*-protonated materials, it gives the substitution product **4** on reaction with methoxymethylene Meldrum's acid **5**, and on treatment with propiolic ester gives a 1,3,4-trisubstituted pyrrole **6** by a novel cycloaddition–condensation sequence.

We have shown previously that flash vacuum pyrolysis (FVP) of the Meldrum's acid derivatives **1** (R^7 = H) gives convenient access to a range of 1-substituted and 1,2-disubstituted 1*H*-azepin-3(2*H*)-ones **2** (R^7 = H), which were unobtainable by conventional methods,[1,2] and we have reported the typical reactions of this ring system.[3–6] We have now succeeded in substantially modifying the electron distribution in the conjugated system of these heterocycles, by the synthesis of **3**, which incorporates a strong electron-donating group at the 7-position, and report here some unexpected effects of this substituent on the properties of the ring system.

The key Meldrum's acid derivative **1** (R^1 = Me, R^2 = $R^{2'}$ = H, R^7 = Me_2N) has been reported,[7] though in our hands repetition of the reported treatment of dimethylaminometh-



Scheme 1



1 **2** **3**

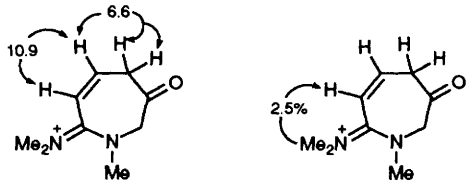
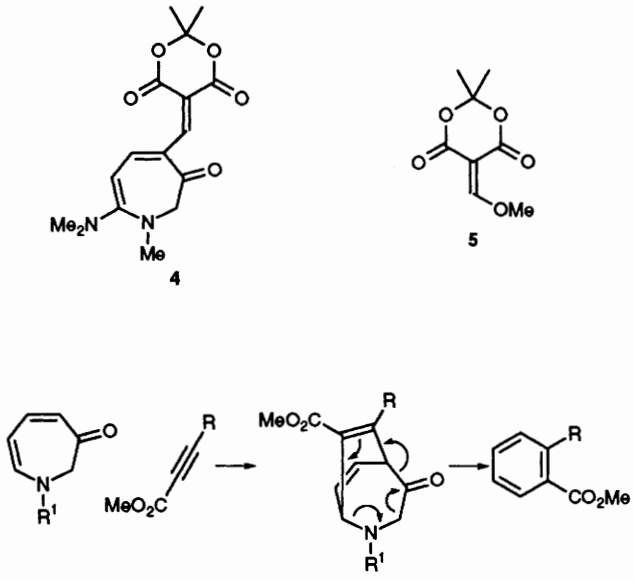


Fig. 1 Selected coupling constant (Hz) and NOE data for the protonated azepinone **3**



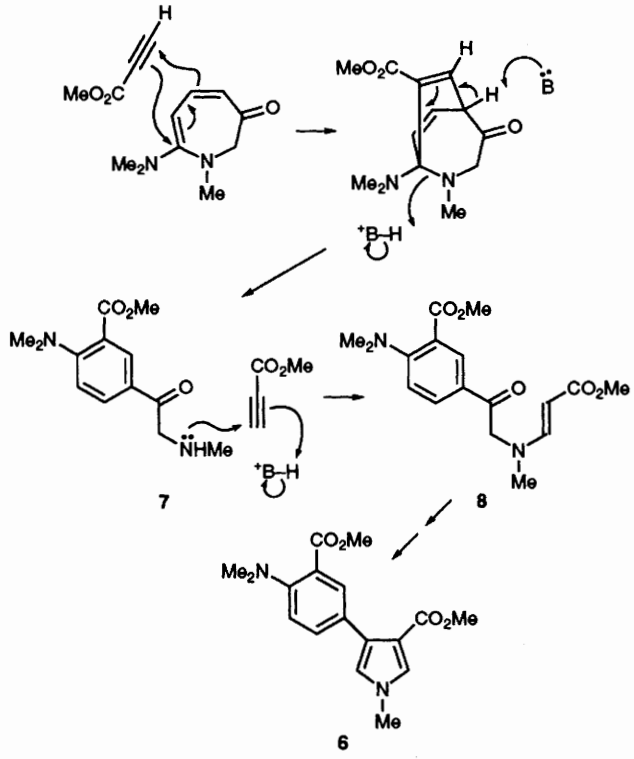
Scheme 2

ylene Meldrum's acid with dimethylacetamide dimethyl acetal in refluxing toluene[7] gave only a low yield of product. However, the efficiency of the reaction was dramatically increased to give yields of *ca.* 80%, if an excess of dimethylamine was present in the reaction mixture. Pyrolysis of **1** (R^1 = Me, R^2 = $R^{2'}$ = H, R^7 = Me_2N) at 600 °C (10^{-2}–10^{-3} Torr) gave the yellow crystalline azepinone **3**† in >90% yield.

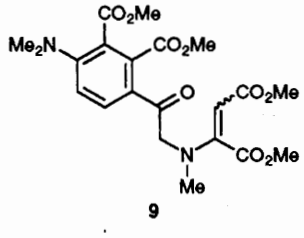
The effect of the dimethylamino substituent on the stereoelectronic properties of the azepinone ring is reflected by a substantial increase in the free energy of activation for ring inversion by comparison with simple derivatives. [$\Delta G^{\ddagger}$ **3** 52 kJ mol^{-1}; $\Delta G^{\ddagger}$ (**2**,[2] R^1 = Ph, R^2 = $R^{2'}$ = Me, R^7 = H) 36 kJ mol^{-1}]. The effect of the electronic interaction with the dienaminone conjugated system is shown by restricted rotation of the dimethylamino group ($\Delta G^{\ddagger}$ 49 kJ mol^{-1}).

The reactivity towards electrophiles is also affected: whereas simple azepinones are quantitatively *O*-protonated by trifluoroacetic acid,[4] the dimethylamino compound **3** gives a stable mixture containing just 22% of *O*- and 78% of *C*-protonated material (Scheme 1). The site of *C*-protonation was confirmed as the 4-position by decoupling and by NOE studies (Fig. 1). The enhanced stability of this species is rationalised by the presence of an amidinium unit, which can effectively delocalise the positive charge (Scheme 1). In further contrast with unactivated azepinones, **3** is sufficiently reactive to give a substitution product **4** with methoxymethylene Meldrum's acid **5** under mild conditions (room temp., acetonitrile, 40% yield). The position of reaction was again confirmed by NOE experiments, and is in line with previous results.[4]

Simple azepinones react with one equivalent of alkyl propiolates or dimethyl acetylenedicarboxylate to give benzene derivatives by cycloaddition across the diene system followed by spontaneous loss of the three atom bridge (Scheme 2).[5] In contrast, the dimethylamino compound **3** reacted cleanly with two equivalents of methyl propiolate (room temp., acetonitrile, overnight) to give a single product (91% crude yield) which, from its mass and NMR spectra, was derived from an initial 2:1 adduct by loss of water. This molecule was identified as the 1,3,4-trisubstituted pyrrole **6** on



Scheme 3



the basis of the following NMR experiments. The ^1H NMR spectrum showed proton resonances due to two OMe, one NMe_2 and one NMe resonance, a pair of mutually coupled (*J* 2.5 Hz) methine protons, and a three proton AMX system indicating a 1,2,4-trisubstituted benzene ring. In steady-state NOE experiments, irradiation of the N-Me proton resonance enhanced only the resonances of the mutually coupled pair of methine protons (consistent with an *N*-methylpyrrole) and irradiation of the N-Me_2 group enhanced only one proton, which showed an *ortho*, but no *meta* coupling. The carbon connectivity around the aromatic ring and through to C-3 and C-2 was established by a two-dimensional INADEQUATE[8] experiment which also established the C-4–C-5 bond. The C-3–C-4 bond was confirmed in a separate one dimensional DOUBTFUL[9] experiment. A two dimensional proton–carbon correlation experiment[10] confirmed the identity of the proton-bearing aromatic carbon atoms.

A possible mechanism for this unexpected transformation is given in Scheme 3. Initial cycloaddition as before is followed by an alternative aromatisation method aided by electron donation by the dimethylamino group, which results in cleavage of the 1,7-bond of the azepinone and releases an α-aminoketone functionality **7**. This can undergo conjugate addition to the second mole of propiolate to give the enamine **8**, which cyclises with loss of water. Similar reactions of α-aminoketones have been reported.[11] In the present series, the mechanism is given further support by the reaction of **3** with dimethyl acetylenedicarboxylate, from which the related

† All new compounds were characterised by elemental analysis or accurate mass measurement.

enamine **9** can be isolated in 35% yield. Clearly, in this instance the electron density in the enamine system is insufficient to promote cyclisation under such mild conditions.

We are most grateful to Lonza Ltd for a generous gift of Meldrum's acid.

Received, 14th June 1993; Com. 3/03422D

References

1 H. McNab, L. C. Monahan and T. Gray, *J. Chem. Soc., Chem. Commun.*, 1987, 140.
2 A. J. Blake, H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1989, 425.
3 H. McNab and L. C. Monahan, *J. Chem. Soc., Chem. Commun.*, 1987, 141.
4 H. McNab, L. C. Monahan and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3163.
5 H. McNab and L. C. Monahan, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3169.
6 H. McNab and L. C. Monahan, *J. Chem. Res.*, (*S*), 1990, 336.
7 A. K. Shanazarov, N. P. Solov'eva, V. V. Chistyakov and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1991, 218. (Ed. Eng., 1991, 178).
8 T. H. Mareci and R. Freeman, *J. Magn. Reson.*, 1982, **48**, 158.
9 S. R. Johns and R. I. Willing, *Magn. Reson. Chem.*, 1985, **23**, 16.
10 A. Bax, *J. Magn. Reson.*, 1983, **53**, 517.
11 For example, E. Winterfeldt, *Chem. Ber.*, 1964, **97**, 1952.