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Dithiolane-Isocyanate Imminium Methylides: A Rapid Stereoselective Entry into γ-Lactams

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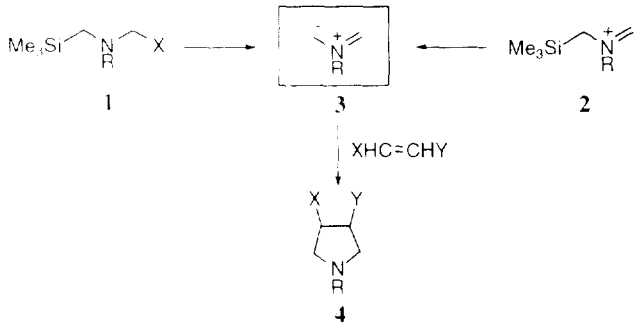
Abstract: *Methods have been developed for the generation and trapping of dithiolane-isocyanate imminium methylides which are a new type of azomethine methylide-derived 1,3-dipole. These species add efficiently and stereoselectively to electron deficient olefins yielding novel dithiolane-protected γ-lactams which can be efficiently deprotected to yield the corresponding lactam systems.*

The considerable pharmacological and biological importance of heterocyclic systems, particularly those that are based upon saturated or partially saturated rings, continues to attract tremendous synthetic effort. In particular, much work has focussed on stereocontrol in the synthesis of such species where the relative disposition of substituents is important.

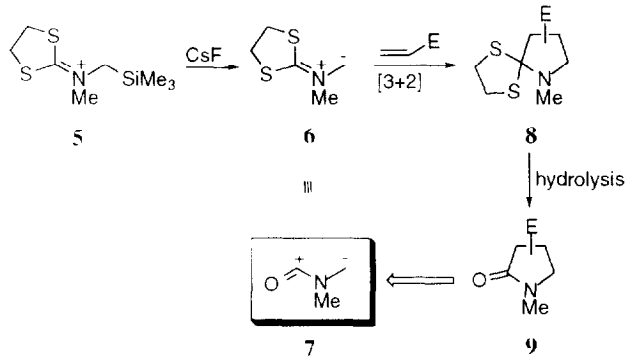
In terms of the stereocontrolled synthesis of heterocyclic five-membered ring frameworks, the 1,3-dipolar cycloaddition strategy remains amongst the most powerful. During the last two decades, the synthetic potential of this approach has been considerably enhanced by the development of mild and versatile methods for the generation and cycloadditions of synthetically useful dipoles, particularly in the case of azomethine[1]- and carbonyl ylides[2]. A particularly mild method for the generation of 'non-stabilised' azomethine ylides involves the desilylation, usually under the influence of fluoride, of (trimethylsilyl)methyl amino **1**- or imminium systems **2**[3]. The resultant azomethine ylides **3** can be trapped with electron deficient dipolarophiles to give access to usefully-functionalised pyrolidines **4**.



In the light of the very widespread occurrence of γ-lactam rings, both in naturally occurring molecules, and in pharmacologically important synthetic systems, we were intrigued by the possibility of producing such a framework directly from a 1,3-dipolar cycloaddition strategy. Although we were aware of a number of reports

on the oxidation of pyrrolidine rings[4] (including proline derivatives[5]) to yield γ-lactams, no direct general approach appeared to be available[6].

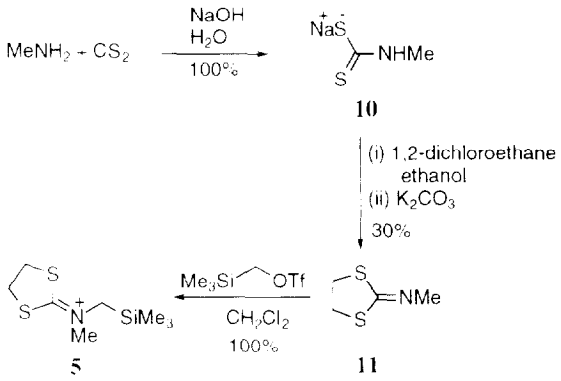
We now report that the dithiolane-isocyanate imminium methylide **6**, generated from desilylation of readily available salt **5**, acts as a synthetic equivalent of the carbonyl-fused azomethine ylide **7**, and undergoes efficient cycloaddition to electron deficient dipolarophiles to yield lactams **9** following hydrolysis of the intermediate dithiolanes **8** (Scheme 1).



5 **6** **8** **7** **9**

Scheme 1

The dipole precursor **5** is easily prepared via amination of carbon disulphide to yield the sodium dithiocarbamate **10** which is alkylated to yield the iminodithiolane **11**[7]. This then undergoes facile alkylation to yield **5** (Scheme 2). The salt **5** prepared as its triflate, is a stable crystalline solid and can be stored under anhydrous conditions for months without any noticeable decomposition.



10 **5** **11**

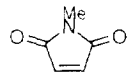
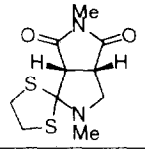
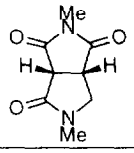
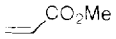
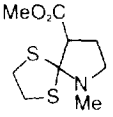
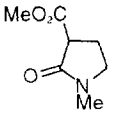
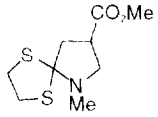
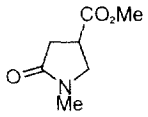
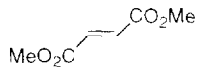
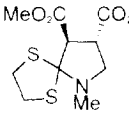
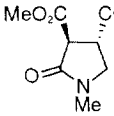
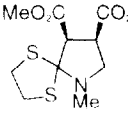
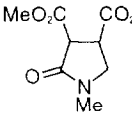
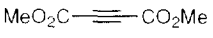
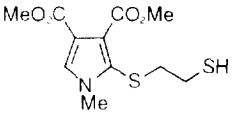
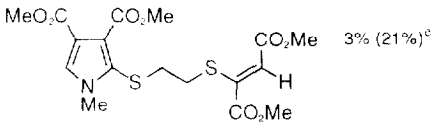
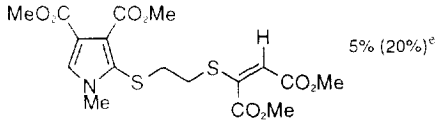
Scheme 2

Salt **5** was found to undergo efficient desilylation using cesium fluoride and, in the presence of electron deficient olefins[8], yielded dithiolane-containing adducts **8**[9], presumably via intermediate dipole **6**. The results of a number of cycloadditions are summarised (Table 1).

Interestingly, cycloaddition to a monosubstituted olefin (entry 2) showed only moderate regioselectivity and yielded a mixture of regioisomers with the 'proximal' isomer (with respect to the ester and dithiolane moieties) predominating. In addition, cycloaddition to non-cyclic disubstituted olefins (entries 3 and 4) is stereospecific, although in the case of addition to dimethyl maleate (entry 4) the initial *cis*-adduct is unstable and

underwent slow conversion over a number of weeks to the *trans*-isomer. Attempted chromatography resulted in rapid and complete stereomutation and only the *trans*-isomer could be isolated.

Table 1.

entry	dipolarophile[a]	cycloadduct(s)[b]	yield	γ-lactam[b]	yield
1)			82%		85%
2)			54%		65%
			25%		60%
3)			87%		70%
4)			80%[c]		54%[d]
5)			54% (13%)[e]		
			3% (21%)[e]		
			5% (20%)[e]		

[a] 1.1 equivalent unless indicated otherwise; [b] All new compounds gave satisfactory spectroscopic and analytical data consistent with the indicated structures; [c] yield estimated from ^{1}H NMR spectrum of unpurified material; [d] total isolated yield of lactams obtained as 1:1 mixture of *cis* and *trans* isomers which could be separated via chromatography; [e] yield in the presence of 2 equivs. DMAD.

It appears these cycloadducts are the first reported dithiolane-protected forms of lactams and thus we were keen to explore their behaviour upon attempted deprotection. The oxygen analogues of these species are known and have been efficiently hydrolysed to lactones using a standard Hg(II) procedure[10]. However, exposing the

dithiolane-containing cycloadducts **8** to a mixture containing HgO/BF_3/H_2O/THF[11] gave only highly insoluble mixtures. Fortunately, a number of alternative hydrolytic procedures are known[12], and by applying the oxidative methodology reported by Hojo[13] (SO_2Cl_2/SiO_2), excellent yields of lactams were obtained (Table 1).

The moderate regiochemistry displayed by dipole **6** (entry 2) was surprising as upon first inspection, it would appear that the termini of the dipole are highly dissimilar and thus would be expected to exhibit good regiochemical control with non-symmetrical dipolarophiles. We have thus calculated the energies and coefficients for the HOMO and LUMO of this dipole using a semi-empirical method[14]. These calculations reveal that in fact, dipole **6** is electronically rather symmetric, this being particularly the case for the coefficients in the HOMO whose interaction with the LUMO of the dipolarophile will have the most significant contribution to the energy of the transition state[15] (Figure 1). Additionally, the calculations also predict that this dipole is not planar but possesses a pucker within the dithiolane ring system (Figure 2).

Figure 1. FMO LCAO coefficients and energy levels.

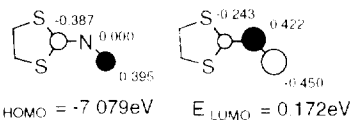
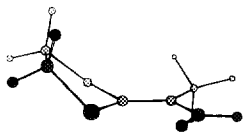


Figure 2. Model of azomethine ylide **6**.



Work directed towards the synthetic manipulation of this novel entry into γ-lactam containing natural products is now in progress.

Acknowledgement

We thank the EPSRC and Glaxo Group Research for financial support.

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8. When the acetylenic dipolarophile, dimethyl acetylenedicarboxylate (DMAD) was used as the trapping agent (entry 5), none of the dithiolane containing adduct was isolated, instead, (presumably via *in-situ* aromatisation) a pyrrole and its 2:1 Michael adducts were recovered (interestingly, in proportions dependent on the initial equivalence of DMAD).
9. Typical procedure: A solution of the imino dithiolane salt **5** (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. Evaporation of the solvent followed by flash silica gel chromatography then furnished the pure dithiolanes.
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