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INTRAMOLECULAR [3+2] CYCLOADDITIONS OF NON-STABILISED AZOMETHINE IMIDATE-METHYLIDES

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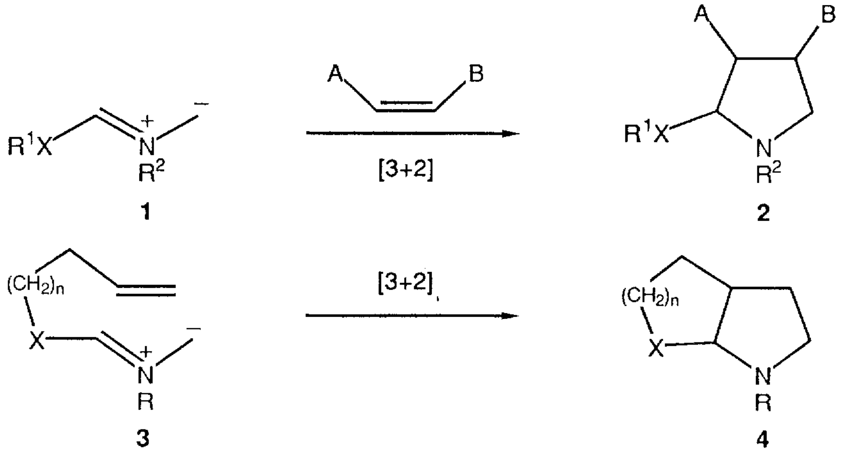
Summary : Non-stabilised azomethine imidate and thioimidate-methylides, generated via fluoride ion induced desilylation of N-(trimethylsilyl)methyl-2-alkoxy imminium salts undergo facile intramolecular cycloaddition with unactivated and electron deficient dipolarophiles affording pyrrolo-[2,3-b] furans and pyrans.

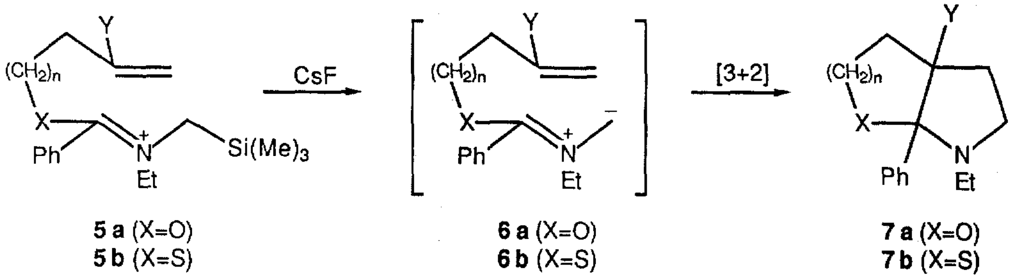
Non-stabilised 1,3-dipoles have become established as extremely useful intermediates for the rapid construction of five membered heterocyclic ring systems[1] (**1**→**2**, scheme 1). Their ease of generation coupled with the highly regio- and stereo-selective nature of their cycloaddition reactions has resulted recently in a number of syntheses which utilize such a cycloaddition as the key step[2].

In principle the intramolecular variant of this reaction (**3**→**4**, scheme 1) should be an equally powerful method for the synthesis of polycyclic systems. However, despite its obvious potential, this reaction has received relatively little attention[3a,3b].



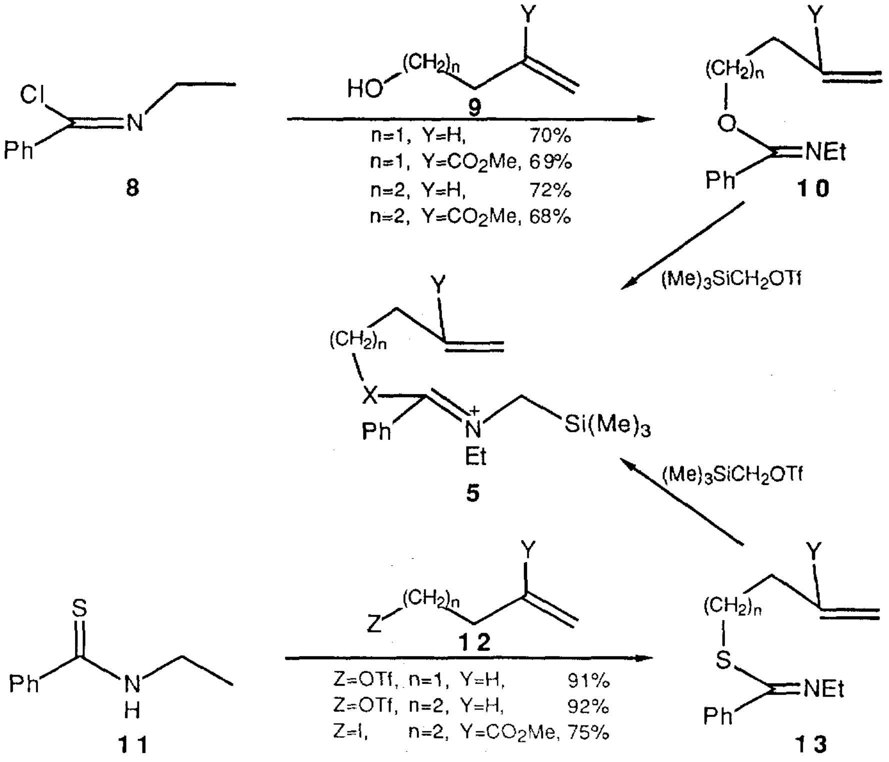
scheme 1

We report here that suitably functionalised azomethine imidate methylides generated from readily available precursors **5**, undergo facile intramolecular cycloadditon with unactivated and electron deficient dipolarophiles to yield pyrrolo [2,3-b] furans and pyrans **7**. The general sequence is summarised in scheme 2.



scheme 2

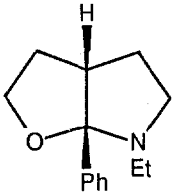
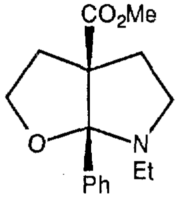
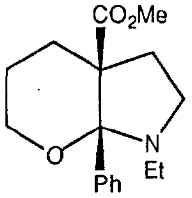
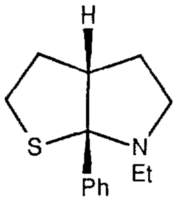
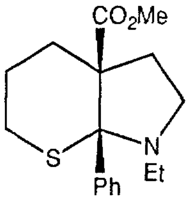
The imidate salts **5a** were readily obtained in good yield by reaction of imidochloride **8** with alkenyl alcohols **9**, followed by N-alkylation of the resulting imidates **10** with (trimethylsilyl) methyl triflate (scheme 3). Thioimidate salts **5b** were prepared via S-alkylation of N-ethyl thiobenzamide **11** using iodides and triflates **12**, followed by N-alkylation of thioimidates **13** with (trimethylsilyl) methyl triflate (scheme 3). Desilylation of salts **5** with caesium fluoride in acetonitrile at 85°C afforded the cycloadducts **7** presumably via intramolecular 1,3-dipolar cycloaddition of ylides **6** (scheme 2).



scheme 3

The results of these cycloadditions are summarised in table 1.

Table 1. Intramolecular [3+2] cycloadditions of imidate and thioimidate methylides **6**.

Entry				Cycloadduct	Yield[a]
1	X=O,	n=1,	Y=H		58%
2	X=O,	n=1,	Y=CO_2Me		96%
3	X=O,	n=2,	Y=CO_2Me		60%[b]
4	X=S,	n=1,	Y=H		70%
5	X=S,	n=1,	Y=CO_2Me		45%

notes

(a): All new compounds gave satisfactory i.r., n.m.r. and mass spectral data which were consistent with the proposed structures.

(b): In this case, the yield was estimated from the n.m.r. spectrum of an inseparable mixture of the cycloadduct and 4-(methoxycarbonyl) pent-4-enyl-1-ol benzoyl ester.

It is noteworthy that all the above cycloadditions are stereospecific[4] and in the case of cycloadditions yielding pendant five membered rings the reaction is facile even when the dipolarophile is an unactivated olefin (entries 1 & 4).

This is in contrast to the intermolecular cycloadditions of these dipoles which have been shown to occur with electron deficient dipolarophiles only. Closure to yield pendant six-membered rings however, occurs only if the dipolarophile is electron deficient[5] (entries 3 & 5); the systems containing unactivated olefins (**5**, Y=H, n=2) fail to yield any of the corresponding cycloadducts[6].

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References and notes

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   b) A number of unsuccessful desilylative intramolecular cycloaddition reactions have also been reported, see for example: A. Padwa, G. Haffmanns, M. Tomas, *J. Org. Chem.*, 1984, 49, 3314., E. Vedejs, F. G. West, *J. Org. Chem.*, 1983, 48, 4773. and A. Padwa, Y. Chen, W. Dent, H. Nimmesgern, *J. Org. Chem.*, 1985, 50, 4006.
4. The stereochemistry of the pyrrolo [2,3-b] furans and pyrans was shown to be exclusively cis by nOe difference spectroscopy.
5. Inspection of models for the possible transition states involved in ring closure to yield pyrrolo [2,3-b] pyrans reveals the existence of unfavourable steric interactions involving the nitrogen substituent and the methylene protons on the newly forming pyran ring.
6. See following paper.

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