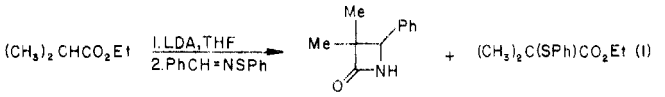
Communications

β-Lactams from Esters and Sulfenimines: A New Route to Monobactams

Summary: Lithium enolates of esters react with nonenolizable and enolizable *S*-trityl sulfenimines to give *N*-tritylsulfenyl β-lactams. An application of this reaction to the synthesis of 4-methylmonobactams (**16** and **17**) and manipulations of the *N*-tritylsulfenyl group are described.

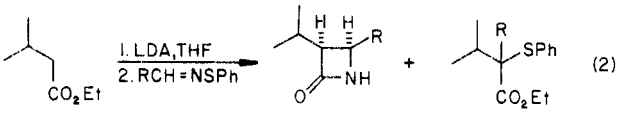
Sir: One objective of our studies of the ester–imine condensation route to β-lactams[1] has been the identification of azomethines which provide rapid access to N-unsubstituted β-lactams. We have found that *N*-trimethylsilyl imines are excellent in this regard as they directly afford the aforementioned substitution pattern.[2,3] Certain *N*-aryl imines are also suitable although oxidative removal of the aryl group is necessary after β-lactam construction.[4-6] Recently, oxime ethers have also been used in this approach to β-lactam synthesis.[7] In this report, we show that sulfenimines can now be added to the list of azomethines which provide access to β-lactams upon reaction with ester enolates. In addition, we describe an application of this method to the synthesis of 4-methylmonobactams.

We began by examining the reaction shown in eq 1. Treatment of the lithium enolate of ethyl isobutyrate (**1**) with *N*-(phenylsulfenyl)benzaldimine (**2a**)[8] in tetrahydrofuran (−78 °C → 25 °C, 20 h) followed by workup with 3 N aqueous hydrochloric acid gave β-lactam **3** (35%, mp 104–105 °C), sulfenylated ester **4** (19%), and diphenyl disulfide (34%). Thus, although **2a** afforded direct access



1 2a 3 4

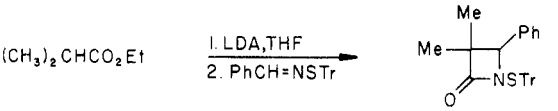
to N-unsubstituted β-lactam **3**, the ambident electrophilicity of the sulfenimine appeared to be causing problems. The generality of this problem was underscored when the reactions shown in eq 2 were examined. Thus,



5 2a R=Ph 6 R=Ph 7 R=H
2b R=Me 9 R=Me 8 R=SPh

ethyl isovalerate (**5**) and **2a** reacted to give β-lactam **6** (37%), esters **7** (30%) and **8** (2%), and diphenyl disulfide (43%).[9] The enolizable sulfenimine **2b**[8] gave only 8% of β-lactam **9** (mp 54–56 °C) along with **7** (18%) and diphenyl disulfide (12%).

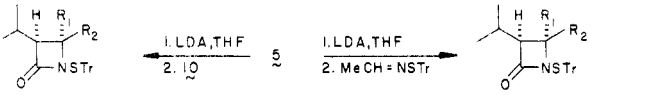
Since it was clear that attack of the enolate on sulfur was a major problem, sulfenimines with a bulkier substituent on sulfur were examined. Thus, treatment of **1** with lithium diisopropylamide followed by sulfenimine **10**[10]



1 10 11

Tr = CPh_3

in tetrahydrofuran (−78 °C → 25 °C, 20 h) gave β-lactam **11** (mp 166–167.5 °C) in 87% yield. No products resulting from sulfenylation of the enolate were observed and the *N*-tritylsulfenyl group survived the 3 N aqueous hydrochloric acid workup. Ester **5** reacted with **10** in a similar fashion to give a 4.5:1 mixture of **12a** (mp 139–143 °C) and **12b**, respectively, in 70% yield. Finally, ethyl isovalerate and the enolizable sulfenimine **13**[11] gave cis β-lactam **14a** (69%, mp 151–156 °C) and trans β-lactam **14b** (2%, mp 113–114.5 °C) after chromatographic separation over silica gel.



12a R_1=H, R_2=Ph 13 14a R_1=H, R_2=Me
12b R_1=Ph, R_2=H 14b R_1=Me, R_2=H

Several aspects of this chemistry are notable. First, sulfenimines appear to be more flexible than oxime ethers with regard to toleration of ester substitution patterns. For example, it has been reported that only lithiated α,α-dialkyl esters react with oxime ethers to give β-lactams under the conditions used here.[7,12] Second, the reaction between

(1) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255. Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941. Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *268*, 233. Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(2) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289. Hart, D. J.; Ha, D.-C.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. Ha, D.-C.; Hart, D. J. *Tetrahedron Lett.* **1985**, *26*, 5493.

(3) For results from other laboratories, see: Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927. Chiba, T.; Nakai, T. *Chem. Lett.* **1985**, 651. Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 937. Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539.

(4) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(5) Georg, G. I.; Gill, H. S.; Gerhardt, C. *Tetrahedron Lett.* **1985**, *26*, 3903.

(6) Burnett, D. A.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1985**, *50*, 5120. Ha, D.-C.; Hart, D. J. *Tetrahedron Lett.* **1985**, *26*, 5493.

(7) Ikeda, K.; Yoshinaga, Y.; Achiwa, K.; Sekiya, M. *Chem. Lett.* **1984**, 369.

(8) Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809. Davis, F. A.; Mancinelli, P. A. *J. Org. Chem.* **1977**, *42*, 398.

(9) All new compounds reported herein gave ^{1}H NMR, IR, and MS or combustion analytical data consistent with the assigned structures. Stereochemical assignments were based on $J_{H_3-H_4}$ values of 1.5–3.0 Hz (trans) and 5–6 Hz (cis).

(10) Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3531.

(11) Compound **13** (mp 129–135 °C) was prepared in 73% yield by using a slight modification of Branchaud's procedure for the preparation of other tritylsulfenimines.[10] Details appear in supplementary material.

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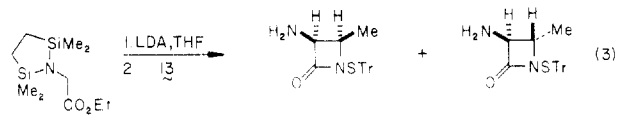
5 and 13 is one of the few examples of β-lactam formation in a reaction involving lithium enolates and an enolizable azomethine.[13-15] Finally, the reactions show stereoselectivities which parallel results obtained with simple lithium enolates and N-trimethylsilyl or N-arylaldimines.[2]

The potential of this route to β-lactams is underscored by the example shown in eq 3. Thus, treatment of glycine



15 16 17

derivative **15**[16] with sulfenimine **13** (−20 °C, 4 h) gave a 5:1 mixture of **16** (mp 146–147.5 °C) and **17**, respectively, in a 78% yield after chromatography over silica gel. The relationship of this reaction to monobactam synthesis is obvious.[17,18]

18 19

In keeping with the objective of developing procedures for the preparation of N-unsubstituted β-lactams, several methods for reductive removal of the N-tritylsulfenyl group were examined. It was found that this task could be accomplished by using several reagents. For example, treatment of β-lactam **11** with tri-*n*-butylphosphine (10 equiv, EtOH–THF, 115 °C, 48 h) gave **3** (75%). Treatment of **11** with trimethylsilyl iodide (CH_2Cl_2, 25 °C, 7 h) also gave **3** (81%).[19] Although 4-alkylated β-lactam **14a** could be converted to **9** by using freshly prepared W-2 Raney nickel[20] (40%) or lithium in ammonia (85%), these conditions resulted in the conversion of 4-arylated β-lactam **11** to amide **18** in 45% and 79% yields, respectively.[21,22] Finally, when **11** was warmed with anhydrous $CuCl_2$ (2 equiv) in tetrahydrofuran–ethanol (75 °C, 5 h), only S–C bond cleavage was observed.[23] Thus, disulfide **19** was obtained in 69% yield as a mixture of diastereomers. This reaction may be particularly useful in monobactam synthesis.

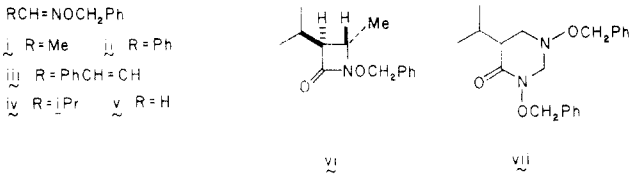
In summary, the condensation of lithium ester enolates with sulfenimines represents a promising new entry to β-lactams. Additional studies including applications to monobactam and carbapenem total synthesis as well as ketene–sulfenimine cycloadditions are underway.[24]

Acknowledgment. We thank Mr. Richard Weisenberger for recording mass spectra at The Ohio State University Campus Chemical Instrument Center. Financial support from the National Institutes of Health (AI-21074) is gratefully acknowledged.

Registry No. 1, 97-62-1; **2a**, 52777-99-8; **2b**, 61501-00-6; **3**, 7486-93-3; **4**, 51364-95-5; **5**, 108-64-5; **6**, 90696-11-0; **7**, 101518-51-8; **8**, 101518-52-9; **9**, 101518-53-0; **10**, 86864-34-8; **11**, 101518-54-1; **12a**, 101518-55-2; **12b**, 101541-77-9; **13**, 101518-56-3; **14a**, 101518-56-3; **14b**, 101518-58-5; **15**, 78605-23-9; **16**, 101518-59-6; **17**, 101518-60-9; **18**, 101518-61-0; **19**, 101518-62-1; **i**, 20134-98-9; **v**, 72399-18-9; **vi**, 101518-63-2; **vii**, 101518-64-3; ethyl 2-bromoisovalerate, 609-12-1.

Supplementary Material Available: Procedure for preparation of **13** (1 page). Ordering information is given on any current masthead page.

(12) Our own studies have shown that the lithium enolate of **5** in THF gives no β-lactam with oxime ethers i and ii. Only the product of apparent Claisen condensation of **5** is obtained (50%). The enolate derived from sequential treatment of **5** (1 equiv) with LDA (1 equiv) and $ZnCl_2$ (1 equiv) in THF gives only trace amounts of β-lactams upon treatment with oxime ethers ii–iv. This enolate, however, does give a 27% yield of vi and a 45% yield of vii upon treatment with oxime ethers i and v, respectively. Treatment of ethyl 2-bromoisovalerate with Zn in THF and i also gives vi (21%).



vi vii

(13) Although not widely used, enolizable *N*-aryl- and *N*-alkylaldimines react with zinc enolates (Reformatsky reagents) to give β-lactams in certain situations: Dardoize, F.; Moreau, J.-L. Gaudemar, M. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *268*, 2228. Dardoize, F.; Moreau, J.-L.; Gandemar, M. *Bull. Soc. Chim. Fr.* **1972**, 3841. Lithium enolates have been reported to give no β-lactam upon treatment with enolizable *N*-alkylaldimines: Gluchowski C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.

(14) For β-amino ester formation from a lithium enolate and an enolizable *N*-(tetrazol-5-yl)aldimine, see: Klich, M.; Teutsch, G. *Tetrahedron Lett.* **1984**, *25*, 3849.

(15) Acid-catalyzed reactions of enolizable imines and ester enolates to afford β-amino esters are known (Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946.) as are reactions between (vinyloxy)boranes and enolizable imines: Otsuka, M.; Yoshida, M.; Kobayaski, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* **1981**, *22*, 2109. Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523.

(16) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.

(17) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176. Koster, W. H.; Cimarusti, C. M.; Sykes, R. B. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Goldman, M., Eds.; Academic Press: New York, 1982; Vol. 3, pp 339–375.

(18) Reference 14 describes a related but lengthier approach to *N*-(tetrazol-5-yl)-2-azetidinones.

(19) Trimethylsilyl iodide has previously been used to cleave N–S bonds of *S*-tritylsulfenamides: Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3538.

(20) Mozingo, R. *Organic Syntheses*; Wiley: New York; 1955; Collect. Vol. 3, p 181.

(21) If freshly prepared W-2 Raney nickel was warmed at 75 °C in ethanol for 48 h followed by treatment with **11** under 1 atm of hydrogen at 25 °C, β-lactam **3** (79%) was obtained.

(22) The generality of these N–S to N–H transformations remains to be established. Details will be reported in our full account of this research.

(23) These conditions have been used to cleave N–S bonds of *S*-tritylsulfenimides.[19]

(24) **Note Added in Proof**: We have shown that the lithium enolate of **1** reacts with the *N*-tritylsulfenyl imine of acetone to give 3,3,4,4-tetramethyl-1-(tritylsulfenyl)-2-azetidinone in 60% yield.

(25) Phillips Petroleum Graduate Fellow, 1985.

(26) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

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The ((β-Phenylethyl)oxy)carbonyl ("Homobenzyloxycarbonyl", hZ) Amino-Protecting Group

Summary: The ((β-phenylethyl)oxy)carbonyl group ("homobenzyloxycarbonyl", hZ) is shown to be generally deblocked by catalytic hydrogenolysis, especially via the catalytic transfer technique using freshly precipitated palladium–carbon in the presence of ammonium formate.

0022-3263/86/1951-1930$01.50/0