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Thiocarbonyl-based 1,3-dipolarophiles for the synthesis of C(2)-unsubstituted penems*

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Abstract: The azomethine ylid strategy for β-lactam synthesis, which involves the fragmentation of a β-lactam-based oxazolidinone to give a carboxylated azomethine ylid, has been extended to the C(2)-unsubstituted penem scaffold associated with C(6)-exoalkylidene penems. This involved the use of *S*-methyl dithioformate as a reactive 1,3-dipolarophile, which was most effectively employed by initial trapping with cyclopentadiene and subsequent regeneration of *S*-methyl dithioformate via a retro Diels–Alder reaction in the presence of the requisite oxazolidinone. This provided access to the penam scaffold, and this overall sequence was very effectively accelerated by microwave irradiation. The synthesis of C(2)-unsubstituted penems was then accomplished by application of an oxidative elimination sequence.

Keywords: Thiocarbonyls; dithioformates; penems; β-lactams; azomethine ylids.

AZOMETHINE YLID STRATEGY FOR β-LACTAM SYNTHESIS: INTRODUCTION AND BACKGROUND

Scope of the basic cycloaddition process

Over recent years, we have developed a novel, direct and convergent, and structurally versatile approach to the synthesis of bicyclic β-lactams **2** based on the intermolecular cycloaddition of a β-lactam-based azomethine ylid with a suitable 1,3-dipolarophile. The essential features and scope of this chemistry are outlined in Scheme 1, and the azomethine ylid reactivity required is released by thermolysis of the β-lactam-based oxazolidinone **1** (in this paper, R = 4-nitrobenzyl, PNB) [1]. The azomethine ylid reactivity generated from **1** has been trapped by a range of alkenes and alkynes, to provide carbapenams and Δ^1-carbapenems, respectively, as well as aldehydes and ketones (to give oxapenams), imines and azirines (generating azapenams and azacephams, respectively), and sulfur-based dipolarophiles [2–5]. The latter class of dipolarophile is the focus of this paper and will be discussed in more detail below.

In more general terms, we have usually observed a high degree of regioselectivity, and, although in some cases only modest yields of cycloadducts were obtained (however, see below), this is compensated for by the very direct entry afforded by this azomethine ylid-based approach. It is also appropriate to point out that oxazolidinone **1** is available in enantiomerically pure form (this intermedi-

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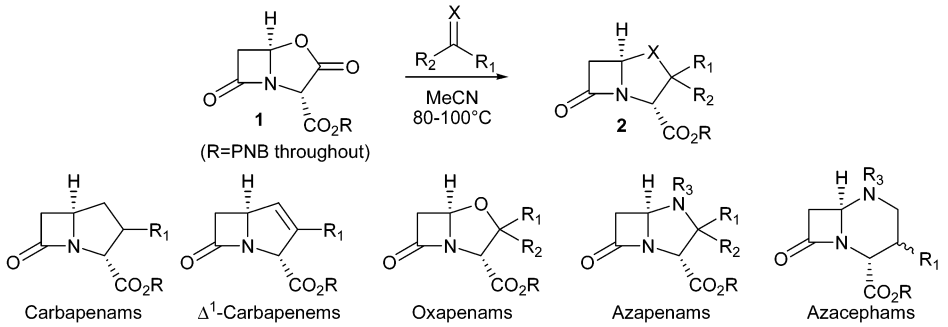


Scheme 1

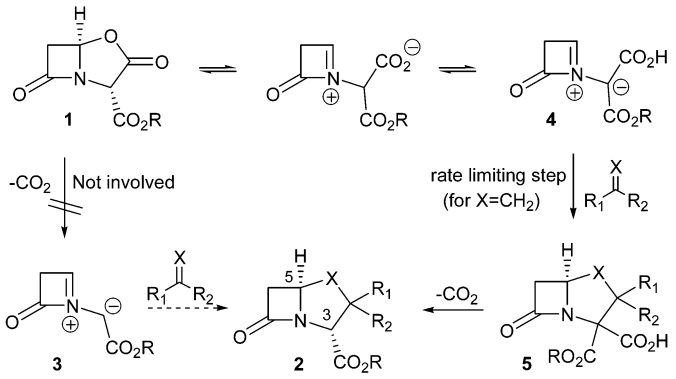
ate is prepared very readily from clavulanic acid [6]), however, it is important to appreciate that cycloadducts **2** are produced as racemates. We have described a C(6)-substituted oxazolidinone, which is enantiomerically pure and does provide enantiomerically and diastereomerically pure cycloadducts (see below) [2].

Elucidation of reaction mechanism: The structure of the azomethine ylid intermediate

The mechanistic features associated with the chemistry shown in Scheme 1 were both unexpected and surprising [7]. While *N*-alkyl or *N*-aryl oxazolidinones are well established as precursors to simple azomethine ylids [8], the unusual structure of **1** opens an alternative and dramatically different mechanistic pathway, which we have exploited in a number of ways. These mechanistic features are of particular significance within the context of the work described in this paper, and it is appropriate to review our earlier studies.

A central aspect of this chemistry is the structure of the azomethine ylid intermediate generated from oxazolidinone **1**. Based on the precedent associated with earlier work in this area, then an initial and concerted decarboxylation of **1** might be anticipated which would lead to azomethine ylid **3**; this reactive intermediate would be expected to react with a 1,3-dipolarophile to provide the observed cycloadducts **2** [8]. These earlier studies relating to the fate of *N*-alkyl/aryl oxazolidinones were not supported by quantitative kinetic data, but more qualitative observations did suggest that the decarboxylation event was both the initial step and also rate-limiting as the overall rate of reaction was not significantly dependent on the nature of the dipolarophile [8d,e]. This notion was not in accord with our own studies where we noted at the outset that the overall rate of reaction, including the rate at which oxazolidinone **1** was consumed, did depend on the reactivity of the dipolarophile used. This prompted a more detailed study, and key results are summarized here.

i. The overall process does involve a concerted cycloaddition; stereospecific reactions with maleate and fumarate were observed.
ii. A detailed kinetic study was carried out using the reaction of oxazolidinone **1** with *N*-phenyl maleimide. This demonstrated that the cycloaddition process was overall second order and first order with respect to both **1** and *N*-phenyl maleimide.
iii. The apparent ability of oxazolidinone **1** to survive under some reaction conditions (in the presence of less reactive dipolarophiles) was puzzling and merited investigation. It became clear that thermolysis of **1** *in the absence of a dipolarophile* did not lead to decomposition of **1** as would be expected if a pathway involving **1** → **3** was involved. Closer studies revealed that although **1** could be recovered after thermolysis in the absence of a trap, this recovered material was racemic. We then established that **1** underwent a first-order racemization when heated in acetonitrile. Based on these (and other) studies, we have suggested the mechanistic pathway shown in Scheme 2.

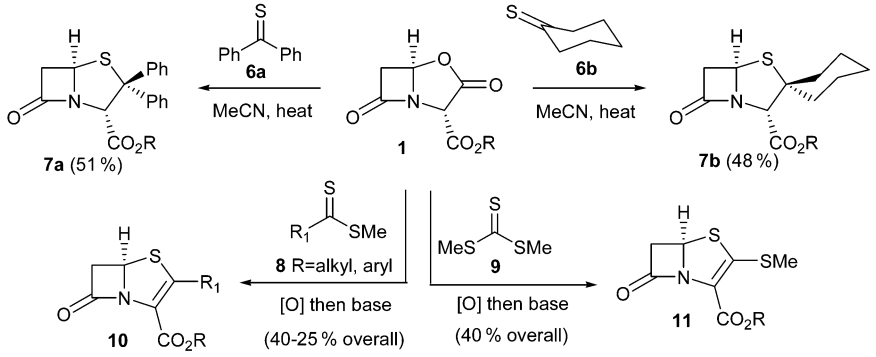


Scheme 2

Our current evidence supports the intermediacy of the *carboxylated* azomethine ylid **4**, and *not* the simpler dipolar species **3**, the result of a direct and concerted decarboxylation of oxazolidinone **1** [7]. Azomethine ylid **4** arises via a stepwise and reversible fragmentation/tautomerization of oxazolidinone **1**. In the absence of a dipolarophile, then reversible formation of **4** would lead to the racemization of oxazolidinone **1**, which we observed. However, when a reactive trap is present, this equilibrium is intercepted and cycloaddition occurs, leading to the carboxylated cycloadduct **5**. This latter intermediate has not to date been isolated or observed, but indirect evidence of its formation is available. It is striking that in all of the cycloadducts **2** we have isolated, and many have been characterized by X-ray crystallography, the C(3) and C(5) stereocenters correspond to the thermodynamically more stable arrangement (as in **2**). This would be consistent with decarboxylation of **5** under equilibrating conditions. Another important consequence of this mechanistic hypothesis is that the key 1,3-dipole **4** is essentially "always available" within the reaction mixture, a feature that has important implications of the chemistry described below.

Application of C=S containing 1,3-dipolarophiles

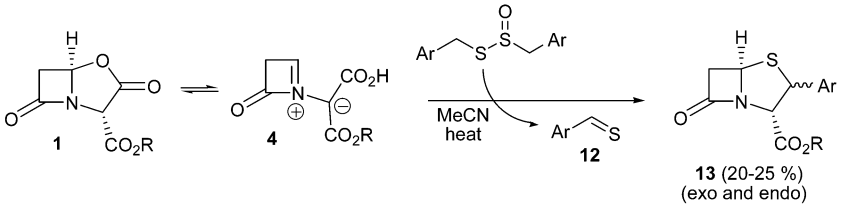
The role of C=S containing dipolarophiles is highly pertinent to this discussion, and again it is appropriate to reflect on our earlier contributions in this area (Scheme 3). We have exploited a range of substrates, including diaryl and dialkyl thioketones (exemplified by **6a** and **6b**), which undergo a highly regioselective cycloaddition to provide a one-step entry to penams **7a/b**. Similarly, dithioesters **8** and trithiocarbonates **9** are effective dipolarophiles, but in these cases, the initial cycloadducts are readily converted (by *S*-oxidation and base-mediated elimination of MeSOH) to the corresponding 2-substi-



Scheme 3

tuted penems **10** and **11**, respectively [5]. Again, the azomethine ylid strategy demonstrates its value by providing a very direct and convergent entry to an important class of β-lactam derivative [9].

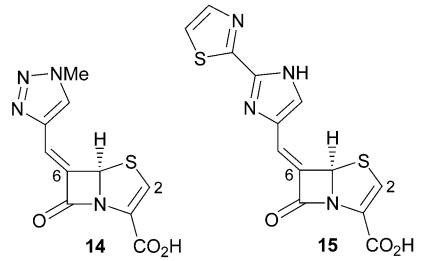
We have also trapped highly reactive thioaldehydes **12** using oxazolidinone **1** (Scheme 4) [10]. This chemistry exploits a key feature of the mechanism outlined in Scheme 2—the "always available" nature of key azomethine ylid **4**—in as much as we relied on the presence of a steady-state concentration of this intermediate—and the requisite thioaldehydes were then liberated in situ by thermolysis of the requisite thiosulfinate [11]. Although yields of adducts **13** were modest, this not only provided additional support for our basic mechanistic hypothesis, but also demonstrated an ability to generate and trap highly reactive and otherwise elusive 1,3-dipolarophiles. These observations, which were also extended to other highly reactive derivatives, played a key role in the exploitation of other thiocarbonyl-based dipolarophiles described below.



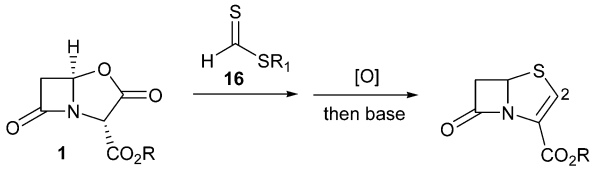
Scheme 4

DITHIOFORMATES AS 1,3-DIPOLAROPHILES: GENERATION OF C(2)-UNSUBSTITUTED PENEMS

In a broader sense, penems represent important pharmaceutical targets [9], and the C(6)-exoalkylidene penems, e.g., BRL-42715 **14** [12a], together with more recently described variants such as **15** [12b], are of particular interest.

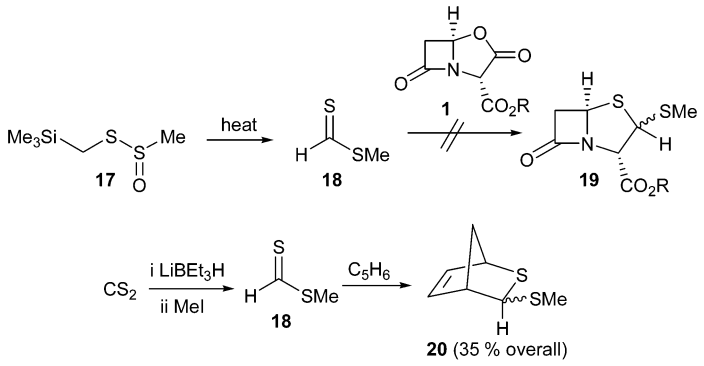


These reactive penem derivatives show potent inhibitor activity against a number of critical enzymes associated with antibiotic resistance, such as the Class A and Class C β-lactamases [13]. The penem moiety contained within **14** lacks a substitutent at C(2), and our objective was to generate this fragment by exploiting a dithioformate **16** as a novel 1,3-dipolarophile and apply the methodology developed for C(2)-substituted penems (see Scheme 3) as outlined in eq 1.



(1)

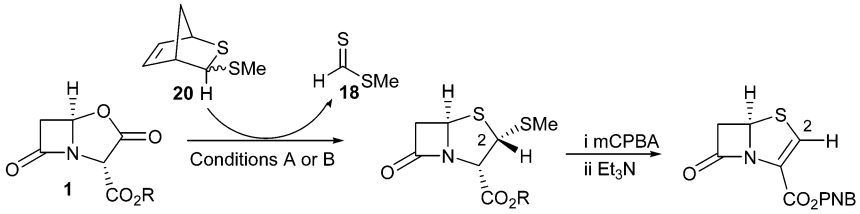
S-Methyl dithioformate **18** is the simplest member of this class of thiocarbonyl derivatives, and two preparative routes to methyl dithioformate **18** have been described (Scheme 5). Unfortunately, the elegant work of Block [14] was not suited to our purpose. Attempts to trap **18**, generated by thermolysis of **17** in the presence of oxazolidinone **1**, failed to provide the desired cycloadduct **19**; fragmentation of **17** does generate other reactive species en route to **18** that could react with either **1** or 1,3-dipole **4**. Oxazolidinone **1** is sensitive to acid, and we observed decomposition of this component when thermolysis of **1** in the presence of **17** was attempted.



Scheme 5

Seyferth has reported an alternative approach to the synthesis of *S*-methyl dithioformate, which involves reduction and in situ methylation of carbon disulfide [15]. This chemistry does provide **18**, but we found that it is difficult to isolate this product cleanly: methyl dithioformate **18**, as well as other related dithioformates we have generated, was volatile and difficult to handle. Nevertheless, **18** is readily observed in solution (δ_H $CDCl_3$ 11.33, HC(S)SMe), and the major difficulty identified was associated with isolation of this intermediate. A successful solution to this problem was to trap **18** as a Diels–Alder cycloadduct and then to release the dipolarophile by a subsequent cycloreversion. *S*-Methyl dithioformate was not sufficiently reactive to be trapped by anthracene, but reaction with cyclopentadiene was straightforward and provided a 1.5:1 mixture of the *exo* and *endo* cycloadducts **20** in 35 % overall yield from carbon disulfide [16].

Subsequent thermolysis (MeCN, reflux) of **20** (to promote the retro Diels–Alder reaction and release methyl dithioformate **18**) in the presence of oxazolidinone **1** gave the desired adduct **19**, but in only 19 % yield (Scheme 6). Coupled with the long reaction time (2 days), this yield was unacceptable. However, this reaction was very effectively accelerated when carried out in a microwave reactor. When



Conditions A: MeCN, reflux, 2 days (19 % of *exo/endo* **19**)

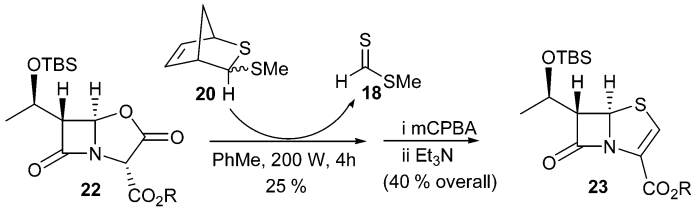
Conditions B: PhMe, microwave irradiation (55 W), 1 h (76 % of *exo/endo* **19**)

Scheme 6

a toluene solution of **1** and **20** was subjected to microwave irradiation, then **19** was isolated in 76 % yield after only 1 h.

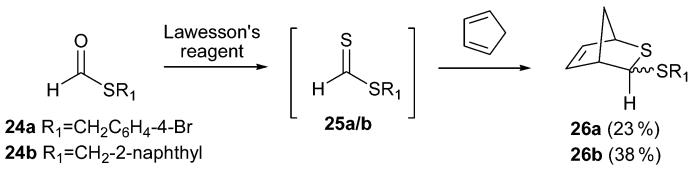
Cycloadduct **19** [as a 2.5:1 mixture of C(2) *exo* and *endo* cycloadducts] was then converted efficiently to the target C(2) unsubstituted penem via mild oxidation using mCPBA and subsequent base treatment, and **21** was isolated in 70 % yield. As seen in our earlier studies, the oxidation of **19** was highly regioselective and the endocyclic sulfur atom proved to be much less reactive than the *exo*-SMe moiety [16].

This chemistry has also been applied to a C(6)-substituted penem **23**, which is relevant to the extension of this approach to the synthesis of C(6)-exoalkylidene penems. This involved use of the enantiomerically pure C(6)-substituted oxazolidinone **22** [1,17]. The advantage of this system is that C(6) and the adjacent stereocenter are retained during the overall process, and the presence of the bulky C(6) residue effectively controls the approach of the dipolarophile in the cycloaddition step. This provides an enantiomerically pure penem **23** albeit in a modest overall yield (Scheme 7).



Scheme 7

There are limitations associated with the reduction/alkylation of carbon disulfide used to generate methyl dithioformate **18**. For example, we were unable to generate *S*-benzyl dithioformate via reduction of CS_2 and in situ alkylation with benzyl bromide. Accordingly, it is appropriate to mention briefly that an alternative route to dithioformates has also been investigated (Scheme 8) [18]. Readily available thioformates **24a** and **24b** have been successfully thionated using Lawesson's reagent. Like methyl dithioformate **18**, the resulting dithioformates **25a/b** could be observed spectroscopically, but again proved difficult to isolate. Both derivatives were, however, trapped using cyclopentadiene to give adducts **26a/b** in modest overall yield. These adducts were also amenable to cycloreversion and have been applied in much the same way as outlined in Scheme 6 for cycloadduct **20**.



Scheme 8

The other aspect of this chemistry that merits comment is the use of microwave acceleration for related 1,3-dipolar cycloaddition reactions [18]. It is feasible that cycloreversion of **20** is accelerated, thereby providing the key 1,3-dipolarophile **18** more rapidly, but we have also observed similar effects of microwave acceleration—much shorter reaction times and improved yields of cycloadducts—using a range of more conventional and more stable dipolarophiles. This suggests that either the rate of formation of azomethine ylid (**1** → **4**, Scheme 2) or the cycloaddition step (**4** → **5**, Scheme 2) may be influenced by these conditions. While the latter is nominally the rate-determining step, this was demonstrated with a simpler alkenyl dipolarophile and it would be premature to assume that C=S-based systems will behave in the same way; for example, the possibility of a stepwise mechanism involving

the sulfur center as a nucleophile cannot be excluded. This aspect of the chemistry does require further investigation, and it will be of interest to probe which step or steps are influenced by microwave irradiation.

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