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THE 1,3-DIPOLAR CYCLOADDITION OF METHYL ACRYLATE TO HINDERED 3-OXIDOPYRAZINIUMS

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Abstract – Methyl acrylate adds to 1,2,5,6-tetramethyl-3-oxidopyrazinium to give a standard 1,3-dipolar cycloadduct – a 3,8-diazabicyclo[3.2.1]octan-2-one – however from the more hindered 5,6-diethyl-1,2-dimethyl-3-oxidopyrazinium, a 4,7-dioxo-3,6-diazabicyclo[3.2.1]octane, the result of extensive rearrangement of the initial 1,3-dipolar cycloadduct, was obtained and its structure determined by X-Ray crystallographic analysis.

We have described several examples of the 1,3-dipolar cycloaddition of 3-oxidopyraziniums with dipolarophiles.[1] Using 1,5-dimethyl-3-oxidopyrazinium (**2**) as an example (Scheme 1), the heterocycle adds to unsymmetrical dipolarophiles in the sense implied by resonance contributor (**2res**), thus with methyl acrylate adduct (**3**) is formed first, the enamide-tautomer (**4**) being the final isolated product.[1c] 3-Oxidopyraziniums are easily and simply available from pyrazin-2-ones[2] via regioselective imine-*N*-alkylation (to give *e.g.* **1**), then simple *N*-deprotonation, either separately with hydroxide,[1a,b,d] before reaction or, more conveniently, by including a tertiary amine base in a reaction mixture comprising the pyrazinium salt and the dipolarophile in acetonitrile.[1e,f]

In our earlier work, we utilized only 3-oxidopyraziniums with hydrogens at both C2 and C6 – the future C1 and C5 ring junction carbons. In order to assess the effect which such substituents might have on the cycloaddition process, and bearing in mind that in a series of benchmark papers by Katritzky and coworkers[3] on the cycloadditions of 3-oxidopyridiniums, there were no examples of adduct formation

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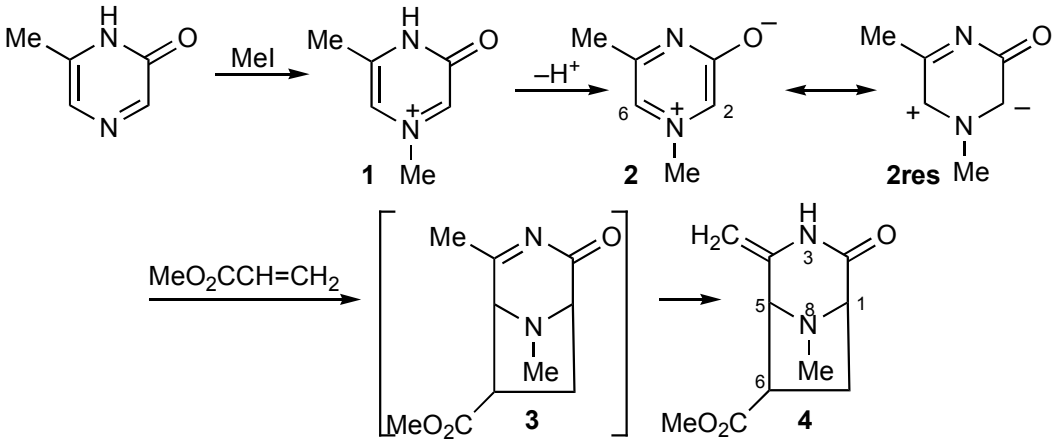
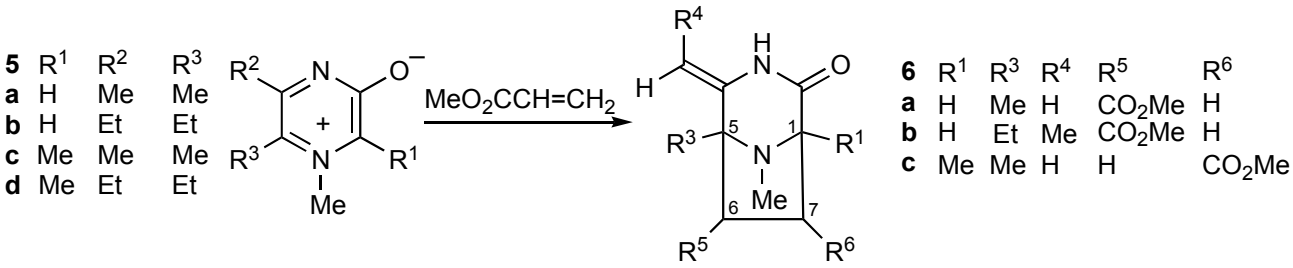
This paper is dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.



Scheme 1

using dipoles in which either one (or two) substituent(s) were located on the 1,3-dipole at the future ring-junction position(s), we examined the reactivity of 1,5,6-trimethyl-3-oxidopyrazinium (**5a**: with a methyl at one of the future ring junction positions – C5), and 5,6-diethyl-1-methyl-3-oxidopyrazinium (**5b**: with an ethyl at the bicyclic C5). Each of these followed the usual pattern in reactions with methyl acrylate to generate the appropriately substituted 3,8-diazabicyclo[3.2.1]octan-2-ones (**6a-b**), with ester located at C6.[1f,1e] In this report we describe two, more hindered situations, in which we utilized 3-oxidopyraziniums with substituents at *both* future ring junction positions – (**5c**) and (**5d**).



Scheme 2

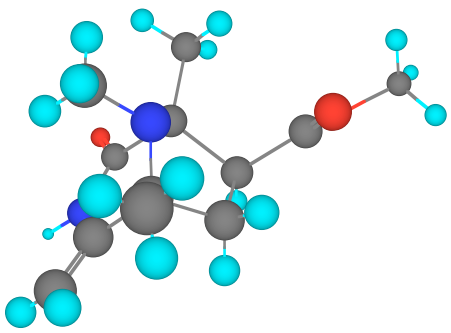


Figure 1. Chem3D representation of the X-Ray crystal structure[4] of methyl *exo*-2-oxo-3,8-diazabicyclo[3.2.1]octane-7-carboxylate (**6c**)

2,5,6-Trimethylpyrazin-3-one and 5,6-diethyl-2-methylpyrazin-3-one were prepared *via* the standard condensation[2a] of a 1,2-diketone (butane-2,3-dione and hexane-3,4-dione respectively) with an α-amino acid amide, alaninamide in this case. *N*1-Methylation of each was unexceptional and each salt was reacted with methyl acrylate in the presence of triethylamine following the method described in detail previously.[1e,f] 1,2,5,6-Tetramethyl-3-oxidopyrazinium (**5c**) produced a 1,3-dipolar cycloadduct, but X-Ray analysis showed this to have structure (**6c**) in which the regiochemistry of addition was reversed from that which we had heretofore observed – the *exo* ester is located at C7. Figure 1 shows a Chem3D representation of this product using the crystallographic co-ordinates.

Spectroscopic examination of the product isolated from the reaction of the more hindered **6d** showed it clearly not to be of the usual diazabicyclo[3.2.1]octan-2-one type. An X-Ray analysis revealed its structure as 2-ethyl-5,6-dimethyl-4,7-dioxo-2-propanoyl-3,6-diazabicyclo[3.2.1]octane (**7**), and Figure 2 shows a Chem3D representation utilising the crystallographic co-ordinates.

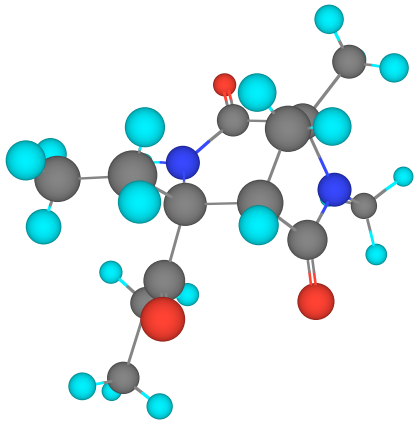
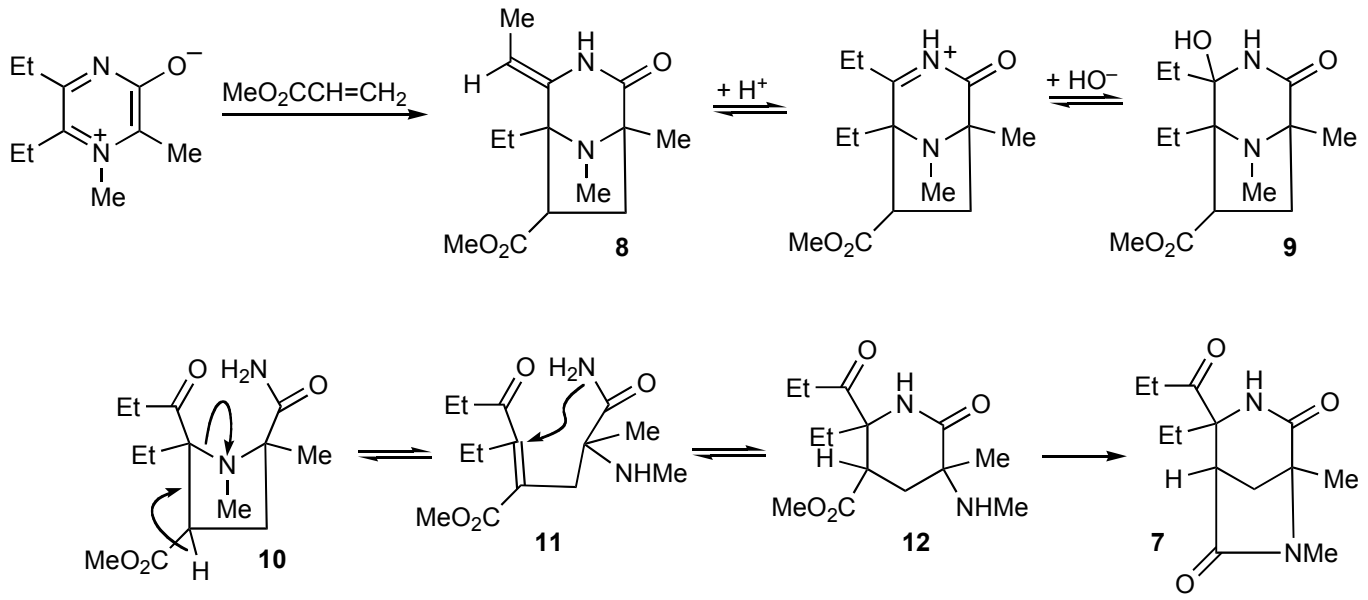


Figure 2. Chem3D representation of the X-Ray crystal structure[5] of 2-ethyl-5,6-dimethyl-4,7-dioxo-2-propanoyl-3,6-diazabicyclo[3.2.1]octane (**7**)

We are fully aware of the synthetic potential inherent in the combination of functionality present in the cycloadducts from 3-oxidopyraziniums and the isolation of the 3,6-diazabicyclo[3.2.1]octane (**7**) illustrates some of that potential, albeit unintentionally. Our interpretation of the formation of **7** is shown in Scheme 3. We start with the assumption that a 'normal' adduct (**8**) is formed first; hydrolytic cleavage of the enamide unit via enamide-β-protonation, and overall water addition (→ **9**), then cleavage of the carbinolamine unit thus formed would reveal the keto-amide (**10**). A 1,2-elimination of the tertiary nitrogen, based on the acidity of the C–hydrogen α to the ester would then give **11** and now an intramolecular aza-Michael would link the other nitrogen to C2 and form the piperidin-2-one unit in **12**. Finally, the five-membered lactam would be formed from the juxtaposed amine and ester functionalities.



Scheme 3

ACKNOWLEDGEMENTS

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4. Crystal data for methyl *exo*-2-oxo-3,8-diazabicyclo[3.2.1]octane-7-carboxylate (**6c**) (58% yield; mp 138-140 °C): $C_{12}H_{18}N_2O_3$, *M* = 238.28, triclinic, *a* = 6.8091(13), *b* = 8.5845(17), *c* = 10.845(2) Å, α = 108.219(3), β = 91.892(4), γ = 97.179(3)°, *U* = 595.6(2)Å^3, *T* = 100 K, space group *P-1* (no. 2), *Z* = 2, μ(Mo-Kα) = 0.096 mm^{-1}, 3484 reflections measured, 2371 unique (*R*int = 0.018) which were used in all calculations. The final *R*(*F*) was 0.038 using 2127 with $I > 2\sigma(I)$, wR2 = 0.101 (all data).
5. Crystal data for 2-ethyl-5,6-dimethyl-4,7-dioxo-2-propanoyl-3,6-diazabicyclo[3.2.1]octane (**7**) (23% yield; mp 146-148 °C): $C_{13}H_{20}N_2O_3$, M = 252.31, triclinic, a = 7.3740(18), b = 8.836(2), c = 11.069(3)Å, α = 101.031(4), β = 101.143(4), γ = 110.114(4)°, U = 637.9(3) Å^3, T = 100 K, space group P-1 (no. 2), Z = 2, μ(Mo-Kα) = 0.094 mm^{-1}, 5068 reflections measured, 2558 unique (Rint = 0.027) which were used in all calculations. The final R(F) was 0.040 using 2376 with $I > 2\sigma(I)$, wR2 = 0.107 (all data).