are mentioned. In those cases, all parameters were optimized except the specific constraint.

Acknowledgment. We thank the U.S. Department of Energy, Office of Energy Research, and the Indiana University Computing Network for support of this work.

1,3-Dipolar Cycloaddition Annulations to the Thieno[2,3-*d*]pyridazine, Thieno[3,2-*c*]pyridine, and Thieno[2,3-*d*]pyrimidine Ring Systems

James S. New,* William L. Christopher, and Paul A. Jass

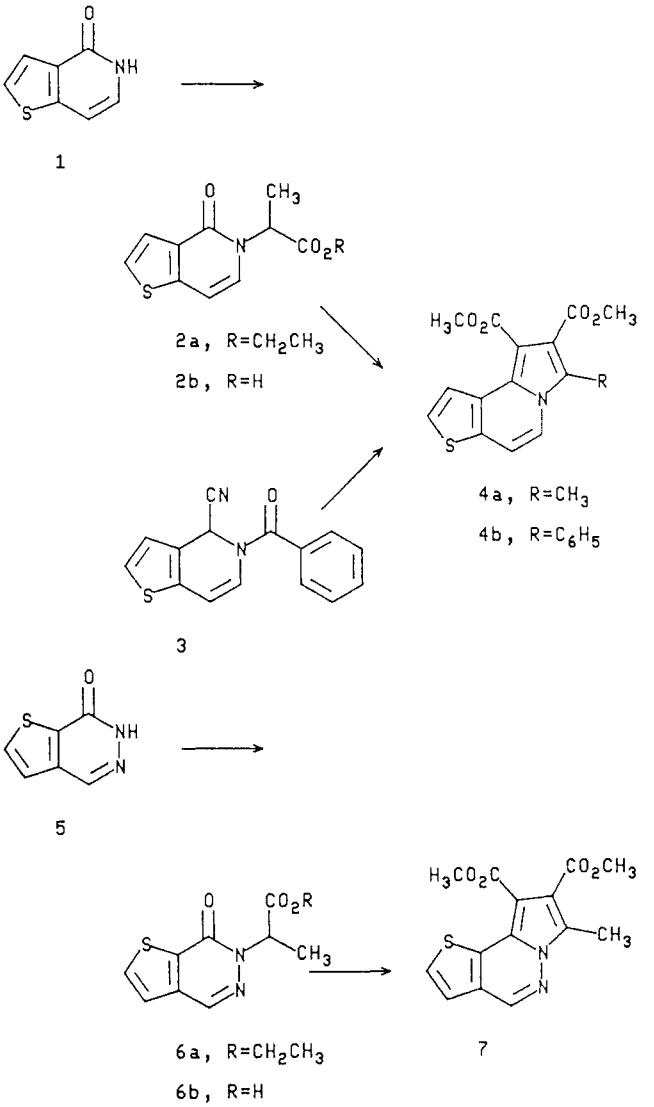
Preclinical CNS Research, Pharmaceutical Research and Development Division, Bristol-Myers Company, 5 Research Parkway, P.O. Box 5100, Wallingford, Connecticut 06492-7660

Received July 1, 1988

A series of recent disclosures in the literature reveal that potent affinity for the benzodiazepine receptor can be achieved in a variety of triheterocyclic molecules that do not contain the benzodiazepine ring system.[1,2] The impetus for the synthesis of such molecules is the development of antianxiety drugs that have a cleaner side-effect profile. An expedient, yet versatile, methodology to elaborate triheterocyclic compounds was found in the mesoionic cycloaddition reaction of dipolarophiles with oxazolones, or the hydrofluoroborate salts of Reissert compounds. Alkylation of thieno[3,2-*c*]pyridin-4(5*H*)-one[3] (**1**) with ethyl 2-bromopropionate generated **2** (Scheme I). The same transformation with thieno[2,3-*d*]pyridazin-7-(6*H*)-one (**5**)[4] generated the analogous product **6**. After basic hydrolysis to their free acids and treatment with acetic anhydride, **2b** and **6b** reacted with dimethyl acetylenedicarboxylate (DMAD) to give **4a** and **7**, respectively. The synthesis of the thieno[2,3-*g*]indolizine structure **4** was also realized through trifluoromethanesulfonic acid[5] treatment of **3**,[6] and subsequent reaction of the derived salt with DMAD in DMF.[7,8]

Alkylation of **8** (Scheme II) was routine,[9] as was obtention of the derived acid **9b**. Reaction of **9b** with DMAD in acetic anhydride at 90 °C for 1 h yielded a complex mixture, which was resolved into **10** (trace), **11** (15%), and **12** (29%). Compound **10** resulted from the Dakin–West[10] reaction of **9b**, but attempts to increase the sporadic yield of this product through optimized (pyridine–acetic anhydride) Dakin–West conditions were unsuccessful. The yield of the desired cycloaddition product **11** could be

Scheme I



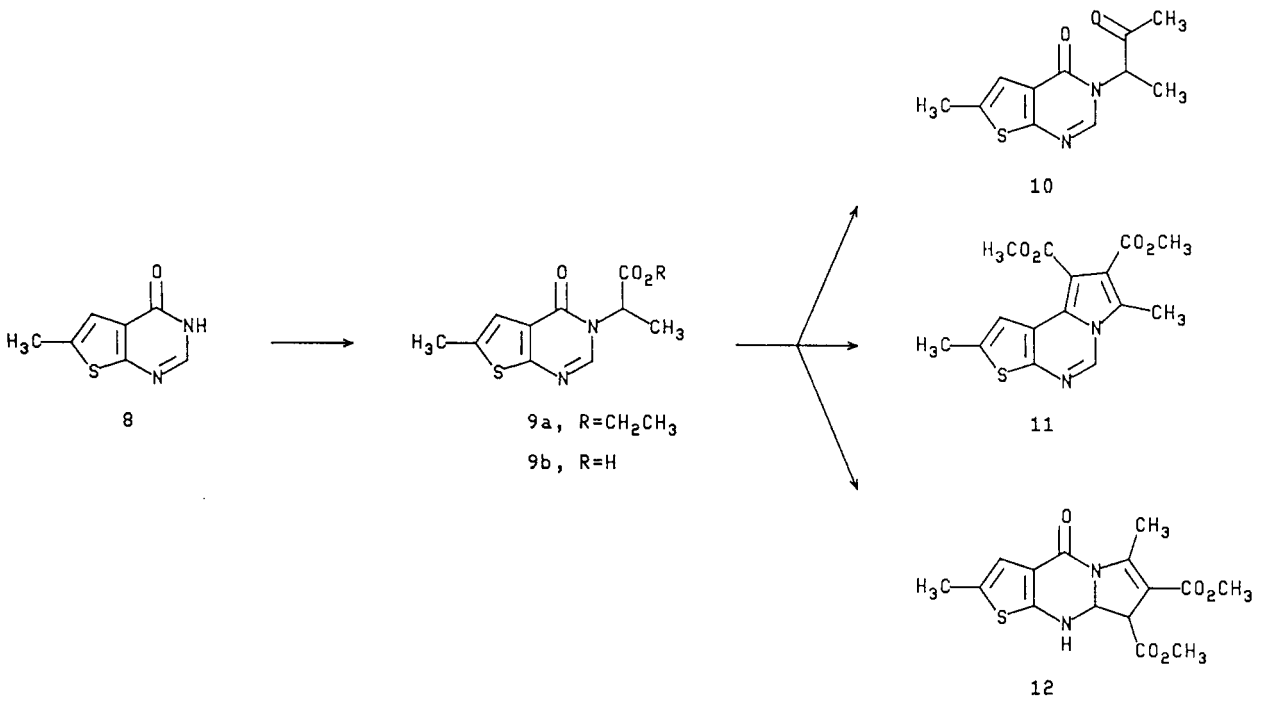
increased slightly (28%) through the use of 10 equiv of DMAD rather than the 1.2 equiv normally employed. This product distribution was temperature dependent since the identical reaction time at 140 °C led to a 6.4% yield of **10** and 14.6% yield of **11**, with only trace amounts of compound **12** being formed. Compound **12** apparently results from the mesoionic species derived from **9b** adding in Michael fashion to DMAD, with subsequent attack of the intermediate anion occurring at the imine linkage rather than the carbonyl group in the pyridazinone ring. Decarboxylation and isomerization of the double bond produces compound **12**.

The formation of this major side product highlights the limitations of a 1,3-dipole possessing an electrophilic center whose reactivity is competitive with that of the dipolarophile. Earlier studies investigating the cycloaddition properties of *anhydro*-3-hydroxythiazolo[3,2-*c*]-quinazolin-4-ium hydroxides to various dipolarophiles did not report any inter- or intramolecular addition of the initial DMAD adduct to the sensitive imine bond in the quinazoline ring.[11] The feasibility of converting **12** into **11** was also explored because mechanistically this transformation appeared reasonable. The reaction of **12** with potassium carbonate in dry acetonitrile under nitrogen did

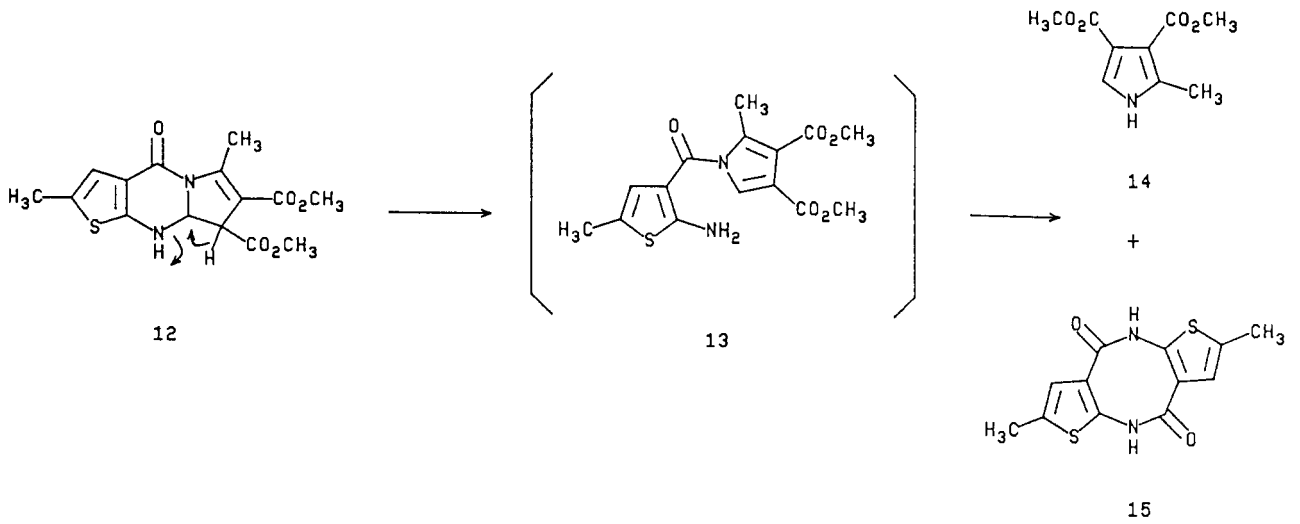
(1) Williams, M. *J. Med. Chem.* **1983**, *26*, 619.
(2) Bare, T. M.; Resch, J. F.; Patel, J. B. *Annu. Rep. Med. Chem.* **1987**, *22*, 11.
(3) Eloy, F.; Deryckere, A. *Bull. Soc. Chim. Belg.* **1970**, *79*, 301.
(4) Robba, M.; Rogues, B.; Bonhomme, M. *Bull. Soc. Chim. Fr.* **1967**, 2495.
(5) Anderson, W. K.; DeRuiter, J.; Heider, A. R. *J. Org. Chem.* **1985**, *50*, 722.
(6) New, J. S.; Jass, P. A.; Barrett, K. A. *J. Heterocycl. Chem.* **1986**, 545.
(7) McEwen, W. E.; Kanitkar, K. B.; Mo-wei Hung, W. *J. Am. Chem. Soc.* **1971**, *93*, 4484.
(8) Only one previous synthesis of this molecule has been reported; see: Maffrand, J. P. Fr. Demande 2,336,132, 1977; *Chem. Abstr.* **1978**, *88*, 105299.
(9) Robba, M.; LeComte, J. M.; Cugnon de Sevricourt, M. *Bull. Soc. Chim. Fr.* **1975**, 587.
(10) Allinger, N. C.; Wang, G. L.; Dewhurst, B. B. *J. Org. Chem.* **1974**, *39*, 1730.
(11) Potts, K. T.; Bordeaux, K. G.; Kuehnling, W. R.; Salsburg, R. L. *J. Org. Chem.* **1985**, *50*, 1666.

0022-3263/89/1954-0990$01.50/0

Scheme II



Scheme III



not produce **11**, but rather gave rise to two new products, which were isolated by flash chromatography in a 2:3 EtOAc–hexane mixture. Their characterization led to structural assignments consistent with compounds **14** and **15** in Scheme III. The generation of an allylic anion in **12** leads to elimination of the 2-aminothiophene derivative with aromatization of the pyrrole ring providing the driving force for the reaction. The intermolecular coupling of this aromatic amine **13** on the carbonyl group of an identical intermediate produces **14** and the dimer **15**. Compound **14** is known and was obtained in 86.2% yield.[12] Compound **15** was usually recovered in yields of 5–20% and was very sensitive to moisture when in solution. This dimeric product was formed in only trace amounts if freshly dried CH_3CN was not employed, or if the reaction was not run under nitrogen. The susceptibility of this molecule to moisture was easily visualized on TLC (2:3 EtOAc–hexane), where **15**, in wet DMSO, slowly yields baseline material, presumably the ring-opened amino acid derivative. This hydrolysis is also evident in the ^1H NMR spectra (DMSO-d_6) of **15**, in which the signal intensity for the two amide protons at 7.87 ppm slowly decreases and a new NH_2 peak at 6.35 ppm is produced. A general review on 1,5-diazocines indicates that the mechanism leading to **15** is not a common synthesis of this ring system,[13] although the bis(dimethylamino) amidine derivative of **15** has been reported, and probably arises from the same 3-amino-2-thiophenecarboxylate intermediate implicated here.[14]

Evaluation of the benzodiazepine receptor binding affinities of the target compounds indicated that only compound **11** had potent avidity for this biological receptor. Its IC_{50} value in displacing [^3H]diazepam from the benzodiazepine receptor was 12.2 nM, relative to the IC_{50} value of 5.5 nM which diazepam displays for this receptor.[15,16]

(12) Gabel, W. W. *J. Org. Chem.* **1962**, *27*, 301.

(13) For a review on the synthesis of eight-membered rings containing one or more heteroatoms, see: Moore, J. A.; Anet, F. A. L. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon Press: 1984; p 653.

(14) Pedersen, E. B.; Carlsen, D. *Tetrahedron* **1977**, *33*, 2089.

(15) Squires, R. F.; Braestrup, C. *Nature* **1977**, *266*, 733.

Experimental Section

All IR spectra were recorded on a Nicolet MX-1 FT-IR spectrometer. The ^1H NMR spectra were recorded in deuteriochloroform with 2% (v/v) tetramethylsilane as the internal reference on a Varian FT-80 or a Bruker AM300 spectrometer. Accurate mass measurements were obtained with Kratos MS50RF spectrometer in the electron-impact mode. Melting points were determined by using a Thomas-Hoover capillary apparatus and are uncorrected. All compounds gave satisfactory C, H, and N analyses (±0.4%) with the exception of **15**, which was analyzed with HRMS.

General Procedure for the Synthesis of Ester Derivatives 2a, 6a, and 9a. Sodium hydride (1.2 g, 50 mmol) is suspended in stirring benzene (100 mL) and treated portionwise with **5** (5.0 g, 33 mmol) at 65 °C. After the ensuing hydrogen evolution is complete, ethyl 2-bromopropionate is added and the reaction is refluxed for 48 h. The excess sodium hydride is destroyed with the dropwise addition of methanol, the reaction mixture is extracted with water, and the organic layer is dried ($MgSO_4$), filtered, and concentrated in vacuo to 5.1 g of solid. Recrystallization from ethyl ether affords 3 g (36%) of product, mp 54–56 °C. The yields for the analogous transformation in the synthesis of **9a** and **2a** were 64.9% (mp 105–107 °C) and 45% (mp 67–69 °C), respectively. Satisfactory analyses were reported (Ed.).

General Procedure for the Synthesis of Acid Derivatives 2b, 6b, and 9b. A suspension of **6a** (5.6 g, 22 mmol) in water (75 mL) is heated on a steam cone and slowly treated dropwise with a 50% sodium hydroxide solution until the ester dissolves. The solution is filtered, chilled, and treated dropwise with concentrated hydrochloric acid until the resulting precipitate formation is complete. The solid is recovered by filtration and recrystallized from ethanol–ethyl acetate (2:1), affording 1.5 g (30.6%), mp 202–203 °C. Yields for the acids corresponding to **9b** and **2b** are 98% (mp 207–210 °C) and 87% (mp 246–249 °C), respectively. Satisfactory analyses were reported (Ed.).

Dimethyl 7-Methylpyrrolo[1,2-*g*]thieno[2,3-*d*]pyridazine-8,9-dicarboxylate (7). A suspension of **6b** (1.0 g, 4.4 mmol) in a mixture of acetic anhydride (50 mL) and dimethyl acetylenedicarboxylate (0.76 g, 5.4 mmol) is slowly heated to 100 °C under nitrogen, with carbon dioxide evolution observed at 60 °C. The reaction mixture is concentrated in vacuo after heating for 1 h, the resultant solid is dissolved in chloroform and washed twice with water, and the organic layer is isolated, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from a mixture of methanol–chloroform (2:1), affording 1.1 g (83%) of an off-white solid: mp 172–173 °C; IR 3090, 2950, 1705, 1520, 1435, 1260, 1220, 1200, 770, 705, 600, cm^{-1}; NMR δ 2.62 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 7.32 (d, J = 5.3 Hz, 1 H), 7.47 (d, J = 5.3 Hz, 1 H), 8.47 (s, 1 H). Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.25; H, 3.97; N, 9.20. Found: C, 54.91; H, 3.90; N, 9.06.

Dimethyl 2,7-Dimethylpyrrolo[1,2-*c*]thieno[3,2-*e*]pyrimidine-8,9-dicarboxylate (11). A suspension of **9b** (1.5 g, 6.3 mmol) in a mixture of acetic anhydride (50 mL) and dimethyl acetylenedicarboxylate (8.9 g, 63 mmol) is heated at 90 °C for 90 min under nitrogen. The reaction mixture is concentrated in vacuo to a dark solid, which is flash chromatographed in ethyl acetate–hexane (2:3), yielding 0.56 g (28%) of **11** and 0.52 g (25%) of **12**. Variable amounts of compound **10** were also formed in the reaction, but its yield seemed independent of the various reaction parameters. Compound **11**: mp 133–136 °C; IR 2960, 1700, 1610, 1560, 1510, 1445, 1320, 1210, 1085, 1045 cm^{-1}; NMR δ 2.56 (s, 3 H), 2.57 (s, 3 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 7.73 (s, 1 H), 8.38 (s, 1 H). Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.82; H, 4.51; N, 8.88.

Dimethyl 4,8,8a,9-tetrahydro-2,6-dimethyl-4-oxopyrrolo[2,1-*b*]thieno[2,3-*d*]pyrimidine-7,8-dicarboxylate (12): mp 211–212 °C; IR 3230, 2955, 1735, 1710, 1630, 1505, 1475, 1390, 1310, 1260, 1200, 1185, 1175, 760 cm^{-1}; NMR δ 2.30 (d, J = 1.5 Hz, 3 H), 2.68 (d, J = 2.0 Hz, 3 H), 3.65 (s, 3 H), 3.73 (s, 3 H), 3.96 (dq, J = 9.0 Hz and J = 2.0 Hz, 1 H), 5.27 (d, J = 9.0 Hz, 1 H), 6.68 (q, J = 1.5 Hz, 1 H), 8.12 (br s, 1 H). Anal. Calcd for $C_{15}H_{16}N_2O_5S$: C, 53.56; H, 4.79; N, 8.33. Found: C, 53.30; H, 4.84; N, 8.31.

Dimethyl 7-Methylthieno[2,3-*g*]indolizine-8,9-dicarboxylate (4a). A suspension of **2b** (2.0 g, 8.9 mmol) is heated in a mixture of acetic anhydride (70 mL) and dimethyl acetylenedicarboxylate (7.6 g, 53 mmol) for 20 min under nitrogen. The reaction mixture is concentrated in vacuo and partitioned between chloroform and water, and the organic fraction is dried ($MgSO_4$), filtered, concentrated in vacuo, and flash chromatographed in ethyl acetate–hexane (2:3). The recovered product is recrystallized from ethyl acetate–hexane (1:1), yielding 1.3 g (46%) of a white solid: mp 136–138 °C; IR 3110, 2950, 1715, 1690, 1625, 1565, 1550, 1440, 1415, 1245, 1215, 1170, 740, 695 cm^{-1}; NMR 2.42 (s, 3 H), 3.90 (s, 6 H), 6.92 (d, J = 7.4 Hz, 1 H), 7.38 (m, 2 H), 8.28 (d, J = 5.5 Hz, 1 H). Anal. Calcd for $C_{15}H_{13}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.82; H, 4.51; N, 8.88.

Dimethyl 7-Phenylthieno[2,3-*g*]indolizine-8,9-dicarboxylate (4b). A solution of **3** (3.3 g, 12.2 mmol) in methylene chloride is treated dropwise with a mixture of trifluoromethanesulfonic acid (2 g, 13.4 mmol) in methylene chloride (40 mL) under nitrogen. After being stirred for 24 h, the yellow-orange solution is concentrated in vacuo, and the resulting solid is redissolved in anhydrous dimethylformamide (125 mL), treated with dimethyl acetylenedicarboxylate (1.7 g, 12.2 mmol) under nitrogen, and heated at 80 °C for 24 h. The reaction mixture is concentrated to dryness and partitioned between methylene chloride and water, and the organic layer is dried ($MgSO_4$), concentrated in vacuo, and flash chromatographed in ethyl acetate–hexane (3:7). The product is recovered as 0.75 g (17.4%) of a clear gold oil, which crystallizes in methanol, affording white crystals: mp 97–98 °C; IR 2950, 1730, 1700, 1620, 1600, 1555, 1507, 1480, 1415, 1340, 1245, 1210, 1160, 1065, 760, 700 cm^{-1}; NMR δ 3.74 (s, 3 H), 3.84 (s, 3 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.56 (m, 5 H), 7.87 (d, J = 5.5 Hz, 1 H), 7.93 (d, J = 7.5 Hz, 1 H), 8.53 (d, J = 5.5 Hz, 1 H). Anal. Calcd for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.78; H, 4.13; N, 3.83.

Dimethyl 2-Methyl-1*H*-pyrrole-3,4-dicarboxylate (14) and 2,7-Dimethyldithieno[2,3-*b*:2′,3′-*f*][1,5]diazocine-4,9-(5*H*,10*H*)-dione (15). A solution of **12** (0.1 g, 0.29 mmol) and potassium carbonate (41 mg, 0.29 mmol) is refluxed for 5 h in dry acetonitrile (15 mL) under nitrogen. The light yellow solution is filtered and concentrated in vacuo to a yellow solid. Flash chromatography (2:3 EtOAc–hexane) of this material yields two products: compound **14** (49 mg, 86.2%) as a white solid, mp 159 °C (lit.[12] mp 159 °C), and compound **15** (16 mg, 20%) as a bright yellow solid, mp 209–210 °C: IR 3404, 3200, 1733, 1560, 1540, 1480, 760 cm^{-1}; NMR (DMSO-d_6) δ 2.22 (s, 3 H), 2.45 (s, 3 H), 6.64 (s, 1 H), 7.01 (s, 1 H), 7.87 (s, 2 H); HRMS molecular weight calcd for **15** ($C_{12}H_{10}N_2O_2S_2$) 278.0184, obsd 278.0190.

Registry No. **1**, 27685-92-3; **2a**, 118376-56-0; **2b**, 118376-65-1; **3**, 29389-86-4; **4a**, 118376-57-1; **4b**, 118376-64-0; **5**, 697-72-3; **6a**, 118376-58-2; **6b**, 118376-66-2; **7**, 118376-59-3; **8**, 108831-66-9; **9a**, 118376-60-6; **9b**, 118376-67-3; **10**, 118376-61-7; **11**, 118376-62-8; **12**, 118376-63-9; **14**, 90610-59-6; **15**, 118376-68-4; ethyl 2-bromopropionate, 535-11-5; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Full spectral data (IR, ^1H and ^{13}C NMR) for compounds **2a,b**, **6a,b**, **9a,b**, and **10** (2 pages). Ordering information is given on any current masthead page.

(16) Iversen, L. L. *Nature* **1978**, *275*, 477.

(Benzyloxy)nitromethane: A New Reagent in Bicyclic β-Lactam Synthesis

Anthony G. M. Barrett,* Minn-Chang Cheng, Christopher D. Spilling, and Sven J. Taylor

Department of Chemistry, Northwestern University, Evanston, Illinois 60208

Received August 12, 1988

β-Lactams are outstanding antibiotics, and novel, concise chemistry for their elaboration is constantly being sought. The utility of nitroalkenes in carbapenam construction was

0022-3263/89/1954-0992$01.50/0