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S-Alkyl Dithioformates as 1,3-Dipolarophiles. Generation of C(2)-Unsubstituted Penems

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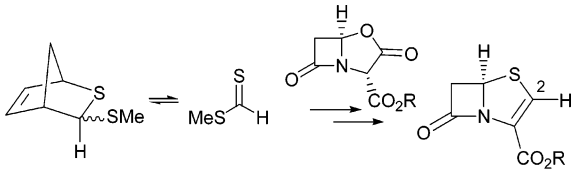
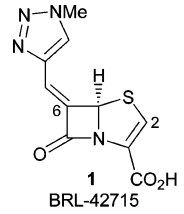
ABSTRACT



S-Alkyl dithioformates, generated by a cycloreversion process, react as 1,3-dipolarophiles with β-lactam-based azomethine ylids to provide, after (net) elimination of MeSH, C(2)-unsubstituted penems. The overall cycloreversion/cycloaddition sequence was accelerated by microwave irradiation.

Penems represent a continuing area of interest within the β-lactam area.[1] In particular, 6-exoalkylidene variants such as **1**[2a] and **2**[2b] have attracted attention because of their potent activity against class A and class C β-lactamases and bacterial signal peptidase, respectively, profiles that makes this group of C(2)-unsubstituted penems attractive both for clinical application and as biological probes for β-lactamase structure and function.[3]

We have previously described a versatile entry to bicyclic β-lactams, including C(2)-substituted penams and penems



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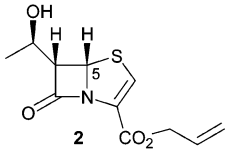

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resulting from the generation of β-lactam-based azomethine ylid reactivity.[4]

Oxazolidinone **3** (PNB = 4-nitrobenzyl) reacts (via a sequential ring cleavage to give azomethine ylid **4** and *then* cycloaddition followed by decarboxylation)[4b,d] with thioketones to provide racemic penams **5** ($R_1 = R_2$ = alkyl, aryl). Use of dithiocarboxylates and trithiocarbonates as 1,3-dipolarophiles leads, after net loss of MeSH, to C(2)-

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(1) Georg, G. I., Ed. *Bioorg. Med. Chem. Lett.* (Symposia-in-Print no. 8), **1993**, *3*, 2159−2313. *The Organic Chemistry of β-Lactams;* Georg, G. I., Ed.; VCH: New York, 1992. Perrone, E.; Franceschi, G. In *Recent Prog. Chem. Synth. Antibiot.* Lukacs, G., Ohno. M., Eds.; Springer: Berlin, 1990; Vol. 1, pp 613−703.

(2) (a) Osborne, N. F.; Atkins, R. J.; Broom, N. J. P.; Coulton, S.; Harbridge, J. B.; Harris, M. A.; Stirling-François, I.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 179−188. (b) Allsop, A.; Brooks, G.; Edwards, P. D.; Kaura, A. C.; Southgate, R. *J. Antibiotics* **1996**, *49*, 921−928. Allsop, A. E.; Brooks, G.; Bruton, G.; Coulton, S.; Edwards, P. D.; Hatton, I. K.; Kaura, A. C.; McLean, S. D.; Pearson, N. D.; Smale, T. C.; Southgate, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 443−448.

(3) For an example of the use of a novel 6-exoalkylidene variant related to **1** as a probe for the β-lactamase structure and mechanism of action using X-ray crystallography, see: Nukaga, M.; Abe, T.; Venkatesan, A. M.; Mansour, T. S.; Bonomo, R. A.; Knox, J. R. *Biochemistry* **2003**, *42*, 13152−13159.

(4) (a) Martel, S. R.; Wisedale, R.; Gallagher, T.; Hall, L. D.; Mahon, M. F.; Bradbury, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309. (b) Martel, S. R.; Planchenault, D.; Wisedale, R.; Gallagher, T.; Hales, N. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1897. (c) Gallagher, T. *J. Heterocycl. Chem.* **1999**, *36*, 1365−1354. (d) Brown, D.; Brown, G. A.; Martel, S. R.; Planchenault, D.; Turmes, E.; Walsh, K. E.; Wisedale, R.; Hales, N. J.; Fishwick, C. W. G.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1270−1280. (e) Brown, G. A.; Martel, S. R.; Wisedale, R.; Charmant, J. P. H.; Hales, N. J.; Fishwick, C. W. G.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1281−1289.

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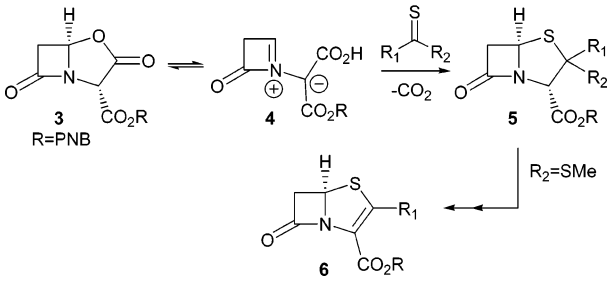
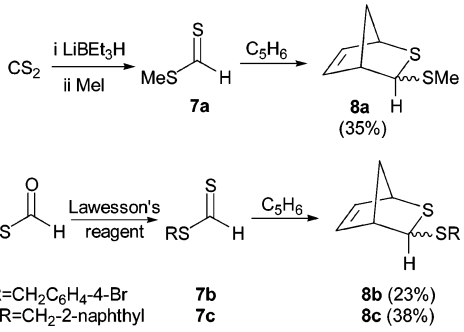
Scheme 1. Azomethine Ylid Strategy for the Synthesis of Penams and Penems



substituted penems **6** (R_1 = alkyl, aryl, *S*-alkyl) (Scheme 1).[5] The extension of the azomethine ylid strategy to the synthesis of the C(2)-unsubstituted penem moiety (i.e., **6**, R_1 = H) that is associated with **1** and **2** is the focus of this paper.

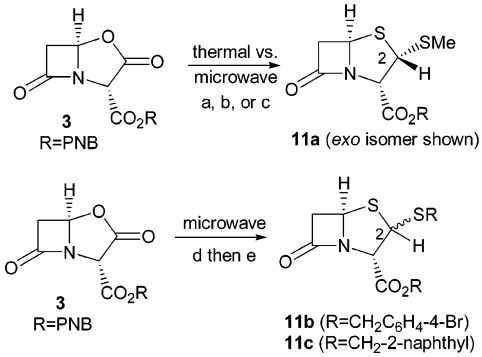
Achieving this objective required access to dithioformates **7** and an evaluation of the ability of these units to function as effective 1,3-dipolarophiles. Only a very limited range of dithioformates have been reported to date,[6,7] and various approaches to *S*-alkyl dithioformates **7** were evaluated (Scheme 2).

Scheme 2. Generation and Trapping of Dithioformates



S-Methyl dithioformate **7a** is available by reduction of CS_2 with $LiBEt_3H$ followed by *S*-methylation.[7] We found it most convenient (see below) to trap **7a** with cyclopentadiene to give the corresponding cycloadduct **8a** as a 1.5:1 mixture of *exo* and *endo* isomers in 35% yield.[8] The *S*-benzyl variants

Scheme 3. Dithioformates as 1,3-Dipolarophiles[a]



[a] Thermal vs microwave conditions studied: (a) (thermal) **8a**, MeCN, 2 days, 80 °C (19%); (b) (microwave) screw cap pressure vessel, **8a**, PhMe, 55 W, 1 h (76%) or **8a**, $emimPF_6$ (10 mol %), 55 W, PhMe, 1 h (56%); (c) (microwave) *open* vessel, **8a**, PhMe, 200 W, 5 h (62%) or **8a**, $emimPF_6$ (10 mol %), 55 W, PhMe, 4 h (40%); (d) (microwave) open vessel, **8b**, PhMe, 200 W, 4 h, (45%); (e) (microwave) screw cap pressure vessel, **8c**, PhMe, $emimPF_6$ (10 mol %), 55 W, 1 h, (45%).

7b and **7c** were best obtained by direct thionation of the corresponding thioformates **9**[9] and **10**[9] using Lawesson's reagent.[10] In both cases, the target dithioformates **7b** and **7c** were not isolated but were trapped in situ with cyclopentadiene to give cycloadducts **8b** and **8c**, respectively, in moderate yields for this two-step sequence.[11,12]

Cycloadducts **8a**−**c** were especially attractive for our purposes, representing a potentially controlled supply of the requisite dithioformate (via 4 + 2 cycloreversion); the retro Diels−Alder reaction provides an in situ source of dipolarophile that is compatible with release of the key azomethine ylid intermediate **4** from oxazolidinone **3**.[13]

This strategy was validated, and thermolysis of **8a** in the presence of oxazolidinone **3** provided the racemic cycloadduct **11a** as a 2.5:1 mixture of *exo* and *endo* isomers (Scheme 3). The structure of *exo*-**11a** was confirmed by X-ray crystallography (see Supporting Information).

However, this thermal process (conditions a) did require 2 days to go to completion and this only achieved a very

(5) (a) Planchenault, D.; Wisedale, R.; Gallagher, T.; Hales, N. J. *J. Org. Chem.* **1997**, *62*, 3438. (b) Highly reactive thioaldehydes have also been generated and trapped in situ: Brown, G. A.; Anderson, K. M.; Large, J. M.; Planchenault, D.; Urban, D.; Hales, N. J.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1897−1900.

(6) Block, E.; Aslam, M. *Tetrahedron Lett.* **1985**, *26*, 2259−2262.

(7) (a) Seyferth, D.; Womack, G. B. *Organometallics* **1984**, *3*, 1891−1897. (b) Gandhi, T.; Nethaji, M.; Jagirdar, B. R. *Inorg. Chem.* **2003**, *42*, 4798−4800. Jagirdar et al.[7b] were able to isolate **7a** by distillation. Block[6] and Seyferth[7a] did not isolate this volatile component but trapped it in situ as a Diels Alder cycloadduct and as an Fe-based coordination complex, respectively.

(8) Similar *exo* and *endo* cycloadducts based on thioaldehydes have been characterized previously. Kirby, G. W.; Lochead, A. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1325−1327. Vedejs, E.; Stults, J. S.; Wilde, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5452−5460.

(9) Bax, P. C.; Holsboer, D. H.; Van der Veek, A. P. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 562−567.

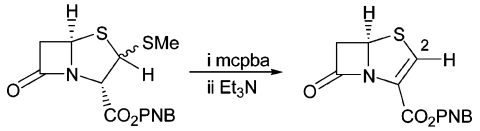
(10) *S*-Benzyl dithioformate ($PhCH_2SC(S)H$) could not be prepared using the reduction/*S*-alkylation strategy associated with **7a** but was obtained by direct thionation of the corresponding thioformate ($PhCH_2SC(O)H$) using Lawesson's reagent. NMR ($CDCl_3$) for $PhCH_2SC(S)H$: δ_H 11.28; δ_C 216.8). However, we were unable to isolate this product in an efficient manner, but this served as a model for the preparation of **7b** and **7c**.

(11) **8b** and **8c** were obtained as a 0.6:1 and 1.7:1 mixture of *exo* and *endo* isomers, respectively.

(12) One of the issues contributing to the yields obtained for **8b/c** was purification of the desired product from the residues associated with the thionation step. Ley (Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358−361) has reported a solid-phase variant of Lawesson's reagent. In our hands, this reagent worked well for the thionation of amides, but we were unsuccessful in our attempts to thionate *S*-benzyl thioformate ($PhCH_2SC(O)H$); see ref 10.

(13) Mechanistic studies provide evidence that oxazolidinone **3** is in equilibrium with the carboxylated azomethine ylid **4**. This pathway provides an equilibrium concentration of **4**, and we have exploited this to trap highly reactive and short-lived 1,3-dipolarophiles.[5b]

Scheme 4. Generation of a C(2)-Unsubstituted Penem



11a (*exo* and *endo*) **12** (70%)

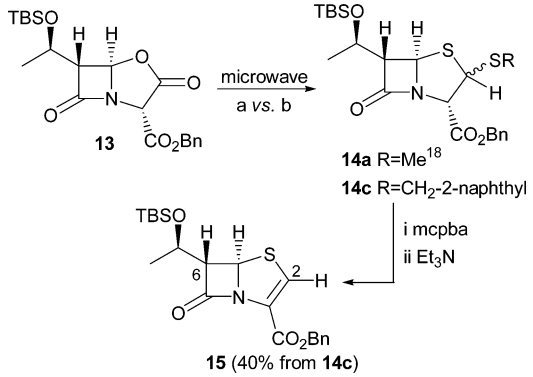
modest 19% yield of cycloadduct **11a**.[14] This hurdle was overcome by carrying out the fragmentation of **8a** and subsequent 1,3-dipolar cycloaddition step with microwave irradiation (conditions b and c). Using toluene as a solvent, a 76% yield of the target cycloadduct **11a** was isolated following irradiation of **3** and **8a**.[15] Cycloadduct **11a** was obtained in 56% yield when the same reaction was carried out for 1 h using 10 mol % of an ionic liquid (emimPF_6) as an additive.[16] This reaction was carried out using both sealed and open vessel conditions. On the basis of other observations,[14] microwave irradiation is expected to accelerate the retro Diels−Alder reaction of **8a** but may also promote the 1,3-dipolar cycloaddition step between **4** and **7a**. Significantly, we have observed considerable rate and yield increases when **3** has been reacted with stable dipolarophiles, e.g., *N*-phenyl maleimide, under the same microwave conditions.

A similar cycloreversion/1,3-dipolar cycloaddition sequence was also achieved using cyclopentadiene adducts **8b** and **8c** to provide the bicyclic β-lactams **11b** and **11c** (Scheme 3).

Elaboration of **11a** to the corresponding C(2)-unsubstituted penem was carried out by *S*-oxidation followed by base treatment to give the C(2)-unsubstituted penem **12** in 70% yield (Scheme 4). The base-mediated elimination step was also examined under microwave radiation conditions but provided **12** in a lowered yield (40%).

We were interested in extending the processes outlined in Schemes 3 and 4 to a C(6)-substituted penem. In the event,

Scheme 5. Extension to a C(6)-Substituted Variant[a]



13 **14a** R=Me[18]
14c R=CH_2-2-naphthyl
15 (40% from **14c**)

[a] Microwave conditions employed: (a) screw cap pressure vessel, **8c**, PhMe, 55 W, 1 h, 25%; (b) open vessel, **8c**, PhMe, 200 W, 4 h, 25%.

the C(6)-O-silylated hydroxyethyl β-lactam-based oxazolidinone **13**[17] reacted with **8c** to give the corresponding dipolar cycloadduct **14c** in 25% yield. Subsequent oxidation and elimination proceeded to give the C(2)-unsubstituted penem **15** in 40% yield (Scheme 5).[18]

In summary, simple *S*-alkyl dithioformates **7a**−**c** are viable 1,3-dipolarophiles, which can be released in situ, reacting with β-lactam-based oxazolidinones **3** and **13** to provide, after oxidation and elimination, C(2)-unsubstituted penems, represented by **12** and **15**. Importantly, the overall cycloreversion/dipolar cycloaddition sequence (e.g., **3** + **8** → **11**, Scheme 3) was accelerated very significantly by microwave irradiation.

Acknowledgment. We thank GSK for financial support and Anob Kantacha for crystallographic analysis of *exo*-**11a**, and we acknowledge the support provided by the EPSRC Mass Spectrometry Service Centre at the University of Swansea.

Supporting Information Available: Experimental and characterization data for all new compounds and crystallographic details for *exo*-**11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) We tried to trap **7a** (generated by reduction of CS_2 and *S*-methylation as outlined in Scheme 2) directly using oxazolidinone **3** and thereby avoiding the need to prepare **8a**. Crude **7a** (in THF) was added to oxazolidinone **3** (MeCN, 80 °C) and cycloadduct **11a** was isolated in 15% yield. However, this yield was obtained after a reaction time of only 1 h, indicating the high inherent reactivity of **7a** as a 1,3-dipolarophile. This observation suggests that cycloreversion of **8** is rate limiting.

(15) We used the CEM Discover system as the microwave reactor. Reactions were carried out on 0.25 mmol scale in a screw cap pressure vessel in a PhMe solution in two stages. Stage 1: 150 W, 5 min, max temp 150 °C. Stage 2: 55 W, 60 min, max temp 200 °C. Attempts to accelerate the direct reaction of **7a** with **3** (see ref 14) under microwave conditions led only to decomposition. For recent disclosures of microwave-assisted 1,3-dipolar cycloadditions, see: Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452−456. Wilson, N. S.; Sarko, C. R.; Roth, G. P. *Tetrahedron Lett.* **2001**, *42*, 8939−8941. Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett.* **2003**, *5*, 4915−4918.

(16) Broadly similar yields and *exo/endo* ratios were observed when these reactions were carried out (with and without ionic liquid) on a 1 mmol scale under "open vessel" conditions (PhMe, 200 W, 4 h).

(17) See ref 4a and: Grabowski, E. J. J.; Reider, P. J. Eur. Pat. 78026; *Chem. Abstr.* **1983**, *99*, 122171. Oxazolidinone **13** is not readily amenable to purification. The yield of **14c** observed then reflects the preparation of **13** as well as the cycloaddition step. We have noted[4a] that the presence of the C(6)-substituent does reduce the efficiency of the cycloaddition reactions as compared to reactions involving **3**.

(18) Attempts to improve the yield of cycloadducts derived from **13** were investigated. For example, cycloadduct **14a** was generated in a one-pot process. This involved carrying out the initial diazo insertion step under microwave-assisted conditions, which were significantly faster (10 min vs 5 h) than without microwave irradiation, and **8a** was added directly to crude **13** and subjected to our standard microwave cycloaddition conditions. This provided **14a** but in a low (17%) yield.