3-Oxidopyraziniums – [4+2] *versus* [3+2] cycloadditions

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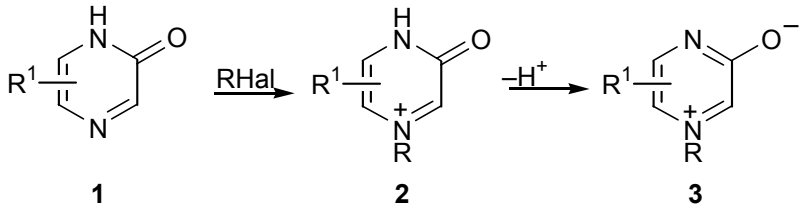
Abstract
The reaction of 1,5,6-trimethyl-3-oxidopyrazinium with methyl methacrylate provides the first example of such a species reacting in a cycloaddition as a 2-azadiene [4+2], as opposed to a 1,3-dipole [3+2].

Keywords: 3-Oxidopyrazinium, 2-azadiene, dipolar cycloaddition

Introduction

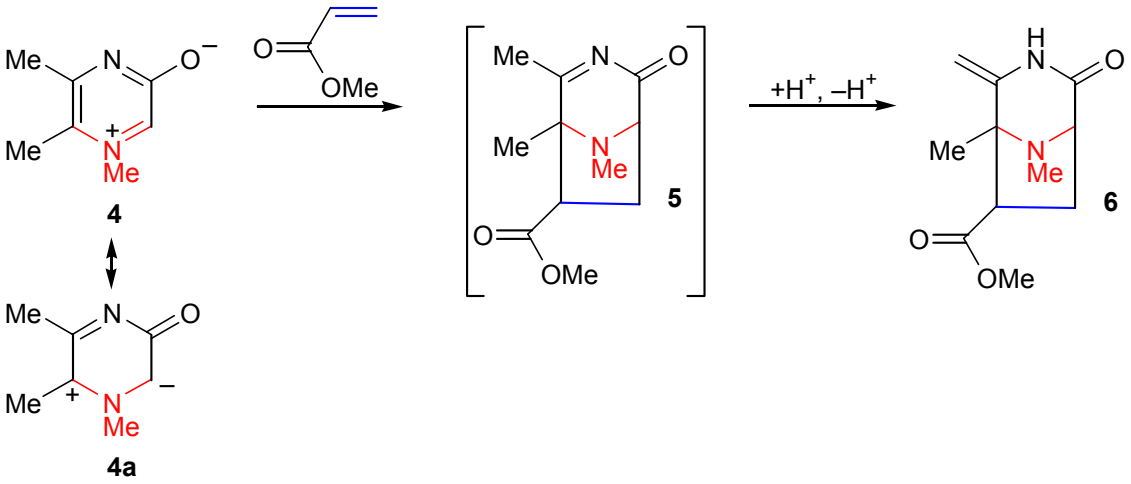
We have been studying[1-5] the cycloaddition reactions of 3-oxidopyrazinium species **3** ('3,4-dihydro-3-oxopyrazinium, inner salts', according to *Chemical Abstracts*). These are very easily obtained from pyrazin-2-ones, **1** *via* regioselective quaternisation to give salts **2** which can be *N*-deprotonated under very mild conditions to generate the oxidopyraziniums **3** (Scheme 1).



1 **2** **3**

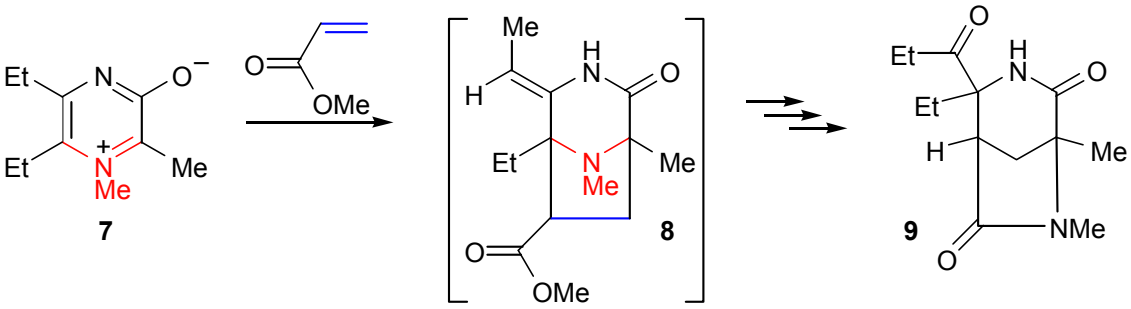
Scheme 1

In our previous work we showed that species **3** react as 1,3-dipoles towards alkenes such as methyl acrylate generating 3,8-diazabicyclo[3.2.1]octanes, for example the 3-oxidopyrazinium **4** derived from 5,6-dimethylpyrazin-2-one reacted as a 1,3-dipole (red) (in the sense indicated by resonance contributor **4a**) with the dipolarophile (blue) methyl acrylate to produce **6**[3] *via* the presumed less stable, tautomeric initial adduct, **5** (Scheme 2).



Scheme 2

In seeking to enlarge the number of examples of these cycloadditions, we prepared the much more hindered 3-oxidopyrazinium **7** and examined its reaction with methyl acrylate. The product **9**, though derived from a comparable initial adduct **8**, the apparent result of a 1,3-dipolar cycloaddition, clearly showed the effect of the greater encumbrance, in that this initial product underwent extensive rearrangement, initiated by hydrolysis, to form **9** (Scheme 3), presumably during work-up.[5]



Scheme 3

Results and Discussion

We have now examined the reaction of methyl methacrylate with oxidopyrazinium **4**. This is the first example of the use of a more hindered alkene with an oxidopyrazinium and the product, **12**, the structure of which was determined by X-ray crystallography, proved to have been formed *via* a different mode of initial addition. Figure 1 shows two Chem3D representations of the structure of the product **12**.

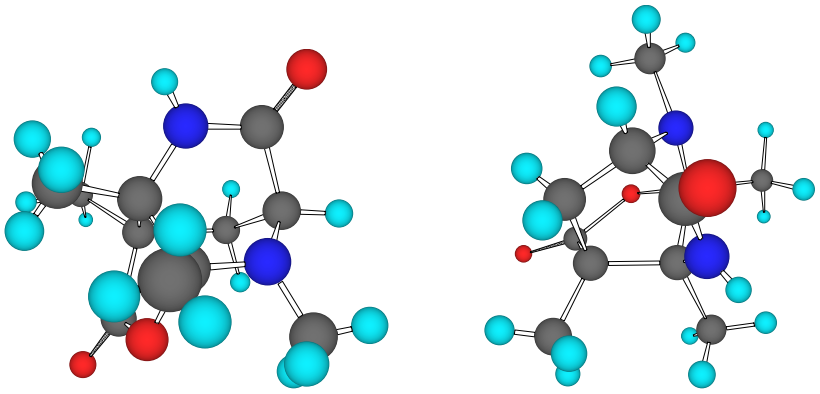
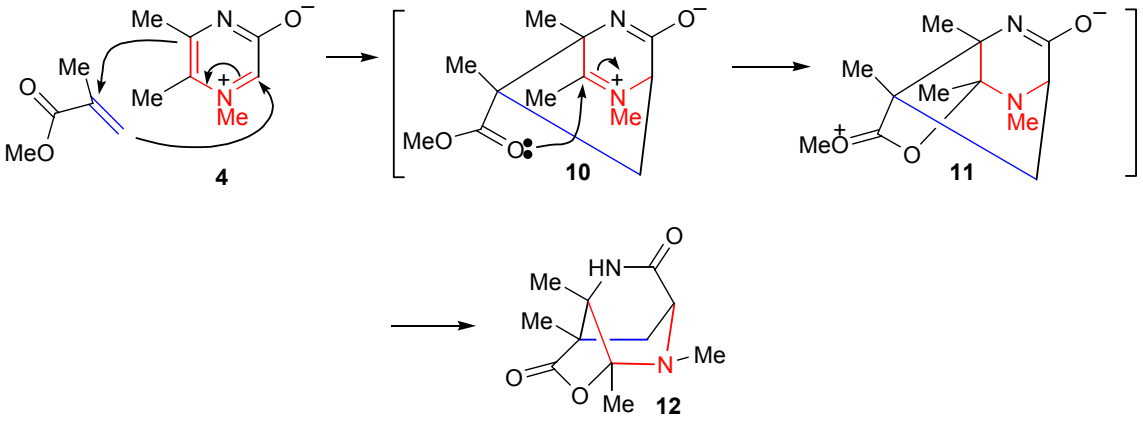


Figure 1 Chem3D representations of the lactone-lactam **12**.

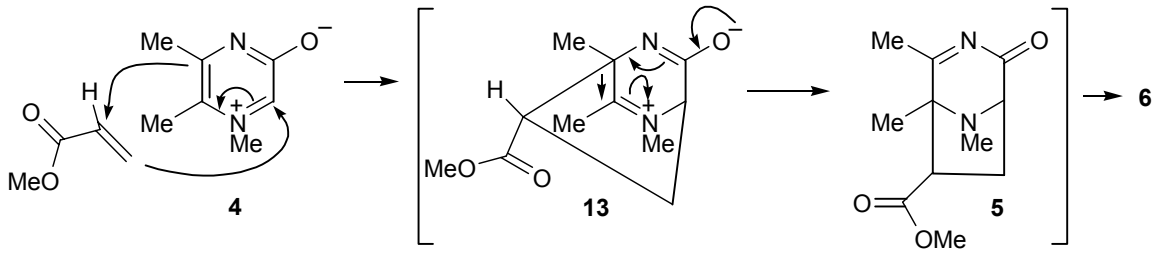
We interpret (Scheme 4) the formation of structure **12** as involving firstly a Diels–Alder type cycloaddition in which the oxidopyrazainium acts as an azadiene (red) and the methacrylate as a dienophile (blue) generating structure **10**. Intramolecular interaction between the ester carbonyl and the iminium carbon (arrows on **10**) would then produce **11** from which the product would be derived by *N*-protonation and hydrolysis of the MeO^{+}=C unit.



Scheme 4

This result calls into question our previous assumption that the several 3,8-diazabicyclo[3.2.1]octane products we have identified[1-5] were formed by a 1,3-dipolar cycloaddition mechanism in parallel to that described in Katritzky's extensive studies[6] on 3-oxidopyridiniums (3-hydroxypyridinium, inner salts, according to *Chemical Abstracts*). The structures of these earlier 3-oxidopyrazinium adducts are not in question, being firmly established by spectroscopic and, in one case, X-ray crystallographic, methods. We suggest, in the light of the results presented in this paper, that it is now necessary to consider an alternative: that our 3,8-diazabicyclo[3.2.1]octane products are in fact produced *via* initial [4+2] addition followed by a rearrangement (arrows on **13**), as indicated in Scheme 5 for the formation of

adduct **6**. We will be pursuing a resolution to this dichotomy *via* both further experimental work and theoretical calculations. It is also possible that [3+2] cycloadditions to 3-oxidopyridiniums[6] may also proceed *via* such a sequence: [4+2] followed by rearrangement. It is relevant that in the extensive studies[7] by Hoornaert *et al.* on neutral pyrazinones, [4+2] cycloadditions are observed – in these neutral substrates, a [3+2] dipolar cycloaddition sequence is not available.



Scheme 5

Experimental Section

General Procedures. All commercial reagents were obtained from the Aldrich Chemical Co or BDH Chemicals. The reagents of analytical grade were used without purification. Solvents of General Purpose Grade (GPR) were distilled prior to use. Column chromatography was performed on silica gel 60-120 mesh. The melting point is uncorrected in degrees Celsius and was recorded on an Electrothermal Digital melting point apparatus. The IR spectrum was recorded on a Mattson 1000 FT spectrometer in the range of 4000 to 400 cm^{-1}. Carbon, nitrogen and hydrogen contents were obtained using a LECO 932 CHNS Mattson 1000 spectrophotometer. NMR spectra were recorded on a Bruker Spectrospin. Chemical shifts are reported in ppm relative to TMS as internal standard. Reactions were routinely monitored by thin layer chromatography on silica gel plates.

Compound characterization.

A solution of 2,4-dihydro-1,5,6-trimethyl-3-oxopyrazin-1-ium iodide (1.5 g, 5.6 mmol), Et_3N (1.6 ml, 11.2 mmol, 2 equiv), and methyl methacrylate (1.52 ml, 16.8 mmol, 3 equiv) in dry MeCN (100 ml) was heated at reflux for 2 h. Solvents were removed from the resulting orange solution under vacuum, H_2O (30 ml) was added and the product was extracted with CH_2Cl_2 (3 x 30 ml). The combined dried extracts were evaporated leaving a reddish brown oil from which, by careful chromatography over silica, eluting with *n*-hexane:EtOAc (1:2) the lactone-lactam **12** (0.88 g, 59%) was obtained as reddish-brown plates. Mp, softening at 178 °C dec at 184 °C. Anal. calcd. for $C_{11}H_{16}N_2O_3$ C, 58.9; H, 7.1; N, 12.5% found C, 59.9; H, 7.3; N, 11.9% IR (KBr) ν cm^{-1}: 3458 (N-H), 2957 (C-H), 1789 (C=O, lactone), 1714 (C=O, amide), ^1H ($CDCl_3$, 250

MHz); 6.45 (s, 1H, N-H), 3.25 (d, 1H, *J*=2 Hz), 2.53 (s, 3H, N-CH_3), 2.49-2.41 (dd, 1H, *J*=10,4 Hz), 1.53-1.46 (d, 1H, *J*=10 Hz), 1.43 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C ($CDCl_3$, 62.9 MHz); 178.2, 173.9, 100.2, 64.1, 56.9, 45.7, 33.9, 32.6, 29.8, 17.9, 15.9; *m/z* (EI) 225 (30%), 136 (32), 124 (98), 123 (100).

Crystal data

A sample suitable for crystallographic analysis was obtained as colourless plates from MeOH. Data were collected on a Bruker Smart Apex CCD diffractometer.
Wavelength :0.71073 Å
Temperature : 100(2) K
Reflections collected /unique : 2576/2576
Completeness to θ = 28.32 : 95.2%
Space group : P2(1)/c
a = 6.9990(12) Å
b = 7.4670(13) Å β = 94.686(3) deg.
c = 20.857(4) Å
V = 1086.4(3) $Å^3$
Z = 4
R indices [I>2σ(I)] : R1 = 0.0406, wR2 = 0.0857
R indices (all data) : R1 = 0.0586, wR2 = 0.0893
The structure was solved with SIR2004[8] and refined with SHELXL97.[9]

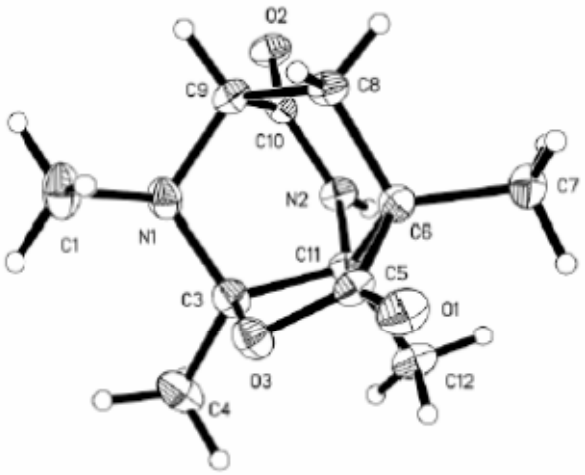


Figure 2. ORTEP representation of the crystal structure of lactone-lactam **12** showing the numbering system used in Table 1.

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

atom	x	y	z	U(eq)
C(1)	6264(2)	385(2)	3327(1)	30(1)
C(3)	4659(2)	3135(2)	3655(1)	21(1)
C(4)	5957(2)	4590(2)	3434(1)	30(1)
C(5)	3981(2)	2222(2)	4679(1)	19(1)
C(6)	2117(2)	2214(2)	4256(1)	19(1)
C(7)	408(2)	2531(2)	4642(1)	24(1)
C(8)	2006(2)	392(2)	3894(1)	19(1)
C(9)	2724(2)	660(2)	3225(1)	21(1)
C(10)	1352(2)	1926(2)	2855(1)	18(1)
C(11)	2557(2)	3677(2)	3760(1)	18(1)
C(12)	2364(2)	5573(2)	4009(1)	25(1)
N(1)	4598(2)	1586(2)	3246(1)	22(1)
N(2)	1341(2)	3490(2)	3165(1)	18(1)
O(3)	5426(2)	2693(1)	4327(1)	23(1)
O(1)	4238(2)	1886(1)	5243(1)	25(1)
O(2)	386(2)	1608(1)	2347(1)	23(1)

Supplementary Information Available

The cif describing the structure determination of compound **12** is available as supplementary information. The crystal data have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 654470.

References

1. Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781.
2. Yates, N. D.; Peters, D. A.; Beddoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331.
3. Helliwell, M.; You, Y.; Joule, J. A. *Acta Crystallogr. Sect. E: Cryst. Struct. Commun.* **2006**, *E62*, o1293.
4. Helliwell, M.; You, Y.; Joule, J. A. *Acta Crystallogr. Sect. E: Cryst. Struct. Commun.* **2006**, *E62*, o2318.
5. Helliwell, M.; Yun, Y.; Joule, J. A. *Heterocycles* **2006**, *70*, 87.
6. Dennis, N.; Katritzky, A. R.; Takeuchi, Y. *Angew. Chem. Int. Ed.* **1976**, *15*, 1. Katritzky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827.
7. Alen, J.; Smets, W. J.; Dobrzan´ska, L.; De Borggraeve, W. M.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2007**, 965 and references cited therein.
8. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G; Spagna, R. SIR2004: an improved tool for crystal structure determination and refinement *J. Appl. Cryst.* **2005**. *38*, 381.
9. Sheldrick, G. M. (1997) SHELXS97. Program for crystal structure solution. University of Göttingen, Germany.