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GENERATION AND CYCLOADDITIONS OF TETRAHYDROFURYL, PYRANYL, AND OXEPANYL-2-IMMINIUM METHYLIDES

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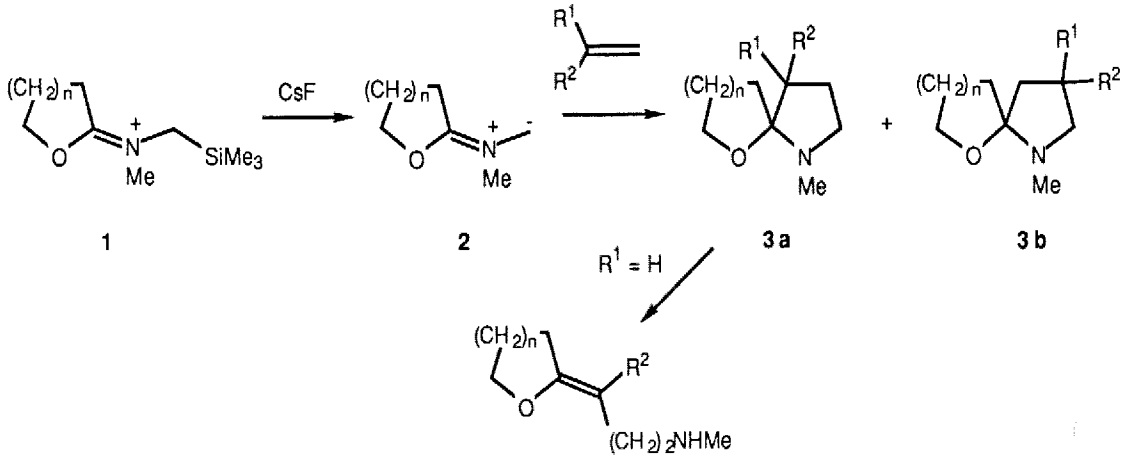
Summary: Tetrahydrofuryl, pyranyl, and oxepanyl-2-imminium methylides, generated via fluoride anion-induced desilylation of the corresponding N-(trimethylsilyl)methyl imminium cations undergo facile 1,3-dipolar cycloaddition to a range of electron deficient olefins to yield novel spirocyclic systems.

As part of our general interest in the 1,3-dipolar cycloaddition chemistry of azomethine ylides,[2] we wished to explore the possibility of generating azomethine imidate methylides **2** which contain a saturated oxygen ring system directly attached to the 1,3-dipolar moiety. We anticipated that cycloaddition of these systems would yield novel spirocycles **3** which are aza-analogues of the spirocyclic ether units found in a number of pharmacologically important systems.[3]

We report here that imidate methylides **2** are readily generated via fluoride anion-induced desilylation of imminium salts **1**, themselves easily obtained via methylation of the corresponding N-(trimethylsilyl)methyl imidates.[4] Azomethine ylides **2** undergo cycloaddition to a number of electron deficient dipolarophiles to yield spirocycles **3** which, depending on their structure, can undergo further transformation into olefins **4** (scheme).



1 **2** **3a** **3b**

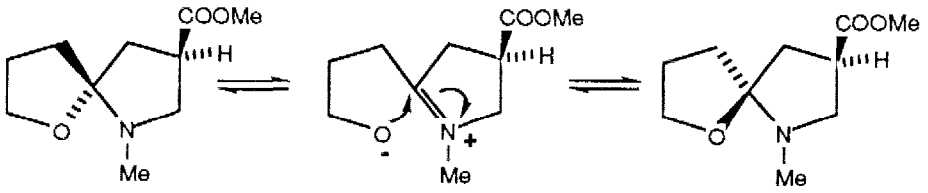
4

Scheme

As a general procedure, methyl triflate (1.1 mmol, 125µl) was slowly added to a stirred solution of the N-(trimethylsilyl)methyl imidate[4] in anhydrous dichloromethane (4ml) at 0°C, and this solution allowed to warm to room temperature over 1hr. Evaporation gives the corresponding imidate salt **1** as a viscous colourless oil. To a stirred solution of salt **1** in anhydrous DME (4ml) at -70°C was added the dipolarophile (10 equivs.) followed by anhydrous cesium flouride (4 equivs.) and the resulting mixture allowed to warm to room temperature over 2hr. After the addition of dichloromethane (20ml), the mixture was filtered through a celite pad and evaporated. Purification then involved either Kugelrhor distillation or column chromatography. The results of a number of experiments are summarized in the table.

A number of points are noteworthy:

a) The structures of the spirocycles were verified[5] by a combination of high-field NMR techniques (notably: 2D $^1H,^1H$- and $^1H,^{13}C$- shift correlation and 1D ^1H-^1H NOE experiments). Inspection of the NMR spectra of each of the cycloadducts **3** reveals that they exist as mixtures of diastereoisomers. Moreover, for most of the spirocyclic compounds the NOE experiments revealed the presence of strong saturation-transfer effects[6] between analogous protons of the diastereoisomeric pairs, indicating that the relevant epimeric forms are in a state of dynamic exchange at a rate which is slow on the δ time-scale and fast on the relaxation time-scale. Interconversion of the isomers occurs presumably via the following mechanism, as illustrated on an arbitrary member of the spirocyclic compounds:



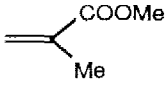
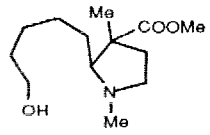
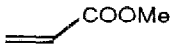
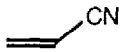
Interestingly, at room temperature, in both cycloadducts of type **3b**, R^1=H, R^2=CN, the aforementioned saturation-transfer phenomenon is absent, indicating a significantly slower exchange rate for these species.

b) Cycloadditions involving methyl methacrylate as dipolarophile show a striking regiospecificity , the exact regiochemistry being dependent on the ring size of the imidate precursor (entries 1,2 and 3).

c) Cycloadducts of type **3a**, R^1 = H could not be isolated due to their facile ring-opening to yield esters **4** (entries 4 - 9). These esters appear to be a single stereoisomer and are tentatively assigned the configuration as shown in the scheme.

d) Cycloaddition of the tetrahydrooxepanyl ylide **2**, n = 3 with methyl methacrylate gave an unusual product in which the seven-membered ring had formally undergone C-O fission (entry 3).

Table. Cycloadditions of azomethine ylides **2**.

entry	salt 1	dienophile	product[a]	yield (%)[b]
				
1	n=1		**3a** n=1, R^1=Me, R^2=COOMe	65 (4:1)
2	n=2		**3b** n=2, R^1=Me, R^2=COOMe	69 (1.1:1)
3	n=3			42
				
4	n=1		**3b** n=1, R^1=H, R^2=COOMe **4** n=1, R^2=COOMe	26 (2.5:1) 54
5	n=2		**3b** n=2, R^1=H, R^2=COOMe **4** n=2, R^2=COOMe	8 (1.2:1) 23
6	n=3		**4** n=3, R^2=COOMe	59
				
7	n=1		**3b** n=1, R^1=H, R^2=CN **4** n=1, R^2=CN	26 (1.5:1) 58
8	n=2		**3b** n=2, R^1=H, R^2=CN **4** n=2, R^2=CN	28 (1.1:1) 61
9	n=3		**4** n=3, R^2=CN	87

[a] All new compounds gave IR, NMR and mass spectral data which were consistent with the proposed structures.
[b] The epimeric ratios at room temperature in $CDCl_3$ are given in parentheses.

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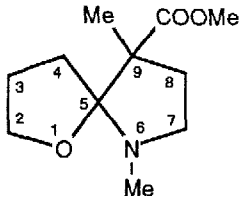
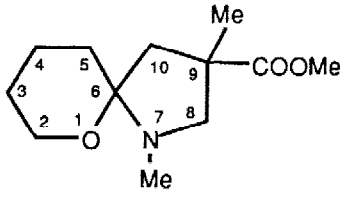
References and notes

1. On leave from the NMR laboratory of the Institute for General and Analytical Chemistry, Technical University, H-1521 Budapest, Hungary.
2. *a)* Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B.; Szantay, C. Jr. *Tetrahedron Lett.*, **1988**, *29*, 5325. *b)* Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.*, **1989**, *30*, 4447. *c)* Alanine, A. I. D.; Fishwick, C. W. G. *Tetrahedron Lett.*, **1989**, *30*, 4443.

3. See for example: a) Westley, J. W. (editor), *Polyether Antibiotics,* Decker, New York, **1983**, vol 2. *b)* Kihara, T.; Kusatabe, Nakamura, G.; Isono, K. *J. Antibiot.*, **1981**, *34*, 1073.
4. See preceding paper.
5. Representative NMR data are given below:



Major isomer; ^{1}H NMR ($CDCl_3$), δ: 1.28 (3H, s, C-9 Me); 1.58 (1H, ddd, H_x-8); 1.78 (1H, ddd, H_x-4); 1.83-1.99 (2H, m, H_2-3); 2.23 (3H, s, NMe); 2.54 (1H, ddd, H_y-4); 2.61 (2H, ddd, H_x-7); 2.70 (1H, ddd, H_y-8); 2.90 (1H, ddd, H_y-7); 3.56 (1H, ddd, H_x-2); 3.63 (3H, s, COOMe); 3.90 (1H, ddd, H_y-2).
^{13}C NMR ($CDCl_3$), δ: 24.4 (Me); 26.1 (C-3); 28.8 (C-4); 31.2 (C-8); 33.0 (NMe); 50.1 (C-7); 51.5 (OMe); 55.7 (C-9); 69.2 (C-2); 106.7 (C-5); 174.7 (C=O).
Minor isomer; ^{1}H NMR ($CDCl_3$), δ: 1.20 (3H, s, C-9 Me); 1.70 (1H, ddd, H_x-8); ~1.78 (1H, overlapping, H_x-4); ~1.90 (2H, overlapping, H_2-3); 2.23 (3H, s, NMe); 2.33 (1H, ddd, H_y-8); ~2.54 (2H, overlapping, H_x-7, H_y-4); 3.04 (1H, ddd, H_y-7); 3.63 (3H, s, COOMe); ~3.63 (1H, overlapping, H_x-2); 3.99 (1H, ddd, H_y-2).
^{13}C NMR ($CDCl_3$), δ: 18.6 (Me); 26.5 (C-3); 28.8 (C-4); 32.1 (C-8); 33.5 (NMe); 50.7 (C-7); 51.8 (OMe); 55.7 (C-9); 69.2 (C-2); 105.3 (C-5); 176.0 (C=O).



Major isomer; ^{1}H NMR ($CDCl_3$), δ: 1.33 (3H, s, C-9 Me); ~1.35-~1.50 (2H, overlapping, H_2-3); ~1.38 (1H, overlapping, H_{eq}-5); 1.40 (1H, d, H_x-10); ~1.50 (1H, overlapping, H_x-4); 1.69 (1H, ddd, H_{ax}-5); ~1.77 (1H, overlapping, H_y-4); 2.29 (3H, s, NMe); 2.73 (1H, d, H_x-8); 3.00 (1H, d, H_y-10); 3.43 (1H, d, H_y-8); 3.48 (1H, m, H_{ax}-2); 3.67 (3H, s, COOMe); 3.71 (1H, m, H_{eq}-2).
^{13}C NMR ($CDCl_3$), δ: 22.1 (C-4); 25.0 (Me); 25.9 (C-3); 32.0 (NMe); 32.8 (C-5); 43.3 (C-10); 46.0 (C-9); 52.1 (OMe); 63.6 (C-2); 63.8 (C-8); 94.1 (C-6); 177.5 (C=O).
Minor isomer; ^{1}H NMR ($CDCl_3$), δ: 1.36 (3H, s, C-9 Me); ~1.35-~1.50 (2H, overlapping, H_2-3); ~1.38 (1H, overlapping, H_{eq}-5); ~1.50 (1H, overlapping, H_x-4); 1.69 (1H, ddd, H_{ax}-5); ~1.77 (1H, overlapping, H_y-4); 2.08 (1H, d, H_x-10); 2.30 (3H, s, NMe); 2.32 (1H, d, H_y-10); 2.83 (1H, d, H_x-8); 3.29 (1H, d, H_y-8); 3.50 (1H, m, H_{ax}-2); 3.66 (3H, s, COOMe); 3.78 (1H, m, H_{eq}-2).
^{13}C NMR ($CDCl_3$), δ: 22.1 (C-4); 26.8 (Me); 25.9 (C-3); 31.8 (NMe); 32.8 (C-5); 43.3 (C-10); 45.5 (C-9); 52.0 (OMe); 62.9 (C-8); 63.6 (C-2); 94.1 (C-6); 178.0 (C=O).

6. The observed transfer of saturation is in most cases virtually complete at RT (using 4s pre-irradiation times), resulting in strong transferred NOEs and thus precluding a straightforward identification of the diastereoisomers using NOE analysis. Further investigations in this regard are underway.

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