74097-78-2; **8c**, 74097-79-3; **8d**, 74097-80-6; **8e**, 74097-81-7; **8f**, 74097-82-8; **8g**, 74097-83-9; **8h**, 74097-84-0; **8i**, 74097-85-1; **9a**, 29984-96-1; **9b**, 74097-86-2; **9c**, 74097-87-3; **9d**, 74113-07-8; **9e**, 74097-88-4; **9f**, 74097-89-5; **9g**, 74097-90-8; **9h**, 74097-91-9; **9i**, 74097-92-0; **10**, 74097-93-1; **11**, 74097-94-2; **12**, 74097-95-3; **13**, 74097-96-4; **14**, 74097-97-5; **15**, 74097-98-6; methyl isopropyl ketone, 563-80-4; *p*-tosylhydrazine, 1576-35-8; 2-pentanone, 107-87-9; 2-octanone, 111-13-7; benzylacetone, 2550-26-7; methyl isobutyl ketone, 108-10-1; acetone, 67-64-1; 2-butanone, 78-93-3; acetophenone, 98-86-2; *tert*-butyl methyl ketone, 75-97-8; *r*-3,*c*-5-diethyl-3,5-dimethyl-1-pyrazolin-4-one, 74097-99-7; *r*-3,*c*-5-dipropyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-00-3; *r*-3,*c*-5-dihexyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-01-4; *r*-3,*c*-5-diisobutyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-02-5; *r*-3,*c*-5-diphenethyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-03-6; *r*-3,*c*-5-di-*tert*-butyl-3,5-dimethyl-1-pyrazolin-4-one, 74098-04-7.

Supplementary Material Available: Complete descriptions of isolation and purification methods, yields, physical constants, and ^{1}H NMR, IR, and analytical data for compounds **4c–f**, **5a**, **5c–f**, **5h**, **7c–f**, **7h**, **8g**, **8h**, **9c–f**, **9h**, **1c–f**, **1h**, **14**, and **15** (18 pages). Ordering information is given on any current masthead page.

Preparation of β-Lactams by the Condensation of Lithium Ester Enolates with Aryl Aldimines

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Received March 24, 1980

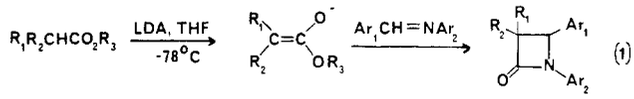
The condensation of simple lithium ester enolates with appropriately substituted aryl imines produces β-lactams in yields from 35 to 95%. Excellent stereoselectivity is observed in the preparation of β-lactams with chiral centers at C-3 and C-4 of the β-lactam ring. When chiral ester enolates are used, asymmetric induction occurs to yield optically active β-lactams with up to 60% ee. Synthetic and mechanistic details of these reactions are discussed.

β-Lactams are known to be key components of many biologically active compounds such as penicillin and cephalosporin antibiotics.[1] Recent syntheses of norcardicin,[2] thienamycin,[3] and totally synthetic penems[4] and the apparent antibiotic potential for simple β-lactams have provided a continuing impetus for research on β-lactam chemistry.[5] Here we report a rather simple procedure for synthesis of certain aryl-substituted β-lactams by condensation of ester enolates and aryl aldimines. These ester–imine condensation reactions we describe are analogous to corresponding stereoselective hydroxylation reactions of enolates with ketones or aldehydes.[6]

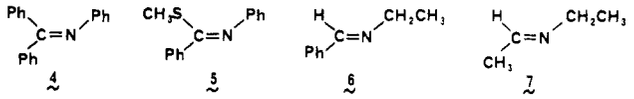
The most common procedure for preparing β-lactams is based on the cycloaddition of a ketene and an imine.[7] However, preparations of β-lactams by the reaction of a carbanionic reagent and an imine have been reported.[8-10] Related titanium tetrachloride promoted condensation reactions on imines with silylated ester enolates have also been reported.[11] Advantages of our procedure over those procedures described above include the use of readily available esters as starting materials, high yields resulting from the use of LDA as a base, and the ability to prepare optically active β-lactams by using chiral esters as starting materials. Recent work in both this laboratory and others has shown that alkylations of chiral esters can proceed in high synthetic yield with good stereoselectivity.[12] Here we show that asymmetric synthesis of β-lactams is feasible using chiral ester enolates in these enolate–imine condensation reactions.

Results and Discussion

Our procedure for the synthesis of β-lactams involves an electrophilic substitution by an imine on a nucleophilic ester enolate (eq 1). Examples of β-lactams prepared by



using this procedure are listed in Table I along with their melting points. It is evident from these results that a variety of β-lactams are accessible by reaction 1. However, a major limitation of our procedure is the apparent requirement that an aryl aldimine containing an aryl substituted nitrogen be used in the ester enolate–imine condensation. As a result, the β-lactams listed in Table I contain aromatic substituents on N-1 and C-4, the part of the β-lactam ring corresponding to the imine used. This required imine substitution is evidently due to the fact that the imine must be both electrophilic and unhindered for successful 1,2 addition to occur. For example, attempts to affect the reaction of benzophenone anil **4** with the



enolate of **li** led to recovered starting material, presumably

(1) *Spec. Publ.—Chem. Soc.* **1977**, *No. 28*.
(2) Koppel, G. A.; McShane, L.; Jose, F.; Copper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933–5.
(3) Johnston, D. B. R.; Schmitt, S. M.; Bouffard, F. M.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313–5.
(4) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6306–10.
(5) Cama, L. D.; Christensen, B. G. *Annu. Rep. Med. Chem.* **1978**, *13*, 149.
(6) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076–77. Heathcock, C. H.; Dirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *Ibid.* **1979**, *101*, 7077–9. Evans, D. A.; Vogel, E.; Nelson, J. V. *Ibid.* **1979**, *101*, 6120–3. Meyers, A. I.; Reider, P. J. *Ibid.* **1979**, *101*, 2501–2. Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *Ibid.* **1979**, *101*, 7723–5.
(7) Bose, A. K.; Manhas, M. S. "Beta-lactams: Natural and Synthetic"; Wiley Interscience: New York, 1971; Part I, pp 161–86.
(8) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255–6.
(9) Luche, J. L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1969**, 3500–5.
(10) Simova, E. R.; Kurtev, B.; Mladenova, M. *Izv. Otd. Khim. Nauki (Bulg. Akad. Nauk.)* **1970**, *3*, 497–508.
(11) Ojima, I.; Inaba, O.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643–6.
(12) Kaneko, T.; Turner, D. L.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1979**, 103–6 and references therein.

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Table I. β-Lactams Prepared via Ester Enolate-Imine Condensation

ester ($R_1R_2CHCO_2R_3$)				imine (Ar_1CHNAr_2)			β-lactam	procedure[a]	% yield	mp, °C
no.	R_1	R_2	R_3	no.	Ar_1	Ar_2				
1a	Ph	OH	Et	2a	Ph	Ph	3a	C	70	187-189
1b	Ph	OH	menthyl	2a	Ph	Ph	3a	C	74[b]	190-191
1c	PhCONH	CH_3	Et	2a	Ph	Ph	3b	A	91	149-151
1d	PhCONH	CH_3	menthyl	2a	Ph	Ph	3b	A	75[c]	181-183
1e	Ph	CH_3	Et	2a	Ph	Ph	3c	B	90[d]	137-139
1f	Ph	CH_3	menthyl	2a	Ph	Ph	3c	B	85[e,f]	167-169
1g	Ph	H	Et	2a	Ph	Ph	3d	B	35[f]	129-130
1h	$-(CH_2)_5-$		Et	2a	Ph	Ph	3e	B	84	141.5-142.5
1i	CH_3	CH_3	Et	2a	Ph	Ph	3f	B	75	147.5-148.5
1i	CH_3	CH_3	Et	2b	p-$(CH_3O)C_6H_4$	Ph	3g	B	82	87-89
1i	CH_3	CH_3	Et	2c	p-ClC_6H_4	Ph	3h	B	95	91-92.5
1i	CH_3	CH_3	Et	2d	Ph	p-$CH_3C_6H_4$	3i	B	84	137-139
1i	CH_3	CH_3	Et	2e	p-ClC_6H_4	p-$CH_3C_6H_4$	3j	B	80	141.5-143
1i	CH_3	CH_3	Et	2f	p-$[(CH_3)_2N]C_6H_4$	Ph	3k	B	66	141-142
1i	CH_3	CH_3	Et	2g	2-furan	Ph	3l	B	67	108-109
1i	CH_3	CH_3	Et	2h	2-thiophene	Ph	3m	B	89	112-113
1j	PhCONH	H	Et	2a	Ph	Ph	3n	A	45	159-160

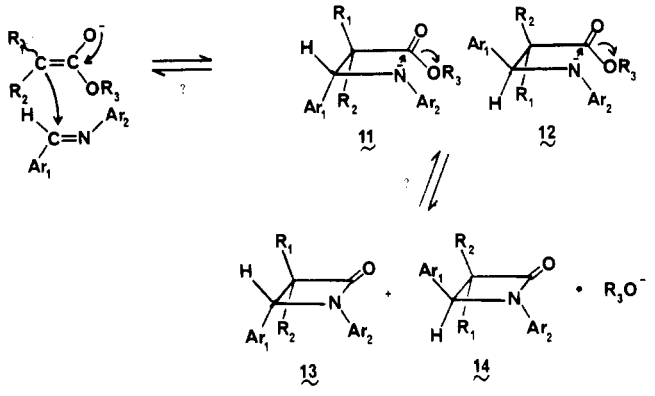
[a] See the Experimental Section. [b] Observed 14% ee. [c] Observed 4% ee. [d] An 8:1 mixture of diastereomers (by NMR) was obtained. [e] Observed 60% ee. [f] The trans isomer was prepared.

because of the steric constraints imposed by the two phenyl groups. Similar attempts to react enolate **1i** with *S*-methylthiobenzanilide (**5**), **6**, or **7** also failed. In the latter two cases, deprotonation of the alkyl-substituted imine α to the nitrogen may have occurred to generate an azaallyl anion.

There is more versatility in the type of esters which can be used to prepare β-lactams since ester enolates can be readily prepared from both substituted and unsubstituted esters by hindered amide base deprotonation.[13] Thus C-3 of the eventual β-lactam ring could contain a variety of substituents; heteroatom substituents or a mixture of two alkyl or aryl substituents have no adverse effect on the ultimate yield of β-lactam product. However, the addition proceeds poorly if α,α-disubstituted esters are not used. For example, all attempts to generate a β-lactam from either ethyl acetate or ethyl propionate in the presence of *N*-benzilideneaniline (**2a**) resulted in recovered imine plus other incompletely characterized products (IR spectra failed to show either β-lactam or β-amino ester products.) Since the addition of ester enolates to imines occurs only after the reactions are warmed to 0 °C these failures may be due to a lack of stability of the enolate under the reaction conditions. The titanium tetrachloride promoted condensation of silylated ester enolates with imines would be a preferable route to β-lactams in these cases.[11]

High stereoselectivity was typically observed when preparing β-lactams with chiral centers at C-3 and C-4 of the lactam ring. For example, for compounds **3a**, **3b**, **3d**, and **3n**, only the trans diastereomer was formed in the ester enolate–imine reaction while compound **3c** was prepared as an 8:1 mixture of trans–cis diastereomers. We believe this stereoselectivity can be explained in terms of the probable mechanism for this reaction (Scheme I). The high stereoselectivity of these reactions must be the result of kinetic or thermodynamic factors associated with the first step of Scheme I since the carbon–carbon bond is formed in this step. If step 1 is irreversible, the observed preference for trans β-lactam products could be due to factors directly analogous to those discussed by others as a basis for stereoselectivity in hydroxylation reactions of ketone enolates.[6] According to these arguments, steric factors imposed by R_1–Ar or R_2–Ar interactions in a "closed" or "cycloaddition"-type transition state account

Scheme I



for the products we have obtained. However, on the basis of results obtained in asymmetric syntheses (vida infra), it is apparent that the stereoselectivity of step 1 could also be due to a thermodynamic preference for **11** or **12** coupled with an equilibration of **11** and **12** through regeneration of enolate and imine.

An alternative mechanism to that proposed in Scheme I would involve a ketene intermediate. In this alternative mechanism, the ester enolate would thermally decompose to form a ketene[14] which would then undergo a cycloaddition with the imine to give the observed products. We consider this mechanism unlikely since lithium ester enolates are relatively stable,[15] and such a mechanism cannot explain the high asymmetric induction observed in one reaction of a chiral ester enolate (vida infra).

If a mechanism such as that described in Scheme I is correct, the reaction of chiral ester enolates with imines could lead to optically active β-lactams. To examine this possibility, we used chiral *l*-menthyl esters as ester enolate precursors. The alkoxy enediolate formed by deprotonation of *l*-menthyl mandelate was allowed to react with *N*-benzilideneaniline (**2a**) to yield, after chromatography, β-lactam **3a** in 74% yield with an enantiomeric excess (ee) of ca. 14%. As in the case of the ethyl ester **1a**, only one diastereomer was formed. The reaction of the dianion from *l*-menthyl *N*-benzoylalaninate (**1d**) with **2a** similarly

(13) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582–4. Rathke, M. W.; Lindert, A. *Ibid.* **1971**, *93*, 2318–20.

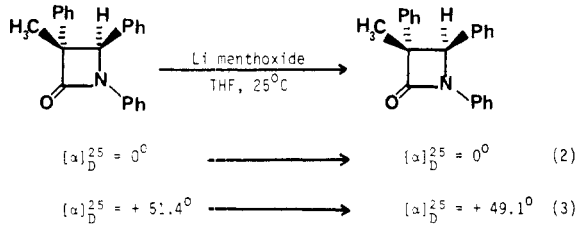
(14) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038–9.

(15) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050–1.

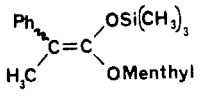
(16) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67–72.

gave β-lactam **3b** in 75% isolated yield with an ee of ca. 4%. Finally, the enolate generated from the *l*-menthyl ester **1f** was allowed to react with **2a** to yield β-lactam **3c** in 85% synthetic yield with 60% ee. While the product obtained from the corresponding ethyl ester was an 8:1 mixture of diastereomers, this asymmetric synthesis of **3c** led to the trans β-lactam stereospecifically. The observation of a relatively high ee (60%) in this latter reaction is significant both for mechanistic reasons and as the best reported asymmetric synthesis of a β-lactam.

There are several possible explanations for the high asymmetric induction observed in the synthesis of **3c** from **1f** and **2a** and for the other asymmetric syntheses. First, a resolution could occur if the lithium menthoxide byproduct of the reaction could cleave the β-lactam product of **13** (or **14**) and its enantiomer to give the ring-opened lithium amide ester and if the diastereomeric (by virtue of the presence of the *l*-menthyl group) lithium amide esters were in turn in equilibrium by cleavage of the C_3–C_4 bond. Control experiments summerized by eq 2 and 3



eliminate this possibility. A second explanation for the high asymmetric induction observed in reaction of **1f** and **2a** would be that the intermediate chiral ester enolate had been generated with substantial (>60%) stereoselectivity and that this enolate had then kinetically formed the chiral lithium amide ester with high stereoselectivity. As a third possibility, only the first step in Scheme I could have been reversible. Trapping the intermediate enolate as its trimethylsilyl enol ether (**15**) and then attempting to correlate



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the relative amounts of the two possible diastereomeric enolates with the observed asymmetric induction could differentiate between these possibilities. The enolate from **1f** was therefore generated at −78 °C (under the same conditions as the β-lactam asymmetric synthesis) and then trapped by the addition of Me_3SiCl[16] to yield an ca. 3:2 mixture of diastereomers by NMR. We did not attempt to assign stereochemistry to the major isomer. Nevertheless, the fact that the stereoselectivity seen in enolate formation is substantially less than that seen in formation of the optically active β-lactam **3c** is a strong argument favoring a reversible first step in Scheme I. The lower ee's seen in the preparation of **3a** and **3b** may arise because the lithium ester enolates derived from **1b** and **1d** are more reactive than that from **1f**. As a result, an equilibration like that suggested above to account for a high ee in the synthesis of **3c** may not have occurred in these two cases.

Conclusion

The ester enolate–imine condensation described above is a viable way to prepare selected β-lactams in good to high yield with excellent stereoselectivity. When chiral ester enolates are used, modest to good asymmetric syntheses can be obtained. The most effective asymmetric syntheses of β-lactams obtained by using these procedures apparently result from thermodynamic rather than kinetic factors.

Experimental Section

General Methods. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a Lauda K-4/R constant-temperature bath. Infrared spectra of carbon tetrachloride solutions were recorded on a Perkin-Elmer 297 spectrophotometer. ^1H NMR data were recorded on a Varian T-60 NMR spectrometer in either CCl_4 or $CDCl_3$ as solvent with Me_4Si as internal standard. Chemical shifts are reported as δ values in parts per million relative to internal standard (δ_{Me_4Si} = 0.0). Melting points were determined on a Thomas-Hoover capillary apparatus. All melting and boiling points are reported in degrees Celsius and are uncorrected. Unexceptional inert-atmosphere techniques were used in all reactions.[17] Tetrahydrofuran (THF) was dried over sodium–benzophenone ketyl and freshly distilled before use. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves. *n*-Butyllithium in hexane was obtained from Aldrich and titrated before use.[18] Unless otherwise noted, all other materials were reagent grade and were used without further purification. Thin-layer chromatography (TLC) was performed by using E. Merck silica gel $60F_{254}$ precoated plastic plates. Column chromatography was performed on a medium-pressure system[19] by using E. Merck 230–400-mesh silica gel and eluting with freshly distilled CH_2Cl_2. Elemental analyses were performed by the Center for Trace Characterization at Texas A&M University.

The imines and esters used in this study were available through commercial sources or were prepared via standard literature procedures.[20] All compounds gave satisfactory physical and spectral data.

Preparation of β-Lactams. Procedure A. The dianion of the appropriate ester was generated at −78 °C in a flame-dried flask equipped with a magnetic stirbar by addition of the ester as a THF solution (2–5 mmol of ester and 5–10 mL of dry THF) to 2.2 equiv of LDA (in 15 mL of dry THF). After being stirred for 15 min at −78 °C, a THF solution of the appropriate imine (2–5 mmol of imine and 5–10 mL of dry THF) was added dropwise. The dry ice/acetone bath was allowed to expire (about 4–5 h), after which the reaction was stirred for an additional 3–8 h at room temperature. The reaction was worked up by diluting the reaction mixture with ca. 20 mL of diethyl ether and washing successively with portions (3 × 20 mL) of 10% aqueous acetic acid (v/v), saturated $NaHCO_3$, and saturated NaCl solutions. The organic layer was dried over anhydrous Na_2SO_4 or $MgSO_4$, and the ether was removed in vacuo. The resulting crude product was chromatographed on silica gel with dichloromethane elution.

Procedure B was used for preparation of lithium ester enolate and was identical with procedure A with the exception that 1.1 equiv of LDA was used.

Procedure C was used for preparation of dilithium enediolates and was identical with procedure A except that the reaction mixture was warmed to 0 °C for 2 h and then recooled to −78 °C before addition of the imine.

A representative example of each procedure is supplied below. Experimental procedures, spectral data, and elemental analyses for the other β-lactams listed in Table I are given as supplementary material.

(−)-*trans*-3-Hydroxy-1,3,4-triphenylazetidin-2-one (3a). The enediolate generated from **1b** (1.45 g, 5 mmol) was allowed to react with **2a** (0.91 g, 5 mmol) to yield, after chromatography, 1.11 g (74%) of **3a** as a white solid: mp 190–191 °C; $[\alpha]^{25}_D$ −3.50° (c 2.0, $CHCl_3$). The spectral data was identical with that observed

(17) Brown, H. C. "Organic Syntheses via Boranes"; Wiley-Interscience: New York, 1975.
(18) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–9.
(19) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247–9.
(20) Preparation of imines: Layer, R. W. *Chem. Rev.* **1963**, 490–510. Simple esters: Hauser, C. R.; Hudson, B. E.; Abramovitch, B.; Shrivers, J. C. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, pp142–4. Derivatives of α-amino acids: Harada, K.; Hayakawa, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 191–4. Scheibler, H.; Bumgarten, P. *Chem. Ber.* **1922**, *55*, 1358–63.

for the racemic β-lactam. The enantiomeric excess (ee) was determined to be ca. 14% through the use of the chiral shift reagent Eu(tfc)$_3$.[21,22] The shift reagent was added to an NMR sample until separation of the enantiotopic benzylic protons on C-4 of the β-lactam ring was observed. The relative areas under the peaks were then determined by integration.

(+)-1,4-Diphenyl-3-*N*-(benzoylamino)-3-methylazetidin-2-one (3b). The dianion from **1d** (0.993 g, 3 mmol) was allowed to react with **2a** (0.543 g, 3 mmol) to yield, after chromatography, 0.80 g (75%) of a white solid: mp 181–183 °C; $[\alpha]^{25}_D$ +0.57° (*c* 3.5, CH_2Cl_2). The spectral data was identical with that observed for the racemic β-lactam. The ee was observed to be ca. 4% by the method outlined above for **3a**.

(+)-*trans*-3-Methyl-1,3,4-triphenylazetidin-2-one (3c). The enolate generated from **1f** (1.44 g, 5 mmol) was allowed to react with **2a** (0.91 g, 5 mmol) to yield, after chromatography, 1.24 g (85%) of **3c** as a white solid: mp 167–169 °C; $[\alpha]^{25}_D$ +51.4° (*c* 3.5, CH_2Cl_2). Spectral data was identical with that observed for the racemic β-lactam. The ee was observed to be ca. 60% by the method outlined above for **3a**.

Attempted Resolution of Racemic 3c with Menthoxide. Lithium menthoxide was generated in 5 mL of THF from *n*-butyllithium (1.65 mL of a 1.57 N solution, 2 mequiv) and *l*-menthol (0.28 g, 1.8 mmol) at room temperature. To this stirred solution was added racemic **3c** (0.38 g, 1.2 mmol) as a THF solution (3 mL of THF) by using a syringe (upon addition of the β-lactam, the color changed from colorless to bright yellow). The reaction was stirred for 6 h at room temperature. It was worked up by being washed once with 10 mL of H_2O and once with 10 mL of saturated NaCl and then extracted with diethyl ether. The ethereal layer was dried ($MgSO_4$) and the solvent was removed in vacuo. After chromatography to remove the menthol, NMR and IR spectra confirmed that **3c** was the product, and polarimetry showed it to be racemic.

Control Experiment with Optically Active 3c. The above procedure was repeated with the exception that optically active **3c** ($[\alpha]^{25}_D$ +51.4° (*c* 3.5, CH_2Cl_2)) was used. After chromatography, NMR and IR spectra confirmed the presence of **3c**; $[\alpha]^{25}_D$ +49.1° (*c* 3.5, CH_2Cl_2).

(21) Tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III) derivative, available from Aldrich Chemical Co.
(22) This experiment was initially performed in these laboratories by Mr. David L. Turner.

Acknowledgment. We gratefully acknowledge financial support of this research by the National Institutes of Health (Grant No. GM 26268) and NIH Biomedical Research Funds administered by Texas A&M University.

Registry No. 1a, 774-40-3; **1b**, 74185-85-6; **1c**, 32619-69-5; **1d**, 74219-50-4; **1e**, 2510-99-8; **1f**, 32213-55-1; **1g**, 101-97-3; **1h**, 3289-28-9; **1i**, 97-62-1; **1j**, 1499-53-2; **2a**, 538-51-2; **2b**, 783-08-4; **2c**, 2362-79-0; **2d**, 2272-45-9; **2e**, 15485-32-2; **2f**, 889-37-2; **2g**, 3237-23-8; **2h**, 5918-68-3; **3a**, 74185-86-7; **3b**, 74185-87-8; *cis*-**3c**, 30358-30-6; *trans*-**3c**, 74185-88-9; **3d**, 16141-49-4; **3e**, 31492-21-4; **3f**, 5438-81-3; **3g**, 74185-89-0; **3h**, 74185-90-3; **3i**, 74185-91-4; **3j**, 74185-92-5; **3k**, 74185-93-6; **3l**, 69187-09-3; **3m**, 69187-10-6; **3n**, 34092-17-6.

Supplementary Material Available: Experimental procedures, spectral data, analytical data, and references for the β-lactams in Table I (4 pages). Ordering information is given on any current masthead page.

Syntheses of 1,2,4-Benzothiadiazine 1-Oxides and 1,2,4-Benzothiadiazines

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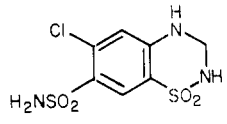
Received April 11, 1980

Reaction of ortho esters or dimethylformamide acetal with *o*-aminobenzenesulfinamides **9** gave 1,2,4-benzothiadiazine 1-oxides **6**. Reaction with 1 equiv of tributylphosphine provided the 1,2,4-benzothiadiazines **11**. Excess tributylphosphine caused rearrangement to the benzothiazoles **12**. A mechanism is proposed for this rearrangement via an intermediate such as **13**. The rearrangement of **13** on heating in benzene to an isomeric compound **16** provided additional support for this mechanism.

There is a wealth of literature on the 1,2,4-benzothiadiazine 1,1-dioxides[1] because of their utility as diuretics and antihypertensive agents, e.g., hydrochlorothiazide **1**[2] and diazoxide **2**.[3] However, there seems to be a dearth



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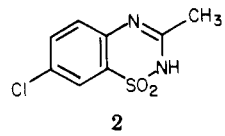

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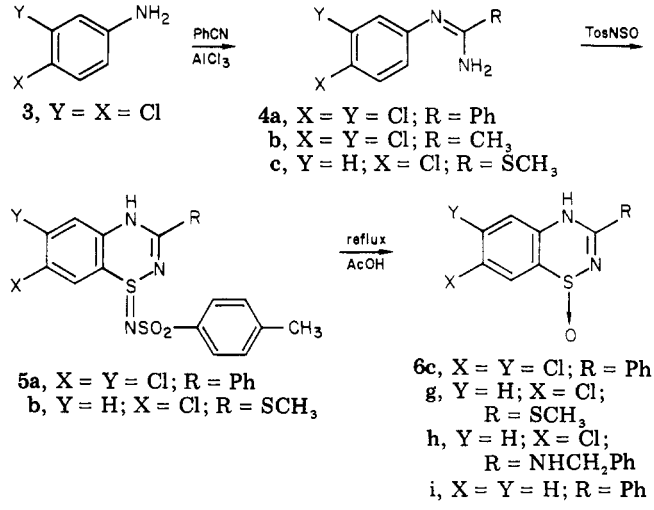
of work on the S^{II} and S^{IV} analogues, the 1,2,4-benzothiadiazines, and their *S*-oxides. Remarkably, there is only one paper to our knowledge describing a synthesis of 1,2,4-benzothiadiazine 1-oxides **6**[4] and two reports of the use of this synthesis.[5,11] A recent communication[6] described the formation of 7-chloro-3-phenyl-1,2,4-benzo-

Scheme I



3, Y = X = Cl

4a, X = Y = Cl; R = Ph
b, X = Y = Cl; R = CH_3
c, Y = H; X = Cl; R = SCH_3

5a, X = Y = Cl; R = Ph
b, Y = H; X = Cl; R = SCH_3

6c, X = Y = Cl; R = Ph
g, Y = H; X = Cl; R = SCH_3
h, Y = H; X = Cl; R = $NHCH_2Ph$
i, X = Y = H; R = Ph

(1) Werner, L. H. In "Burger's Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed; Wiley Interscience: New York, 1980; Part III, Chapter 40.
(2) Werner, L. H.; Halamandaris, A.; Ricca, Jr., S.; Dorfman, L.; deStevens, G. *J. Am. Chem. Soc.* **1960**, *82*, 1161.
(3) Topliss, J. G.; Konzelmann, L. M.; Shapiro, E. P.; Sperber, N.; Roth, F. E. *J. Med. Chem.* **1964**, *7*, 269.

0022-3263/80/1945-3416$01.00/0