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Hetero-1,3-Dipolar Cycloadditions of Dithiolane-Isocyanate Imminium Methylides: A Novel Route to 1,3-Oxazolidine- and Thiazolidine-2-thiones.

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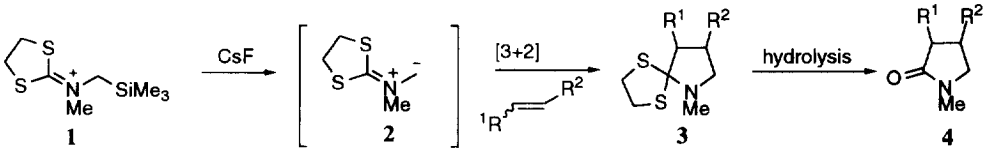
Abstract: Dithiolane- isocyanate imminium methylides which are a new type of azomethine methylide-derived 1,3-dipole undergo efficient and regioselective cycloaddition to conjugated carbonyls and thiocarbonyls to yield predominantly 1,3-oxazolidine- and thiazolidine-2-thiones formed from the initial cycloadducts via loss of thiirane.

We have recently described[1] the generation and cycloadditions of dithiolane-isocyanate imminium methylides **2**, which are a new type of azomethine ylide-derived 1,3-dipole (Scheme 1). These remarkable systems, which can be generated under very mild conditions from readily available precursors **1**,[2] were found to undergo efficient cycloaddition to a range of olefinic dipolarophiles to yield dithiolane-protected γ-lactams **3** which could be efficiently deprotected to yield the corresponding γ-lactams **4** in high yields (Scheme 1).



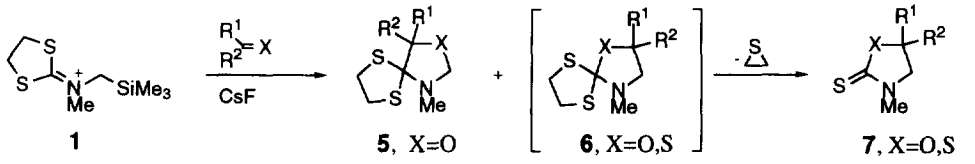
Scheme 1

The efficiency of these cycloadditions to olefins prompted us to explore the cycloadditions of dipole **2** to hetero-dipolarophiles, an area which has attracted relatively little attention despite the high dipolarophilic nature of the C=X bond[3] and obvious potential in heterocyclic synthesis[4].

We now report that the dithiolane-isocyanate imminium methylide **2**, generated from desilylation of readily available salt **1**, undergoes efficient cycloaddition to conjugated[5] carbonyls and thiocarbonyls to initially yield adducts **6** along with (where X=O) small amounts of the regioisomer **5** (Scheme 2). In the case of addition across a carbon-oxygen double bond, although clearly present in the crude reaction mixture (n.m.r), adducts **6** (X=O) could not be isolated and upon chromatography, the thiones **7** (X=O) were obtained, presumably *via* an acid-catalysed loss of thiirane[6] from adducts **6**, along with the adducts **5** (Scheme 2). Upon addition of **2** across

a carbon-sulphur double bond, the initial spirocyclic adduct **6** (X=S) is more stable and could be isolated. Conversion to the thiazolidine-2-thione **7** (X=S) was achieved by refluxing in chloroform (48 hours).

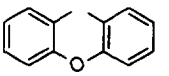
The results of a number of cycloadditions are summarised (Table 1).



Scheme 2

In a typical procedure a solution of the imino dithiolane salt **1** (1mmol) and the dipolarophile (1.1mmol) in the appropriate solvent (4ml) was added to cesium fluoride (4mmol) 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. Evaporation of the solvent followed by silica gel chromatography then furnished the pure cycloadducts.[7]

Table 1 Cyloaddition of azomethine ylide **2** to hetero-dipolarophiles.

Entry[a]	Carbonyl compound			Products **7**+**5** (% yield)[b]
	R^1	R^2	X	
1.	Ph	H	O	**7a** (59%) + **5a** (11%),
2.	4-(NO_2)-C_6H_4	H	O	**7b**(51%)[c] + **5b** (7%)
3.	2-napthyl	H	O	**7c**(28%) + **5c**(3%)
4.	4-(OMe)-C_6H_4	H	O	**7d**(52%) + **5d**(7%)
5.	Ph	Ph	O	**7e**(47%)
6.	(E)-C_6H_4CH=CH	H	O	**7f**(59%) + **5f**(11%)
7.	2-pyridyl	H	O	**7g**(63%)
8.			S	**7h**(43%)[c]

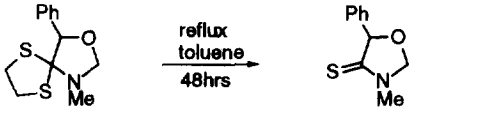
[a] Cycloadditions in acetonitrile except entry 8 in dimethoxyethane. [b] Product and yield after silica gel chromatography
[c] Quantitative from spirocycle **6** i on reluxing in chloroform (48hours).

The following points are noteworthy:

It is interesting that in all cases the regioisomeric preference is for cycloadduct type **6**, this being the only product from cycloaddition to benzophenone (**6e**, entry 5), pyridine-2-carboxaldehyde (**6g**, entry 7), and

xanthione[8] (**6h**, entry 8).The orientation preference in these reactions is in agreement with Frontier Molecular Orbital theory.[9] The regioselectivity appears to be a result of union of the larger LUMO coefficient on the carbon atom of the carbonyl group with the larger HOMO coefficient on the unsubstituted carbon of the 1,3-dipole.

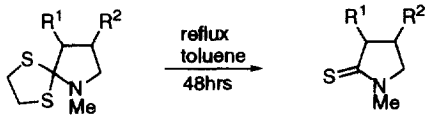
Conversion of the minor regioisomers **5a** to thiolactams **8a**, was achieved by refluxing in toluene (48 hours) (Scheme 3).



5a **8a**, 48%

Scheme 3

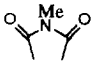
We have observed similar thermally-induced thiirane eliminations on heating lactam mercaptals **3** (prepared via addition of dipole **2** to olefins, Scheme 4).[1]



3 **9**

Scheme 4

Table 2 Thermolysis of adducts **3** to yield thiolactams **9**.

Entry	R^1	R^2	Product (% yield)[a]
1.	CO_2Me	H	**9a** (86%)
2.	H	CO_2Me	**9b** (70%)
3.	(*trans*)-CO_2Me	CO_2Me	(*trans*)-**9c** (92%)
4.			**9b** (95%)

[a] yield after isolation by silica gel chromatography

In summary, we have demonstrated that the readily available 1,3-dithiolane imminium methylide **2**, acts as a synthetic equivalent of a thiocarbonyl substituted azomethine ylide. Trapping with hetero-dipolarophiles allows simple access to oxazolidine-2-thiones and thiazolidine-2-thiones respectively. The overall sequence represents an intriguing application of the 1,3-dipolar cycloaddition approach to mixed heterocyclic frameworks. Studies are now in progress directed towards the synthetic application of this technique.

Acknowledgement.

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References and notes.

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4. Cycloaddition of azomethine ylides across several classes of heterodipolarophile are known, see: Lown, J.W. in *1,3-Dipolar Cycloaddition Chemistry*; Ed. Padwa, A.; Wiley, Vol. 1, p. 653 and references therein. A C=O double bond is the most common trapping agent, for some more recent examples see: (a) Kohra, S.; Ueda, K.; Tominaga, Y.; *Chem. Pharm. Bull.* **1995**, 43, 204. (b) Tominaga, Y.; Takada, S.; Kohra, S. *Heterocycles* **1995**, 105. (c) Tominaga, Y.; Ogata, K.; Kohra, S.; Hojo, M.; Hosomi, A. *Tetrahedron Lett.* **1991**, 32, 5987. (d) Tominaga, Y.; Yanagai, T.; Hojo, M.; Miyashiro, Y.; Hosomi, A. *J. Org. Chem.* **1990**, 55, 5308. (e) Padwa, A.; Haffmans, G.; Tomas, M. *J. Org. Chem.* **1984**, 49, 3314.
5. On attempted cycloaddition to simple non-conjugated aldehydes and ketones (eg. acetone, cyclohexanone and butyraldehyde), no reaction was observed.
6. Decomposition of similar 1,4,5,9-hetero spiro[4.4]nonanes has been observed, see: (a) Ueno, Y.; Nakai, T.; Okawara, M. *Bull. Chem. Soc. Japan* **1970**, 43, 168. (b) Baba, A.; Yano, K.; Amishiro, N.; Matsuda, H. *Bull. Chem. Soc. Japan* **1991**, 64, 2661.
7. All new compounds gave satisfactory spectroscopic and analytical data consistent with the indicated structures; representative data (entry 1): 3-methyl 4-phenyl oxazolidine-2-thione **7a** colourless needles (m.p.129-130°C; DCM/pet.). νmax(mull)cm^{-1}: 2960, 2880, 1530, 1430, 1330, 1310, 1180. ^{1}H NMR($CDCl_3$):δ 3.25(3H,s,NMe), 3.74(1H,dd,J=7,7.5Hz,Hβ-4), 4.19(1H,dd,J=7,7.5Hz,Hα-4), 5.64(1H,t,J=7Hz,Hβ-5), 7.31-7.48(5H,m). MS m/z(%): 193(M+, 56), 132(21), 104(100), 91(25), 78(19). Anal. $C_{10}H_{11}NOS$ requires(%) C 62.18 N 5.76 N 7.25 found(%) C 61.90 H 5.50 N 7.05. 9-phenyl, 6-methyl 1,4-dithia-6-aza-8-oxaspiro[4.4]nonane **5a** colourless oil. νmax(film)cm^{-1}: 2920, 2880, 1480, 1440, 1240, 1200. ^{1}H NMR($CDCl_3$):δ 2.49(3H,s,NMe), 2.79(1H,m,H-2'), 2.99-3.20(3H,m,H-2,3), 4.47(1H,d,J=12Hz,H-7α), 4.48 (1H,d,J=12Hz,H-7β), 5.40(1H,s,H-9), 7.31-7.40(3H,m), 7.50-7.60(2H,m). MS m/z(%): 253(M+, 70), 193(81), 147(66), 119(91), 105(43), 87(100), 77(31), 60(24), 44(34). Anal. $C_{12}H_{15}NOS_2$ requires(%) C 56.92 H 5.93 N 5.53 found(%) C 56.60 H 5.60 N 5.40. Complete experimental details will be published elsewhere.
8. Lawesson, S.O.; Scheibye. S.; Shabana, R. *Tetrahedron* **1982**, 38. 993.
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