Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5163-5166, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01026-X

Cyclic-Fused Azomethine-, Imidate-, and Thioimidate Methylides: An Efficient Regiocontrolled Entry into Spiro-fused Pyrrolidines

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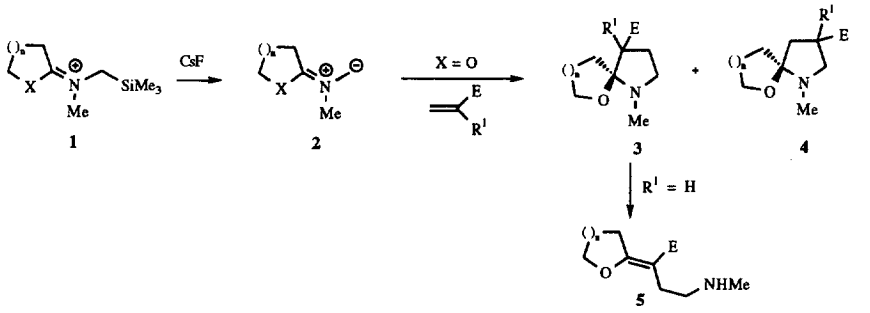
Abstract: Generation of azomethine ylides, imidate methylides, and thioimidate methylides which are exocyclic to indane, benzofuran, benzothiophene, and benzopyran moieties respectively, in the presence of electron deficient dipolarophiles, gives direct access to spiro-fused pyrrolidines in good yields and excellent regioselectivity. Copyright © 1996 Elsevier Science Ltd

Concerted cycloaddition processes represent a powerful and often highly controlled entry into a wide variety of heterocyclic systems. Additional features associated with these processes include mild conditions, versatility, and in particular, the ability to gain rapid access to complex, polycyclic ring frameworks.[1]

Spiroketals in particular, have attracted considerable synthetic attention due to their occurrence in a number of biologically interesting systems. Indeed, cycloaddition-based approaches to spiroketals based on the Diels-Alder reaction have been reported.[2]

In contrast , aza-analogues of the spiroketals, where an oxygen is replaced by nitrogen have received much less attention. Similarly, other, mixed heteroatom analogues such as oxa-thia based systems have not been studied.

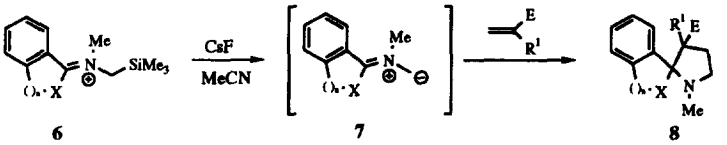
We were intrigued by the possibility of gaining access to such systems via a 1,3-dipolar cycloaddition approach utilising azomethine ylides which are exocyclic to a heterocyclic ring framework **2** (Scheme 1). Preliminary investigations into the viability of this route with simple versions of 1,3-dipoles **2** (X = O), produced from salts **1** (X = O), had indicated that although these cycloadditions occur, in these simple cases, there was a lack of regiocontrol and both possible regioisomers **3** and **4** were produced.[3] Additionally, the 'proximal' regioisomer **3** was unstable and underwent ring-opening to yield vinyl ethers **5** (Scheme 1).



Scheme 1

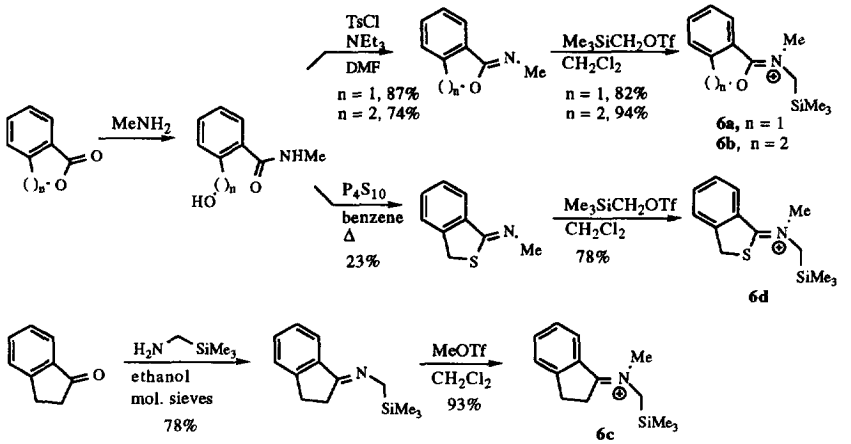
We now report that treatment of salts **6** (X = O, n = 1, 2, and X = S, n = 1 respectively) with fluoride leads to the generation of dipoles **7**, which are the benzo-fused derivatives of **2**. In the presence of olefins, dipoles **7** undergo highly regioselective cycloaddition giving access to a range of previously unknown

spirocycles **8** in good to excellent yields (Scheme 2).[4]



Scheme 2

The dipole precursors **6a-b** and **6d** were readily obtained from cyclisation of the appropriate ω-(hydroxyalkyl)- benzamides[5] or -thioamides respectively (Scheme 3). The indene-based dipole precursor **6c** was prepared from condensation of indanone with trimethylsilyl methylamine[6] followed by methylation (Scheme 3).



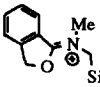
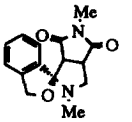
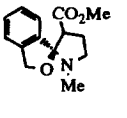
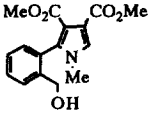
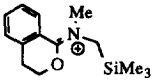
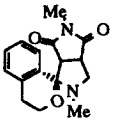
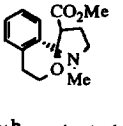
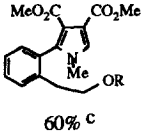
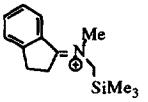
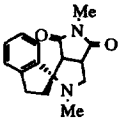
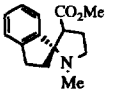
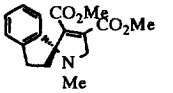
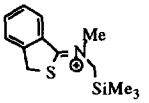
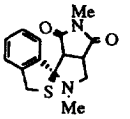
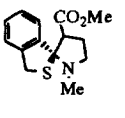
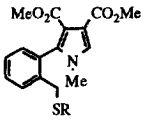
Scheme 3

Interestingly, It was found that the salts **6a-b** and **6d** were obtained exclusively as the Z-isomers as were the corresponding imidate and thioimidate precursors. However, it was noted that upon storage, imidate salt **6b** underwent slow isomerisation to the E-isomer. Additionally, imminium salt **6c** and the corresponding imine precursor were found to have the E-configuration exclusively (Scheme 3).

The results of a variety of cycloadditions[7] are summarised (Table). Analysis of the data in the Table reveals a number of interesting points. In all cases involving reaction of dipoles **7** with the non-symmetrical dipolarophile (column B) the cycloadditions are regiospecific and only the 'proximal' regioisomer, where the substituent on the dipolarophile is located near to the position of spiro-fusion, is observed. This regiospecificity is in marked contrast to the lack of regiocontrol observed previously for the reaction of methyl acrylate with the simpler, non-benzenoid dipoles **2**[3]. Clearly, the fusion of the aromatic ring onto the dipole would be expected to alter the MO coefficients such that the 'large-large' coefficient interaction involving the dipole HOMO and dipolarophile LUMO was increased relative to the case involving dipoles **2**. However, our observations involving cycloaddition in the presence of excess dipolarophile may suggest an alternative mechanistic direction for these cycloadditions involving a stepwise reaction sequence. Thus treatment of salt **6d** with cesium fluoride in the presence of two equivalents of methyl acrylate yields the heterocycle **9** (33%, relative stereochemistry

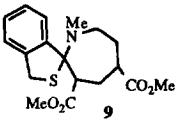
not determined) along with the expected 1,3-dipolar cycloadduct (42%).

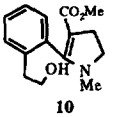
Table

Entry		Dipolarophile[a] A	B	C
	Dipole precursor **6**			$MeO_2C{-}{\equiv}{-}CO_2Me$
1	 **6a**	 88%, exo/endo 1.0	 76%, exo/endo 3.0	 40%
2	 **6b**	 68%, exo/endo 1.0	 68%[b], exo/endo 1.0	 60% [c]
3	 **6c**	 83%, exo/endo 0.8	 82%, exo/endo 1.6	 77%
4	 **6d**	 77%, exo/endo 1.2	 68%, exo/endo 0.7	 46% [c]

[a] 1 Equivalent [b] Formed as an equilibrium mixture with a ring-opened form, see text. [c]See text

Thus, it would appear that **9** results from a Michael addition of the 1,3-dipole to yield an intermediate which can undergo either ring closure to yield the pyrrolidine or further Michael addition with a second mole of acrylate to yield **9** after ring closure. This stepwise pathway is presumably favoured for the present benzo-fused ylide as the intermediates have enhanced mesomeric stability compared to the case for the simpler dipoles **2.**


9


10

For cycloadditions to olefins (columns A and B, Table) the *exo/endo* selectivity was found to depend upon the actual dipole system. Thus, the imidate-derived dipoles (entries 1 and 2) show a preference for formation of *exo* cycloadducts (with respect to the aryl and carbonyl moieties respectively) whereas the indane- and thioimidate ylides show a variation in their stereoselectivities depending on the nature of the dipolarophilic trap. In addition, after prolonged storage, it was noted that some of the cycloadducts, whilst originally isolated as pure, single isomers of either *endo* or *exo* stereochemistry, had undergone partial stereomutation to yield a mixture of the *exo* and *endo* forms.[8] For instance, cycloaddition of N-methyl maleimide to the dipole derived

from salt **6a** (entry 1, column A) yields an approximately equal mixture of *exo* and *endo* isomers which are separable by chromatography. Inspection of a sample of the *exo* isomer by NMR revealed that after one month (in $CDCl_3$), it had undergone partial stereomutation into an *exo/endo* mixture (2.3:1). Similarly, a sample of pure *endo* adduct underwent partial stereomutation but less efficiently (*exo/endo* ratio 0.18:1 after three months). Additionally, cycloadditions to an acetylenic dipolarophile (column C) produce pyrroles, presumably via a cycloaddition/elimination sequence.[9] In the case of addition to the dipole derived from salt **6b** (entry 2, column C), a mixture of pyrroles consisting of the alcohol (R = H, 28%) and the vinyl ether (R = MeO_2C-C=$CHCO_2Me$, 32% as a 3:1 mixture of Z and E isomers) was isolated. Similarly, the thioimidate-derived dipole produced a mixture of pyrroles consisting of the disulphide (entry 4, column C, 31%) and the vinyl sulphide (R = C=$CHCO_2Me$, 15% as a 1:1.4 mixture of Z and E isomers). Finally, it was found that addition of the dipole derived from salt **6b** to methyl acrylate (entry 2, column B) yielded a solvent-dependant equilibrium mixture of the indicated cycloadduct together with the pyrroline **10** ($CDCl_3$, 1:2, CD_3OD, **10** only).

Acknowledgements.

We are grateful to the EPSRC and Glaxo Research and Development Ltd, Stevenage, for their financial support.

References and notes

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2. See: Ireland, R.E.; Habich, D. *Tetrahedron Lett.*, **1980**, 21, 1389.
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4. For some related cycloadditions of imidate, amidine and thioimidate ylides, see: a) Livinghouse, T.; Smith, R. *J. Chem. Soc. Chem. Comm,*. 1983, 210. b) Bazureau, J.P.; Lerestif, J.M.; Hamelin, J. *Tetrahedron Lett.*, **1993**, 34, 4639. c) Jones, R.C.F.; Nichols, J.R.; Cox, M.T. *Tetrahedron Lett.*, **1990**, 31, 2333. d) Padwa, A.; Gasdaska, J.R.; Haffmanns, G.; Robello, H. *J. Org. Chem.*, **1987**, 52, 1027. e) Vedejs, E.; Larsen, S.; West, F.G. *J. Org. Chem.*, **1985**, 50, 2170. f) Livinghouse, T.; Smith, R.; Westling, M. *J. Org. Chem.*, **1986**, 51, 1159. g) Padwa, A.; Haffmans, G.; Tomas, M. *Tetrahedron Lett.*, **1983**, 24, 4303.
5. See: Berube, A.; Lessard, A. *Can. J. Chem.*, **1982**, 1127.
6. See: Griller, D.; McPhee, D.J.; Letellier, M. *Synth. Commun.*,**1988**, 18, 1975.
7. Typical cycloaddition procedure: A solution of the imino triflate salt (1mmol) and the appropriate dipolarophile in anhydrous acetonitrile (4ml) was added to cesium fluoride (4.0mmol) at -78°C. The resulting mixture was allowed to warm to room temperature with stirring and when t.l.c indicated a complete reaction dichloromethane (20ml) was added and the reaction mixture filtered through a celite plug. All new compounds gave satisfactory spectral and analytical data consistent with the proposed structures. Regio- and stereochemical assignments are based on NMR analyses, in particular, involving the use of nOe effects. Sample NMR data:
(entry 1, column B) *exo* δ/ppm($CDCl_3$) 2.01(3H,s,NMe), 2.20(1H,m,Hα-8), 2.58(1H,m,Hβ-8), 2.98(1H,m,Hβ-7), 3.18(1H,dt,J=3,8Hz,Hα-7), 3.41(1H,dd,J=7,8Hz,Hα-9), 3.49(3H,s,OMe), 4.95(2H,AB quartet,J=11Hz,H-2), 7.21(1H,d,J=7Hz,ArH), 7.30-7.39(3H,m,ArH). *endo* δ/ppm($CDCl_3$) 2.11(3H,s,NMe), 2.19(1H,m,Hα-8), 2.43(1H,m,Hβ-8), 2.90(1H,m,Hα-7), 3.26(1H,dt,J=3,8Hz,Hβ-7), 3.39(1H,dd,J=7,8Hz,Hβ-9), 5.01(2H,AB quartet,J=12Hz,H-2), 7.09(1H,d,J=7Hz,ArH), 7.20-7.32(3H,m,ArH).
(entry 4, column A) *endo* δ/ppm($CDCl_3$) 2.04(3H,s,NMe), 2.86(1H,dd,J=7,8Hz,Hβ-7), 3.01(3H,s,NMe), 3.31(1H,t,J=7Hz,Hβ-8), 3.50(1H,d,J=8Hz,Hα-7), 4.00(1H,d,J=7Hz,Hβ-9), 4.23(2H,ABquartet,J=12Hz,H-2), 6.86(1H,d,J=7Hz,ArH), 7.20-7.35(3H,m,ArH). *exo* δ/ppm($CDCl_3$) 2.09(3H,s,NMe), 2.70(1H,m,Hα-7), 3.00(3H,s,NMe), 3.50(2H,m,Hβ-7,Hα-8), 3.71(1H,d,J=7Hz,Hα-9), 4.11((2H,AB quartet,J=12Hz,H-2), 7.20-7.31(4H,m,ArH).
8. Stereoisomerism in the related [4.4] spiroketals is known, see: Kitching, W.; Lawson, E.N.; Woodhall, J.F.; Nishiyami, T. *J. Org. Chem.*, **1989**, 54, 2183.
9. For some similiar examples, see: a) Fishwick, C.W.G.; Foster, R.J.; Carr, R.E. *Tetrahedron Lett.*, **1995**, 36, 9409. b) Padwa, A.; Chiacchio, U.; Venkatramanan, M.K. *J. Chem. Soc. Chem. Comn,*. **1985**, 1108. c) Tsuge, O.; Kanemasa, S.; Kuraoka, S. *Bull Chem Soc Jpn.*. **1985**, 58, 1570. and ref. 4d.

(*Received in UK* 22 *April* 1996; *revised* 17 *May* 1996; *accepted* 24 *May* 1996)