λ_{max} 268 nm (ϵ 17 500); ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3), 4.93 (m, 1 H, 4-H), 5.03 (d, $J_{3'-4}$ = 1.4 Hz, 1 H, 3'-H), 5.37 (dd, J_{1-4} = 2.0 Hz, J_{1-2} = 1.2 Hz, 1 H, 1-H), 6.03 (br, 1 H, NH); MS, m/e (relative intensity) 182 (M^+, 19), 154 (29), 151 (22), 122 (20), 113 (15), 110 (12), 98 (13), 95 (33), 84 (36), 83 (21), 69 (33), 68 (24), 59 (11), 55 (21), 42 (100). The analytical data of **2a–d** and **4a–c** are shown in Table IV (supplementary material).

Quantum Yield Determination. A solution containing **1b** or **2b** (20–26 mM) in acetonitrile was irradiated with a low-pressure mercury lamp (60 W) under an argon atmosphere through a Corning 9-54 color filter at 20–21 °C. After irradiation, the solvent was evaporated under vacuum and methanol was added to the oily residue. The formed or unreacted Dewar 4-pyrimidinone **2b** was converted to the β-lactam **5**.[5a] Analyses of **1b** and **5** were performed by HPLC with hexane–CH_2Cl_2–CH_3CN (92:5:3) as the mobile phase and benzyl cyanide was used as an internal standard. The original Dewar **2b** was estimated by the measured amount of **5** and the correction factor (1.06) based on the yield (94%) determined by HPLC for the conversion of **2b** to **5**.

The light intensity of the low-pressure mercury lamp was measured by cyclopentanone–4-pentenal actinometry (Φ = 0.38 at 254 nm).[15] The measured intensity was (1.41 ± 0.07) × 10^{17} quanta/s.

The quantum yields of **1b** to **2b** and **2b** to **1b** were 0.043 at 5.1% conversion and 0.94 at 3.6% conversion, respectively.

***N*-Methyl-3-(1-amino-2,2-dimethylpropylidene)-4-methoxy-4-methyl-2-azetidinone (5).** From 1.761 g (9.78 mmol) of **1b** in liquid NH_3–ether at −40 °C, a mixture of **2b** (31%) and **1b** (69%) was obtained after 9 h of irradiation. The reaction mixture was dissolved in 200 mL of methanol. The solution was allowed to stand for 44 h at 0 °C. After removal of the solvent, ether was added to the oily residue. On cooling, crude crystals of **5** (0.462 g, 22%) were separated and collected by filtration. The starting material **1b** (1.172 g, 67%) was recovered by column chromatography of the filtrate on alumina. Recrystallization of **5** from methanol–ether–pentane gave colorless needles: mp 152–153 °C; UV (MeOH) λ_{max} 277 nm (ϵ 20500); MS, m/e 212 (M^+). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 61.94; H, 9.42; N, 13.12.

Registry No. **1a**, 32363-51-2; **1b**, 93715-36-7; **1c**, 93715-37-8; **1d**, 93715-38-9; **1e**, 17758-19-9; **2a**, 76599-91-2; **2b**, 93715-39-0; **2c**, 93715-40-3; **2d**, 93715-41-4; **3a**, 93715-42-5; **3b**, 93715-43-6; **3c**, 93715-44-7; (*Z*)-**4a**, 93715-45-8; (*E*)-**4a**, 93715-46-9; (*Z*)-**4b**, 93715-47-0; (*E*)-**4b**, 93715-48-1; (*Z*)-**4c**, 93715-49-2; (*E*)-**4c**, 93715-50-5; **5**, 93715-51-6; 2,6-dimethyl-4(3*H*)-pyrimidinone, 6622-92-0; 6-*tert*-butyl-2-methyl-4(3*H*)-pyrimidinone, 66700-33-2; 2-benzyl-6-*tert*-butyl-4(3*H*)-pyrimidinone, 93715-52-7; 6-methyl-4(3*H*)-pyrimidinone, 3524-87-6; 6-[(methoxycarbonyl)methyl]-2-methyl-4(3*H*)-pyrimidinone, 93715-53-8; 6-[(ethoxycarbonyl)methyl]-2-methyl-4(3*H*)-pyrimidinone, 54554-50-6; 6-[(methoxycarbonyl)methyl]-4(3*H*)-pyrimidinone, 93715-54-9; 2-amino-3,4,5,6-tetrahydropyridine hydrochloride, 16011-96-4; ethyl trimethylacetoacetate, 17094-34-7.

Supplementary Material Available: Chemical name, melting points, molecular ion, and analytical data for 4(3*H*)-pyrimidinones and analytical data for the 4-pyrimidinones **1b–d**, **2a–d**, **3a–c**, and **4a–c** (Tables III and IV) (2 pages). Ordering information is given on any current masthead page.

(15) (a) Dunion, P.; Trumbore, C. N. *J. Am. Chem. Soc.* **1965**, *87*, 4211. (b) Dalton, J. C.; Wriede, P. A.; Turro, N. J. *Ibid.* **1970**, *92*, 1318.

Acyl and Sulfonyl Isocyanates in β-Lactam Synthesis

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The preparation of β-lactams from the reactions of several acyl and sulfonyl activated isocyanates with alkenes was studied. Three compounds, (2,2,2-trichloroethoxy)sulfonyl, 2,2,2-trichloroethanesulfonyl, and trifluoroacetyl isocyanates, were shown to be preparatively useful. After the alkene–isocyanate cycloaddition reaction the N-substituent was removed either reductively or via selective hydrolysis. The reaction was applied to styrene, methylenecyclohexane, 4-methylene-1-phenylcyclohexane, and 5-benzyl- and 5-methyl-3,4-dihydro-2*H*-pyrans.

The β-lactam ring system occurs widely in several structurally diverse classes of clinically important antibacterial agents. These include the penicillins, the cephalosporins, the nocardicins, the carbapenems, and the monobactams.[1] Since these antibiotics are widely applied in human medicine, a plethora of structural variations has been prepared by partial and total synthesis. These chemical studies have, in turn, led to detailed structure–activity profiling and the development of novel more active antibiotics.

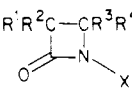
In the total synthesis of these substances it is necessary to decide how to construct the β-lactam ring. Of the many existing strategies, the condensation reaction of an alkene with an activated isocyanate is especially useful. In order for this reaction to be practical, the isocyanate must be carefully chosen. Firstly, the nitrogen must be substituted by an electron-withdrawing group. This is essential to permit the cycloaddition to take place with a sufficiently high rate constant. Secondly, the N-substituent must be easily removable, after the cycloaddition, under mild conditions that do not disrupt the strained and activated

(1) For examples, see: "Cephalosporins and Penicillins Chemistry and Biology"; Flynn, E. H., Ed.; Academic Press: New York, 1972. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Ellis Horwood Ltd.: Chichester, 1980; Volumes 3 and 4. Asai, M.; Haibara, K.; Muroi, M.; Kintaka, K.; Kishi, T. *J. Antibiot.* **1981**, *34*, 621. Parker, W. L.; Koster, W. H.; Cimarusti, C. M.; Floyd, D. M.; Lui, W.-C.; Rathnum, M. L. *Ibid.* **1982**, *35*, 189.

0022-3263/85/1950-0169$01.50/0

β-lactam ring system. Chlorosulfonyl isocyanate (CSI) is widely applied in this context.[2] The chlorosulfonyl substituent is sufficiently activating that CSI condenses with simple alkenes and with alkenyl esters to produce the β-lactams **1a**. In addition, the chlorosulfonyl substituent may readily be cleaved from nitrogen via reductive hydrolysis by using aqueous sodium metabisulfite and sodium hydrogen carbonate to produce **1b**. An outstanding example is the conversion of vinyl acetate into 4-acetoxyazetidin-2-one (**1d**) via the CSI adduct **1c**.[3] This β-lactam **1d** has found widespread use in further synthetic manipulations.[4]

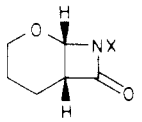
CSI, however, has several preparative disadvantages. Firstly, its reaction with many heterosubstituted alkenes, vinyl carboxylates are a notable exception, do not produce β-lactams. For example, the vinyl ether 3,4,6-tri-*O*-acetyl-D-glucal is dimerized in the presence of CSI.[5] Secondly, removal of the chlorosulfonyl group may be a problem in the primary adducts **1a**. Competitive hydrolysis of the β-lactam ring system giving acyclic products may be the dominant pathways.[6] The development of an activated isocyanate that would overcome these disadvantages would be very important in β-lactam synthetic methodology. We thus set out to explore the reaction of substituted acyl and sulfonyl isocyanates with simple alkenes and with 3,4-dihydro-2*H*-pyran derivatives. There is an auspicious precedent for the examination of arenesulfonyl isocyanates. Effenberger and Gleiter reported that toluene-4-sulfonyl isocyanate (**2**) condensed with 3,4-dihydro-2*H*-pyran (**3**) to produce the β-lactam **4a** at 20 °C or the unsaturated amide **5a** at 80 °C.[7] These authors, however, reported no attempt to desulfonylate **4a** to produce the parent bicyclic β-lactam **4b**.



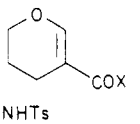
1a, X = SO_2Cl
b, X = H
c, $R^1 = R^2 = R^3 = H$; $R^4 = OAc$; X = SO_2Cl
d, $R^1 = R^2 = R^3 = X = H$; $R^4 = OAc$

2

3



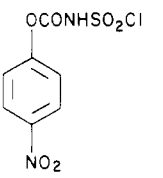
4a, X = Ts
b, X = H
c, X = $SO_2OC_6H_4$-4-Me
d, X = $SO_2OC_6H_4$-4-OMe
e, X = $SO_2C_6H_4$-2-NO_2
f, X = $SO_2OCH_2CCl_3$
g, X = $SO_2CH_2CCl_3$
h, X = $COCO_2Me$
i, X = $COCF_3$



5a, X = NHTs
b, X = $NHSO_2OC_6H_4$-4-Me
c, X = $NHSO_2OC_6H_4$-4-OMe
d, X = $NHSO_2C_6H_4$-2-NO_2
e, X = $NHSO_2OCH_2CCl_3$
f, X = $NHSO_2CH_2CCl_3$
g, X = N=C(OH)CO_2Me
h, X = N=C(OH)CF_3

Preparation of Sulfonyl and Acyl Isocyanates. 4-Nitrophenol was converted into the isocyanate **7c** using the Lohaus procedure.[8] Thus reaction of 4-nitrophenol with CSI in diethyl ether solution gave **6** (100%). On reflux in toluene **6** smoothly rearranged and eliminated hydrogen chloride to produce **7c** (75%). This reactive isocyanate **7c** was fully authenticated by reaction with methanol to produce the carbamate **8** (95%). 2-Nitrobenzenesulfonamide was converted into the isocyanate **9b** (38%), via **9a**, by sequential reaction with *n*-butyl isocyanate and aluminum chloride followed by phosgene in chlorobenzene.[9] Our attempts to prepare the isocyanate **10** by using either of these two synthetic methods were completely unsuccessful. The known[8] isocyanates **7a**, **7b**, and **11a** were all prepared by the Lohaus procedure.[8] Finally, 2,2,2-trichloroethanesulfonyl isocyanate (**11c**) was prepared from the corresponding sulfonamide, via **11b**, by sequential reaction with *n*-butyl isocyanate–aluminum chloride and phosgene. Both novel isocyanates **9b** and **11c** were authenticated as the carbamate derivatives **9c** and **11d**.

In addition to these sulfonyl isocyanates, we examined the use of two acyl isocyanates for β-lactam synthesis. Trifluoroacetyl isocyanate[10-12] was prepared from trifluoroacetyl chloride by reaction with potassium cyanate in a lithium chloride–potassium chloride melt at 480 °C. In our hands this procedure, first described by Lidy and Sundermeyer,[10] proved far superior to alternative documented syntheses.[11,12] The hitherto unknown isocyanate **12a** (55%) was readily prepared from ethyl oxamide and oxalyl chloride.[11] Again, this reactive isocyanate was characterized by reaction with methanol to produce the carbamate **12b** (99%).



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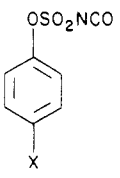
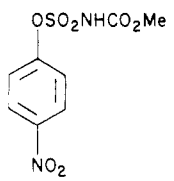


7a, X = Me
b, X = OMe
c, X = NO_2



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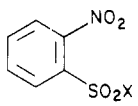
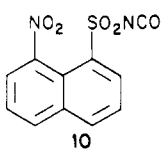
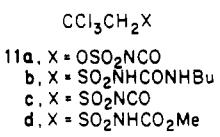


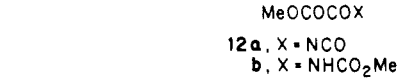
9a, X = NHCONHBu
b, X = NCO
c, X = $NHCO_2Me$



10



11a, X = OSO_2NCO
b, X = $SO_2NHCONHBu$
c, X = SO_2NCO
d, X = SO_2NHCO_2Me



12a, X = NCO
b, X = $NHCO_2Me$

Reactions of Sulfonyl Isocyanates with Styrene, Methylenecyclohexane, and 4-Methylene-1-phenylcyclohexane. The isocyanates **2**, **7a**, **7b**, **7c**, **9b**, **11a**, and **11c** reacted smoothly with styrene, methylenecyclohexane, and 4-methylene-1-phenylcyclohexane to produce the corresponding β-lactams **13a**, **14a–14e**, **14g**, **14h**, and **16b** in good to excellent yields (54–99%). Woodward introduced 2,2,2-trichloroethyl esters as carboxylic acid protecting groups during his total synthesis of cephalosporin C.[13] This protecting group was readily removed, regenerating the carboxylic acid by reduction with zinc in acetic acid. Thus we studied the reduction of the β-lactams **13a**, **14g**, **14h**, and **16b**. The β-lactam **13a** was smoothly reduced in THF solution by zinc–copper couple to produce

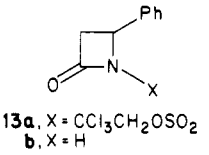
(2) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389.
(3) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539.
(4) For one excellent example, see: Woodward, R. B. *Philos. Trans. R. Soc. London Ser. B* **1980**, *289*, 239.
(5) Hall, R. H.; Jordaan, A.; Lourens, G. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 38. Hall, R. H.; Jordaan, A.; deVilliers, O. G. *Ibid.* **1975**, 626.
(6) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172.
(7) Effenberger, F.; Gleiter, R. *Chem. Ber.* **1964**, *97*, 1576.
(8) Lohaus, G. *Chem. Ber.* **1972**, *105*, 2791.
(9) Ulrich, H.; Sayigh, A. A. R. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 704.
(10) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1976**, *109*, 1491.
(11) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742.
(12) Firth, W. C., Jr. *J. Org. Chem.* **1968**, *33*, 441.
(13) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.

13b[14] (98%). Reduction of **13a** with chromium(II) perchlorate in aqueous DMF was equally efficient and gave **13b** (96%). Reduction of the spirofused β-lactams **14g** and **16b** using activated zinc dust and ammonium chloride in aqueous THF, zinc copper couple in THF at 55 °C, or bis(ethylenediamine)chromium(II) perchlorate[15] in DMF gave the β-lactams **14j**[16] and **16c**. However, these compounds were only produced in modest yields (30–42%). An authentic sample of **16c** was prepared from 4-methylene-1-phenylcyclohexane and CSI via **16a**. The samples of **16c** prepared by either route were identical in all respects and were single isomers. These were tentatively assigned the relative stereochemistry **16c** on the basis of thermodynamic control in the production of **16a** and **16b**. During the reduction of **14g** competitive cleavage of the β-lactam ring took place and amide **15** was obtained as a coproduct (11%). Recently, Ganem et al.[17] have described an alternative route to prepare *N*-[(2,2,2-trichloroethoxy)sulfonyl]azetidin-2-one derivatives. However, these authors have yet to report any reductive desulfonylation experiments.

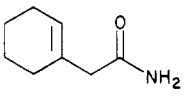
Although the reduction of β-lactam **14g** to produce **14j** was inefficient, reduction of the corresponding 2,2,2-trichloroethanesulfonyl derivative **14h** proved much superior. The reduction of **14h** with activated zinc dust and ammonium chloride in aqueous THF gave **14g** (19%); the major product formed was the β,γ-unsaturated amide **15** (69%). However, reduction of **14h** with sodium dithionite was more successful. Reduction of **14h** with sodium dithionite and 15-crown-5, as phase-transfer catalyst,[18] in DMF gave **14j** (72%). Tetrabutylammonium iodide was a less efficient catalyst: **14j** was obtained in only 24% yield.

Since nitroarenes may be catalytically hydrogenated to produce hydroxylamines and subsequently amines,[19] we sought to use this procedure to convert the β-lactam **14e** into **14j** via the hydroxylamine **14k** and **17**. Hydrogenation of **14e** over palladium on carbon gave only the amine **14f**. Presumably under the reaction conditions, hydroxylamine **14k** was too rapidly reduced. In principle, β-lactams derived from the isocyanate **10** should be more likely to cleave to produce **14j** and **18**.[20] However, in spite of several attempts, we were unable to convert 8-nitronaphthalenesulfonamide[21] into **10**.

Reactions of Sulfonyl Isocyanates with 3,4-Dihydro-2*H*-pyran (3). Vinyl ether **3** reacted smoothly with the isocyanates **7a**, **7b**, **9b**, **11a**, and **11c** to produce the corresponding α,β-unsaturated amides **5b–5f** (57–92%). The isocyanate **7c** reaction with **3** was unsuccessful: only an intractable polymer resulted. In several of these preparations the corresponding β-lactams **4c**, **4d**, **4e**, **4f**, and **4g** were detected by infrared spectroscopy as unstable kinetic products. In each case attempted isolation of these gave only **5b–5f**. Such facile **4** to **5** isomerization reactions have precedent.[7,22] The bicyclic β-lactam **4a** was prepared from **2** and **3**.[7] Attempted reduction of this species with



13a, X = $CCl_3CH_2OSO_2$
b, X = H



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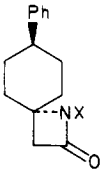
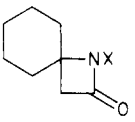
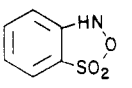


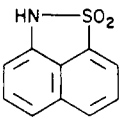
16a, X = SO_2Cl
b, X = $SO_2OCH_2CCl_3$
c, X = H



14a, X = Ts
b, X = $SO_2OC_6H_4$-4-Me
c, X = $SO_2OC_6H_4$-4-OMe
d, X = $SO_2OC_6H_4$-4-NO_2
e, X = $SO_2C_6H_4$-2-NO_2
f, X = $SO_2C_6H_4$-2-NH_2
g, X = $SO_2OCH_2CCl_3$
h, X = $SO_2CH_2CCl_3$
i, X = $COCF_3$
j, X = H
k, X = $SO_2C_6H_4$-2-NHOH

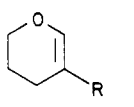


17

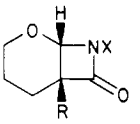


18

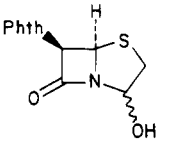
chromium(II) or titanium(III) salts or with aluminum amalgam in THF solution gave only intractable mixtures of non-β-lactam products. In addition, hydrogenation of **4e** over palladium on carbon also gave a non-β-lactam complex mixture. Finally, **19a**[23] reacted with isocyanate **11a** to produce the isolable β-lactam **20a**. This material could not be obtained microanalytically pure, but the structural assignment was in accord with the NMR and infrared data. Reduction of this material **20a** with zinc–copper couple or with aluminum amalgam in THF gave only non-β-lactam products.



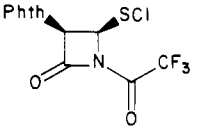
19a, R = Me
b, R = $PhCH_2$



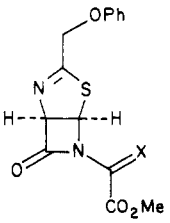
20a, R = Me; X = $SO_2OCH_2CCl_3$
b, R = Me; X = $COCF_3$
c, R = Me; X = H
d, R = $PhCH_2$; X = $COCF_3$
e, R = $PhCH_2$; X = H



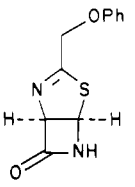
21



22



23a, X = CMe_2
b, X = O



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Reactions of Trifluoroacetyl Isocyanate and 2-Methoxy-2-oxoacetyl Isocyanate (12a) with Alkenes. Acyl isocyanates have been reported to undergo formal [2

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+ 2] cycloaddition reactions with alkenes to produce *N*-acylazetidin-2-one derivatives.[24] However, no attempts have been reported to selectively deacylate these species without fragmentation of the β-lactam ring. We decided to reinvestigate the condensation of trifluoroacetyl isocyanate with alkenes and to study the alkene condensation with **12a**. Trifluoroacetyl isocyanate has been shown to form β-lactams with several alkenes.[25] We chose to examine both these isocyanates since we were confident that after the cycloaddition reaction, release of the parent β-lactam would be straightforward. Sheehan, during studies on the preparation of **21**, used **22** as a key intermediate. In this compound the trifluoroacetyl substituent served as a protecting group that was readily removed by chromatography on Florisil.[26] Secondly, a widely used route for penicillin degradation employs *N*-(2-methoxy-2-oxyacetyl) β-lactams as intermediates. For example, during the degradation of penicillin V, Cooper ozonized **23a** to produce **23b**. This was readily cleaved by methanolic sodium hydroxide to produce **24**.[27]

Trifluoroacetyl isocyanate reacted with methylenecyclohexane to produce **14i**. This crude material was chromatographed on Florisil to produce **14j** (37%) accompanied by the fragmentation product **15** (35%). Alternatively, reaction of crude **14i** with benzylamine at −78 °C gave **14j** (34%) and **15** (11%). The isocyanate (**12a**) was insufficiently electrophilic to add to methylenecyclohexane. Dihydropyran **3** reacted smoothly with both trifluoroacetyl isocyanate and **12a** to give **5h** (76%) and **5g** (70%), respectively. In both these reactions the corresponding β-lactams **4i** and **4h** were detected as intermediates by infrared spectroscopy. However, all attempts either to isolate these compounds or to isolate **4b** after Florisil chromatography or hydrolysis failed. Only non-β-lactam products were detected. However, both the dihydropyran derivatives **19a**[23] and **19b** smoothly condensed with trifluoroacetyl isocyanate to produce the bicyclic β-lactams **20b** and **20d**. Chromatography on Florisil gave the pure β-lactams **20c** and **20e**. Clearly neither **20c** nor **20e** are able to produce the corresponding α,β-unsaturated amide products.

Conclusion

Three isocyanates, *N*-(2,2,2-trichloroethoxy)sulfonyl (**11a**), 2,2,2-trichloroethanesulfonyl (**11c**), and trifluoroacetyl isocyanates, have been shown to be applicable in β-lactam synthesis. The two chlorinated reagents reacted with simple alkenes to produce the corresponding 1*H*-azetidin-2-one derivatives on reductive desulfonylation. Trifluoroacetyl isocyanate reacted with methylenecyclohexane, 5-benzyl-, and 5-methyl-3,4-dihydro-2*H*-pyrans (**19a** and **19b**) to produce the corresponding β-lactams **20c** and **20e** on detrifluoroacetylation on Florisil.

Experimental Section

Materials and Methods. Melting points were determined on a Kofler hot stage and are uncorrected. All solvents and reagents were rigorously purified and dried before use.[28] Silica for chromatography refers to Merck Kieselgel 60M.

***N*-[[(4-Nitrophenyl)oxy]carbonyl]sulfamyl Chloride (6).** $ClSO_2NCO$ (4.5 g) in Et_2O (10 mL) was added over 30 min to a stirred solution of 4-nitrophenol (4.17 g) in Et_2O (30 mL). After a further 2 h evaporation and recrystallization from Et_2O gave **6** (8.4 g, 100%): mp 85 °C; IR ($CHCl_3$) 1775, 1595, 1345, 1285, 1150, 860 cm^{-1}; NMR ^1H ($CDCl_3$) δ 4.6–5.3 (br s, 1 H), 6.91 and 8.16 (ABq, 4 H, J = 9 Hz); mass spectrum, m/e, M^+· absent, 244, 139, 106. Anal. Calcd for $C_7H_5ClN_2O_6S$: C, 29.94; H, 1.80; N, 9.98. Found: C, 30.05; H, 1.83; N, 9.96%.

[(4-Nitrophenyl)oxy]sulfonyl Isocyanate (7c). Urethane **6** (8.4 g) in PhMe (30 mL) was refluxed overnight. Evaporation and distillation gave **7c** (5.5 g, 75%): bp 120 °C (0.04 mm); IR (CH_2Cl_2) 2260, 1525, 1345, 1170, 860 cm^{-1}; NMR ^1H ($CDCl_3$) δ 7.53 and 8.40 (ABq, 4 H, J = 9 Hz); mass spectrum, m/e 244 (M^+·) 190, 155, 106.

***O*-Methyl *N*-[[(4-Nitrophenyl)oxy]sulfonyl]carbamate (8).** Isocyanate (**7c**) (0.25 g) was added to MeOH (5 mL) at 0 °C. After 30 min evaporation and recrystallization from EtOAc–hexane gave **8** (0.27 g, 95%): mp 120–122 °C; IR (nujol) 3190, 1770, 1620, 1590, 1520, 1485, 1255, 1195, 1180, 1165, 895, 760 cm^{-1}; NMR ^1H ($CDCl_3$) δ 3.85 (s, 3 H), 7.2–8.2 (br, 1 H), 7.6, 8.35 (ABq, 4 H, J = 9 Hz); mass spectrum, m/e 276 (M^+·), 243, 144, 138, 105, 90. Anal. Calcd for $C_8H_8N_2O_7S$: C, 34.77; H, 2.92; N, 10.14. Found: C, 34.98; H, 2.92; N, 10.10.

***N*-[(2-Nitrophenyl)sulfonyl]-*N'*-butylurea (9a).** 2-Nitrobenzenesulfonamide (4.6 g) was added to *n*-butyl isocyanate (2 g) and anhydrous $AlCl_3$ (3 g) in $PhNO_2$ (75 mL). After 4 h heating at 80 °C followed by stirring overnight at 80 °C the mixture was added to ice–H_2O (300 mL) containing concentrated hydrochloric acid (10 mL). Hexane was added to the $PhNO_2$ layer to give a precipitate. This was recrystallized from PhMe to give **9a** (3.2 g, 47%): mp 132–140 °C; IR (nujol) 3340, 1680, 1545, 1175 cm^{-1}; NMR ^1H ($CDCl_3$–Me_2CO-d_6) δ 0.6–1.7 (m, 7 H), 3.0–3.4 (m, 2 H), 6.1–6.7 (br, s, 1 H), 7.7–8.4 (m, 4 H); mass spectrum, m/e 301 (M^+·), 258, 202, 186, 115. Anal. Calcd for $C_{11}H_{15}N_3O_5S$: C, 43.83; H, 5.02; N, 13.94. Found: C, 43.61; H, 4.86; N, 13.88.

2-Nitrobenzenesulfonyl Isocyanate (9b). The urea derivative **9a** (3 g) in PhCl (50 mL) was heated to 120 °C and $COCl_2$ (4 g) in PhCl (20 mL) added over 46 min. The mixture was further heated at 120 °C for 2 h, cooled, and evaporated. Recrystallization of the residue from CCl_4–$CHCl_3$ gave **9b** (1.2 g, 53%): mp 73–74 °C; IR ($CHCl_3$) 2240, 1360 cm^{-1}; NMR ^1H ($CDCl_3$) δ 7.6–8.5 (m); mass spectrum, m/e 228 (M^+·), 186, 90.

***O*-Methyl *N*-[(2-Nitrophenyl)sulfonyl]carbamate (9c).** Isocyanate **9b** (0.23 g) was added to MeOH (5 mL) at 0 °C. After 30 min, evaporation and recrystallization from EtOAc–hexane gave **9c** (0.24 g, 92%): mp 195 °C; IR (nujol) 3260, 1770, 1540, 1425, 1240, 1065, 880 cm^{-1}; NMR ^1H ($CDCl_3$–Me_2CO-d_6) δ 3.7 (s, 3 H), 7.5–8.2 (m, 4 H); mass spectrum, m/e, M^+· absent, 227, 201, 185, 92. Anal. Calcd for $C_8H_8N_2O_6S$: C, 36.90; H, 3.10; N, 10.76. Found: C, 36.93; H, 3.09; N, 10.60.

***N*-[(2,2,2-Trichloroethyl)sulfonyl]-*N'*-butylurea (11b).** $CCl_3CH_2SO_2NH_2$[29] (4.3 g) was added to *n*-butyl isocyanate (1.9 g) and anhydrous $AlCl_3$ (3 g) in $PhNO_2$ (75 mL) and the mixture heated at 80 °C for 5 h. After stirring overnight at room temperature, the mixture was added to concentrated hydrochloric acid (20 mL) in iced H_2O (600 mL). Hexane was added to the $PhNO_2$ layer and the resultant precipitate recrystallized from PhMe to give **11b** (4.9 g, 73%): mp 120 °C; IR (nujol) 3350, 1670, 1355, 1160 cm^{-1}; NMR ^1H ($CDCl_3$–Me_2CO-d_6) δ 0.7–1.8 (m, 7 H), 3.15 (t, 2 H, J = 6 Hz), 4.9 (s, 2 H), 6.0–6.5 (br s, 1 H); mass spectrum, m/e 315, 314, 313, 312, 311, 310 (M^+·), 239. Anal. Calcd for $C_7H_{13}Cl_3N_2O_3S$: C, 26.96; H, 4.21; N, 8.99. Found: C, 27.15; H, 4.02; N, 9.20.

2,2,2-Trichloroethanesulfonyl Isocyanate (11c). $COCl_2$ (12 g) in PhCl (100 mL) was added over 1 h to the urea derivative **11b** (18 g) in PhCl (300 mL) at 120 °C. After a further 2 h at 120 °C the mixture was evaporated and distilled to give **11c** (9.38 g, 68%): mp 75 °C (0.25 mmHg); mp 41–41.5 °C; IR ($CHCl_3$) 2240, 1375 cm^{-1}; NMR ^1H ($CDCl_3$) δ 4.6 (s); mass spectrum, m/e, M^+· absent, 180, 178, 176, 132, 130.

***O*-Methyl *N*-[(2,2,2-Trichloroethyl)sulfonyl]carbamate (11d).** Isocyanate **11c** (0.24 g) was added to MeOH (5 mL) at 0 °C. After 30 min, evaporation and recrystallization from EtOAc–hexane gave **11d** (0.24 g, 88%): mp 108 °C; IR (nujol) 3220,

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1730, 1240, 1170, 1150, 920, 885, 810 cm^{-1}; NMR ^1H ($CDCl_3$–Me_2CO-d_6) δ 3.85 (s, 3 H), 4.8 (s, 2 H); mass spectrum, m/e, $M^{+\cdot}$ absent, 202, 200, 160, 158, 96, 94. Anal. Calcd for $C_4H_6Cl_3NO_4S$: C, 17.74; H, 2.24; N, 5.18. Found: C, 17.91; H, 2.19; N, 5.07.

2-Methoxy-2-oxoacetyl Isocyanate (12a). Oxalyl chloride (15 g) was slowly added to $MeOCO{\cdot}CONH_2$ (10.3 g) in $CHCl_3$ (150 mL) and the mixture vigorously stirred overnight. Evaporation and distillation gave **12a** (7.1 g, 55%): bp 45 °C (2 mm); IR (film) 2280, 1780 br, 1110 cm^{-1}; NMR ^1H ($CDCl_3$) δ 4.03 (s); mass spectrum, m/e 129 ($M^{+\cdot}$), 117, 96, 59.

***O*-Methyl *N*-(2-Methoxy-1,2-dioxoethyl)carbamate (12b).** Isocyanate **12a** (0.13 g) was added to MeOH (5 mL) at 0 °C. After 30 min, evaporation and recrystallization from MeOH gave **12b** (0.16 g, 99%): mp 141–142 °C; IR (nujol) 3350, 1800, 1735, 1530, 1120, 1045, 880, 730 cm^{-1}; NMR ^1H ($CDCl_3$) δ 3.85 (s, 3 H), 3.95 (s, 3 H), 9.3–9.9 (br s, 1 H); mass spectrum, m/e, $M^{+\cdot}$ absent. Anal. Calcd for $C_5H_7NO_5$: C, 37.25; H, 4.38; N, 8.69. Found: C, 37.16; H, 4.33; N, 8.60.

Trifluoroacetyl Isocyanate. Trifluoroacetyl isocyanate was prepared from CF_3COCl and KNCO in a LiCl–KCl eutectic at 480 °C according to the method of Lidy and Sundermeyer:[10] bp 38 °C; IR ($CHCl_3$) 2260, 2230, 1765, 1175, 1015 cm^{-1}.

4-Phenyl-1-[(2,2,2-trichloroethoxy)sulfonyl]azetidin-2-one (13a). Isocyanate **11a**[8] (2.5 g) was added to styrene (1.04 g) in Et_2O (1 mL) and the solution refluxed for 2 days. After cooling the white precipitate was recrystallized from EtOAc–hexane to give **13a** (1.93 g, 54%): mp 102–104 °C; IR (CH_2Cl_2) 1810, 1185, 995 cm^{-1}; NMR ^1H ($CDCl_3$) δ 2.60 (dd, 1 H, J = 18, 4.5 Hz), 3.06 (dd, 1 H, J = 18, 7 Hz), 3.96 (s, 2 H), 4.63 (dd, 1 H, J = 7, 4.5 Hz), 6.86 (s, 5 H); mass spectrum, m/e 359, 357 ($M^{+\cdot}$), 168, 136, 104. Anal. Calcd for $C_{11}H_{10}Cl_3NO_4S$: C, 36.82; H, 2.81; N, 3.91. Found: C, 37.0; H, 2.6; N, 3.7.

4-Phenylazetidin-2-one (13b). Method 1. The β-lactam **13a** (175 mg) was added to Zn/Cu couple (40 mg) in THF (4 mL). After stirring overnight the mixture was filtered through Celite and the filtrate washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and evaporated. Recrystallization of the residue from EtOAc–hexane gave **13b** (71 mg, 98%): mp 105 °C (lit.[14] mp 108–109 °C); identical with authentic material. **Method 2.** Chromium(II) perchlorate in H_2O (1.63 M, 0.612 mL) was added to **13a** (175 mg) in DMF (1 mL). After 2 min the green solution was diluted with Et_2O (20 mL) and washed with H_2O (10 mL). Evaporation of the organic phase and recrystallization of the residue from THF–hexane gave **13b** (69 mg, 96%).

7-(Tolyl-4-sulfonyl)-7-azaspiro[3.5]-8-nonanone (14a). TsNCO (**2**) (0.21 g) was added to methylenecyclohexane (0.10 g) in $CHCl_3$ (4 mL). After 4 weeks evaporation and recrystallization of the residue from EtOAc–hexane gave **14a** (0.27 g, 87%): mp 144–145 °C; IR (nujol) 1795, 1380, 1175, 670 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.9–2.4 (m, 10 H), 2.4 (s, 3 H), 2.7 (s, 2 H), 7.23, 7.83 (ABq, 4 H, J = 8 Hz); mass spectrum, m/e 293 ($M^{+\cdot}$), 198, 155. Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.39; H, 6.53; N, 4.77. Found: C, 61.49; H, 6.54; N, 4.80.

7-[(Tolyl-4-oxy)sulfonyl]-7-azaspiro[3.5]-8-nonanone (14b). Isocyanate **7a**[8] (0.21 g) was added to methylenecyclohexane (0.10 g) in CCl_4 (2 mL). After 1 week evaporation and recrystallization of the residue from EtOAc-hexane gave **14b** (0.30 g, 98%): mp 89–90 °C; IR ($CHCl_3$) 1795, 1390, 1180 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.8–2.15 (m, 10 H), 2.33 (s, 3 H), 2.76 (s, 2 H), 7.13 (s, 4 H); mass spectrum, m/e ($M^{+\cdot}$) absent 244, 106, 96. Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.21; H, 6.19; N, 4.53. Found: C, 58.28; H, 6.20; N, 4.56%.

7-[[(4-Methoxyphenyl)oxy]sulfonyl]-7-azaspiro[3.5]-8-nonanone (14c). Isocyanate **7b**[8] (0.46 g) was added to methylenecyclohexane (0.20 g) in $CHCl_3$ (4 mL). After 3 days, evaporation and recrystallization of the residue from EtOAc–hexane gave **14c** (0.57 g, 87%): mp 89–90 °C; IR (nujol) 1790, 1180, 1150 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.8–2.3 (m, 10 H), 2.76 (s, 2 H), 3.78 (s, 3 H), 6.76, 7.20 (ABq, 4 H, J = 9 Hz); mass spectrum, m/e 325 ($M^{+\cdot}$), 229, 122. Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.35; H, 5.89; N, 4.30. Found: C, 55.30; H, 5.84; N, 4.33.

7-[[(4-Nitrophenyl)oxy]sulfonyl]-7-azaspiro[3.5]-8-nonanone (14d). Methylenecyclohexane (0.27 g) was added to **7c** (0.70 g) in CCl_4 (2 mL) at 0 °C. After 30 min, evaporation and recrystallization from EtOAc–hexane gave **14d** (0.90 g, 92%): mp 99–100 °C; IR (nujol) 3430 (impurity), 1795, 1350, 1145, 865 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.55–2.3 (m, 10 H), 3.1 (s, 2 H), 7.55, 8.32 (ABq, 4 H, J = 9 Hz); mass spectrum, m/e 340 ($M^{+\cdot}$), 244, 106, 96, 81. Anal. Calcd for $C_{14}H_{16}N_2O_6S$: C, 49.40; H, 4.74; N, 8.23. Found: C, 49.59; H, 4.69; N, 8.20.

7-[(2-Nitrophenyl)sulfonyl]-7-azaspiro[3.5]-8-nonanone (14e). Isocyanate **9b** (0.23 g) and methylenecyclohexane (0.10 g) were allowed to stand at room temperature for 3 days. Evaporation and recrystallization from EtOAc–hexane gave **14e** (0.32 g, 98%): mp 115–116 °C; IR ($CHCl_3$) 1800, 1550, 1375, 1150, 1130 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.9–2.5 (m, 10 H), 2.96 (s, 2 H), 7.5–8.5 (m, 4 H); mass spectrum, m/e 244, 138, 106, 96, 80. Anal. Calcd for $C_{14}H_{16}N_2O_5S$: C, 51.82; H, 4.97; N, 8.64. Found: C, 51.80; H, 4.70; N, 8.50.

7-[(2-Aminophenyl)sulfonyl]-7-azaspiro[3.5]-8-nonanone (14f). β-Lactam **14e** (0.324 g) and 10% Pd/C (0.10 g) in Et_2O (10 mL) was hydrogenated at atmospheric pressure for 12 h. Filtration, evaporation, and recrystallization from Et_2O gave **14f** (0.261 g, 89%): mp 215–216 °C; IR ($CHCl_3$) 3470, 3370, 1795 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.0–2.4 (m, 10 H), 2.75 (s, 2 H), 5.0–5.5 (br s, 2 H), 6.6–8.0 (m, 4 H); mass spectrum, m/e 294 ($M^{+\cdot}$), 208, 198, 137, 122. Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.10; H, 6.16; N, 9.52. Found: C, 57.27; H, 6.17; N, 9.52.

7-[(2,2,2-Trichloroethoxy)sulfonyl]-1-azaspiro[3.5]-8-nonanone (14g). Isocyanate **11a**[8] (0.25 g) was added to methylenecyclohexane (0.10 g) in CCl_4 (2 mL). After 2 days at room temperature evaporation and recrystallization from CH_2Cl_2 gave **14g** (0.34 g, 99%): mp 137 °C; IR ($CHCl_3$) 1810, 1400, 1125 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.90–2.15 (m, 10 H), 2.85 (s, 2 H), 4.78 (s, 2 H); mass spectrum, m/e 354, 353, 352, 351, 349 ($M^{+\cdot}$), 316, 314, 202, 177, 96. Anal. Calcd for $C_{10}H_{14}Cl_3NO_4S$: C, 34.23; H, 4.03; N, 3.99. Found: C, 34.36; H, 4.01; N, 3.96.

7-[(2,2,2-Trichloroethyl)sulfonyl]-7-azaspiro[3.5]-8-nonanone (14h). Isocyanate **11c** (1.0 g) was added to methylenecyclohexane (0.41 g) in $CHCl_3$ (15 mL). After 1 week, evaporation and recrystallization from EtOAc–hexane gave **14h** (1.17 g, 83%): mp 135 °C; IR (nujol) 1800, 1150, 1050, 915, 870 cm^{-1}; NMR ^1H ($CDCl_3$) δ 0.7–2.24 (m, 10 H), 2.86 (s, 2 H), 4.48 (s, 2 H); mass spectrum, m/e 338, 336, 334 ($M^{+\cdot}$), 300, 298, 161, 159, 96, 91, 81. Anal. Calcd for $C_{10}H_{14}Cl_3NO_3S$: C, 35.87; H, 4.22; N, 4.19. Found: C, 35.85; H, 4.18; N, 4.14.

7-(Trifluoroacetyl)-7-azaspiro[3.5]-8-nonanone (14i). CF_3CONCO (0.14 g) was added to methylenecyclohexanone (0.10 g) in $CHCl_3$ (4 mL). After 3 weeks, evaporation gave crude **14i** (0.24 g): IR ($CDCl_3$) 1820, 1780, 1750, 1170 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.0–2.3 (m), 2.8 (s), 3.2 (s). The material was used without further purification.

7-Azaspiro[3.5]-8-nonanone (14j). Method 1. Activated Zn dust (0.10 g) was added to **14g** (0.35 g) and NH_4Cl (0.11 g) in H_2O–THF (1:4, 20 mL). After 72 h stirring the mixture was filtered through Celite and the solids were rigorously extracted with Et_2O (100 mL). The Et_2O layer was washed with H_2O (20 mL), dried ($MgSO_4$), and evaporated to leave a yellow oil. Chromatography on silica gel gave **14j** (41 mg, 30%) identical in all respects with authentic material[16] and 1-cyclohexeneacetamide (**15**) (15 mg, 11%): mp 146–148 °C; IR ($CHCl_3$) 3520, 3410, 1675 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.63 (m, 4 H), 2.01 (m, 4 H), 2.85 (s, 2 H), 5.5–5.9 (m, 1 H), 5.5–6.9 (br s, 2 H); NMR ^{13}C ($CDCl_3$) δ 22.0, 22.8, 25.4, 28.4, 46.0, 126.8, 133.1, 173.7; mass spectrum, m/e 139 ($M^{+\cdot}$), 79, 67. Anal. Calcd for $C_8H_{13}NO$: C, 69.01; H, 9.42; N, 10.06. Found: C, 69.00; H, 9.50; N, 10.10. **Method 2.** Activated Zn dust (0.10 g) was added to β-lactam **14h** (0.33 g) and saturated aqueous NH_4Cl (0.11 g solid) in THF (4 mL). After 5 weeks vigorously stirring, the mixture was filtered through Celite and the solids rigorously extracted with Et_2O (50 mL). The Et_2O phase was washed with H_2O (10 mL), dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica (eluant hexane–CH_2Cl_2 gradient) gave **14j** (26 mg, 19%) and **15** (94 mg, 69%). **Method 3.** β-Lactam **14h** (33 mg) was added to sodium dithionite (35 mg) and $Bu_4N^+I^-$ (catalytic amount) in DMF (0.40 mL). After stirring for 2 weeks, evaporation and preparative-layer chromatography on Merck Kieselgel GF_{254} (developing solvent hexane:CH_2Cl_2 1:1) gave unreacted **14h** (5.5 mg, 17%) and **14j** (3.3 mg, 24%). **Method 4.** Method 3 was repeated with 15-crown-5 as the phase-transfer catalyst to produce unreacted **14h** (7.1 mg, 21%) and **14j** (10 mg, 72%). **Method 5.** Trifluoroacetyl isocyanate (0.70 g) was reacted with methylenecyclohexane (0.48 g) in $CHCl_3$ (5 mL) as previously

described. The crude β-lactam **14i** was chromatographed on Florisil (10 g) with Et_2O (500 mL) as eluant. Evaporation gave an oil which was chromatographed on silica (eluant hexane–CH_2Cl_2 gradient) to give **15** (0.244 g, 35%) and **14j** (0.257 g, 37%). **Method 6.** The crude β-lactam **14i** [from methylenecyclohexane (0.48 g) and trifluoroacetyl isocyanate (0.70 g)] was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. $PhCH_2NH_2$ (0.59 g) was added, after 2 h the mixture was warmed up to room temperature and evaporated, and the residue was chromatographed on silica to give *N*-benzyltrifluoroacetamide (0.512 g, 51%): mp 74–75 °C (lit.[30] mp 74–75 °C); **15** (75 mg, 11%); **14j** (0.238 g, 34%).

4-Methylene-1-phenylcyclohexane. 4-Phenylcyclohexanone (38.33 g) and $Ph_3P{=}CH_2$ [from $Ph_3P^+Me\ Br^-$ (71.4 g) and *n*-BuLi (0.22 mol) in Et_2O (400 mL)] were condensed[31] to produce 4-phenyl-1-methylenecyclohexane (12.72 g, 34%): bp 124 °C (17 mm); IR (film) 890, 760, 700 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.1–2.85 (m, 9 H), 4.6 (s, 2 H), 7.15 (s, 5 H); mass spectrum, *m/e* 172 ($M^{+\cdot}$), 143, 104. Anal. Calcd for $C_{13}H_{16}$: C, 90.63; H, 9.37. Found: C, 90.34; H, 9.64.

7-(Chlorosulfonyl)-3-phenyl-7-azaspiro[3.5]-8-nonanone (16a). $ClSO_2NCO$ (1.41 g) was added to 4-methylene-1-phenylcyclohexane (1.7 g) in Et_2O (3 mL) at 0 °C. Recrystallization of the resultant precipitate from THF–hexane gave **16a** (2.1 g, 67%): mp 90–91 °C; IR (nujol) 1825, 1405, 1185, 1145, 1080, 1060, 770 cm^{-1}; NMR ^1H ($CDCl_3$–Me_2SO-d_6) δ 1.5–3.1 (m, 9 H), 3.1 (s, 2 H), 7.25 (s, 5 H); mass spectrum, *m/e* 313 ($M^{+\cdot}$), 172, 104. Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.56; H, 5.14; N, 4.46. Found: C, 53.3; H, 5.0; N, 4.5.

7-[(2,2,2-Trichloroethoxy)sulfonyl]-3-phenyl-7-azaspiro-[3.5]-8-nonanone (16b). Isocyanate **11a** (2.53 g) was added to 4-methylene-1-phenylcyclohexane (1.6 g) in Et_2O (3 mL). After standing overnight the mixture was evaporated and the residue recrystallized from EtOAc–hexane to give the β-lactam **16b** (2.75 g, 65%): mp 119–120 °C; IR ($CHCl_3$) 1820, 1410, 1140, 1005, 870, 770, 725 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.8–2.1 (m, 4 H), 2.2–2.5 (m, 4 H), 2.7–2.8 (m, 1 H), 3.0 (s, 2 H), 4.83 (s, 2 H), 7.5 (s, 5 H); mass spectrum, mp 429, 427, 425 ($M^{+\cdot}$), 214, 156, 117. Anal. Calcd for $C_{16}H_{18}Cl_3NO_4S$: C, 45.01; H, 4.25; N, 3.28. Found: C, 44.90; H, 4.10; N, 3.10.

3-Phenyl-7-azaspiro[3.5]-8-nonanone (16c). Method 1. β-Lactam **16a** (1.8 g) in THF (20 mL) was added to $NaHCO_3$ (2.83 g) and Na_2SO_3 (2.23 g) in H_2O (6.8 mL). After vigorous stirring overnight the mixture was extracted with Et_2O (2 × 100 mL). The organic phase was washed with H_2O, dried (Na_2SO_4), and evaporated. Recrystallization of the residue from EtOAc–hexane gave **16c** (0.96 g, 78%): mp 155–157 °C; IR (nujol) 3180, 1740 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.5–1.7 (m, 2 H), 1.7–2.1 (m, 6 H), 2.55 (dt, 1 H, *J* = 12, 3.6 Hz), 2.73 (s, 2 H), 7.25 (m, 5 H), 7.61 (br s, 1 H); mass spectrum, *m/e* 215 ($M^{+\cdot}$), 172, 143, 130, 115, 104. Anal. Calcd for $C_{14}H_7NO$: C, 78.09; H, 7.97; N, 6.51. Found: C, 77.9; H, 8.2; N, 6.3. **Method 2.** Bis(ethylenediamine)chromium(II) perchlorate in DMF[15] (0.125 M, 4 mL) was added to the β-lactam **16b** (0.42 g) in DMF (1 mL) at room temperature. The purple color of the complex instantaneously discharged. After stirring overnight the reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (50 mL). The Et_2O solution was dried (Na_2SO_4) and evaporated and the residue recrystallized from THF–hexane to give **16c** (81 mg, 38%). **Method 3.** β-Lactam **16b** (0.39 g) was added to Zn/Cu couple (0.1 g) in THF (54 mL) and the mixture stirred at 55 °C for 2 days. The mixture was filtered through Celite and the filtrate was evaporated to leave a white solid. Chromatography on silica gave the β-lactam **16c** (82 mg, 42%).

***N*-[(Tolyl-4-oxy)sulfonyl]-5,6-dihydro-4*H*-pyran-3-carboxamide (5b).** Isocyanate **7a**[8] (0.43 g) was added to 3,4-dihydro-2*H*-pyran (**3**) (0.17 g) in $CHCl_3$ (4 mL). After standing overnight, evaporation and recrystallization from CH_2Cl_2 gave **5b** (0.36 g, 60%): mp 117 °C; IR (nujol) 3380, 1705, 1630, 1610, 1500, 1180, 1145, 1030, 875, 830 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.95 (m, 2 H), 2.25 (t, 2 H, *J* = 5.5 Hz), 2.38 (s, 3 H), 4.13 (t, 2 H, *J* = 5.5 Hz, 7.25 (s, 4 H), 7.65 (s, 1 H); mass spectrum, *m/e* $M^{+\cdot}$ absent, 187, 111, 108. Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.49; H, 5.09; N, 4.71. Found: C, 52.29; H, 5.05; N, 4.69.

***N*-[[(4-Methoxyphenyl)oxy]sulfonyl]-5,6-dihydro-4*H*-pyran-3-carboxamide (5c).** Isocyanate **7b**[8] (0.46 g) was added to 3,4-dihydro-2*H*-pyran (**3**) (0.17 g) in $CHCl_3$ (4 mL). After standing overnight, evaporation and recrystallization from EtOAc–hexane gave **5c** (0.44 g, 70%): mp 106–107 °C; IR ($CHCl_3$) 3390, 1725, 1500, 1430, 1170 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.6–2.2 (m, 4 H), 3.8 (s, 3 H), 4.05 (t, 2 H, *J* = 6 Hz), 6.86, 7.23 (ABq, 4 H, *J* = 9 Hz), 7.55 (s, 1 H); mass spectrum, *m/e* 313 ($M^{+\cdot}$), 210, 124, 111. Anal. Calcd for $C_{13}H_{15}NO_6S$: C, 49.81; H, 4.83; N, 4.47. Found: C, 49.80; H, 4.79; N, 4.48.

***N*-[(2-Nitrophenyl)sulfonyl]-5,6-dihydro-4*H*-pyran-3-carboxamide (5d).** Isocyanate **9b** (0.23 g) was added to 3,4-dihydro-2*H*-pyran (0.09 g) in $CHCl_3$ (4 mL) at 0 °C. After standing overnight, evaporation and recrystallization from EtOAc–hexane gave **5d** (0.18 g, 57%): mp 198–200 °C; IR (nujol) 3280, 1690, 1640, 1550, 1180, 1170, 790, 750 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.6–2.5 (m, 4 H), 3.85–4.25 (m, 2 H), 6.4–7.15 (br s, 1 H), 7.55–8.4 (m, 4 H); mass spectrum, *m/e* 312 ($M^{+\cdot}$), 128, 115, 110. Anal. Calcd for $C_{12}H_{12}N_2O_6S$: C, 46.13; H, 3.87; N, 8.97. Found: C, 46.28; H, 3.85; N, 8.98.

***N*-[(2,2,2-Trichloroethoxy)sulfonyl]-5,6-dihydro-4*H*-pyran-3-carboxamide (5e).** Isocyanate **11a**[8] (0.25 g) was added to 3,4-dihydro-2*H*-pyran (**3**) (0.09 g) in CCl_4 (2 mL) at room temperature. After standing overnight, evaporation and recrystallization from CH_2Cl_2 gave **5e** (0.26 g, 78%): mp 132–134 °C; IR ($CHCl_3$) 3395, 1690, 1630, 1610, 1440, 1175, 1090, 1005 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.98 (m, 2 H), 2.3 (t, 2 H, *J* = 6 Hz), 4.10 (t, 2 H, *J* = 6 Hz), 5.02 (s, 2 H), 7.63 (s, 1 H); mass spectrum, *m/e* 340, 338, 336 ($M^{+\cdot}$), 189, 126. Anal. Calcd for $C_8H_{18}Cl_3NO_5S$: C, 28.36; H, 2.98; N, 4.14. Found: C, 28.08; H, 2.89; N, 4.07. The experiment was repeated at −20 °C for 20 min to give a solution containing no isocyanate **11a** but mostly a β-lactam, probably **4g**: IR (CCl_4) 1800 cm^{-1}. Evaporation gave **5e** (0.24 g, 71%).

***N*-[(2,2,2-Trichloroethyl)sulfonyl]-5,6-dihydro-4*H*-pyran-3-carboxamide (5f).** Reaction of isocyanate **11c** (0.24 g) and 3,4-dihydro-2*H*-pyran (**3**) (0.09 g) in $CHCl_3$ (4 mL) for 3 h at room temperature gave, on evaporation and recrystallization from EtOAc–hexane, **5f** (0.30 g, 92%): mp 123–125 °C; IR (nujol) 3100, 1670, 1600, 1240, 1160, 1040, 925, 870, 705 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.6–2.4 (m, 4 H), 4.03 (t, 2 H, *J* = 5 Hz), 4.8 (s, 2 H), 7.63 (s, 1 H), 8.66 (s, 1 H); mass spectrum, *m/e* 325, 323, 321 ($M^{+\cdot}$). Anal. Calcd for $C_8H_{10}Cl_3NO_4S$: C, 29.77; H, 3.13; N, 4.34. Found: C, 30.09; H, 3.07; N, 4.34.

***N*-(Carbomethoxyhydroxymethylene)-5,6-dihydro-4*H*-pyran-3-carboxamide (5g).** Reaction of isocyanate **12a** (0.13 g) with 3,4-dihydro-2*H*-pyran (**3**) (0.09 g) in Et_2O (4 mL) at room temperature for 40 min gave, on evaporation and recrystallization from EtOAc–hexane, **5g** (0.15 g, 70%): mp 66–68 °C; IR ($CHCl_3$) 3380, 1760, 1740, 1170, 990 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.7–2.5 (m, 4 H), 3.9 (s, 3 H), 4.15 (t, 2 H, *J* = 6 Hz), 7.8 (s, 1 H); mass spectrum, *m/e* ($M^{+\cdot}$) absent, 126, 111. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.68; H, 5.20; N, 6.57. Found: C, 50.76; H, 5.17; N, 6.60%.

***N*-(2,2,2-Trifluoro-1-hydroxyethylidene)-5,6-dihydro-4*H*-pyran-3-carboxamide (5h).** Trifluoroacetyl isocyanate[11] (0.14 g), 3,4-dihydro-2*H*-pyran (0.09 g), and $CHCl_3$ (0.5 mL) were allowed to stand at room temperature for 24 h. Evaporation and recrystallization from EtOAc–hexane gave **5h** (0.17 g, 76%): mp 95 °C; IR (nujol) 3370, 1680, 1630, 1185 cm^{-1}; NMR ^1H ($CDCl_3$) 1.6–2.35 (m, 4 H), 4.06 (t, 2 H, *J* = 5 Hz), 6.5–8.1 (br s, 1 H), 7.64 (s, 1 H); NMR ^{13}C ($CDCl_3$) δ (proton decoupled) 19.0 (s), 20.9 (s), 66.6 (s), 105.2 (s), 115.4 (q), 156.1 (s), 161.7 (q), 173.0 (s); mass spectrum, *m/e* ($M^{+\cdot}$) absent, 127, 111, 99. Anal. Calcd for $C_8H_8F_3NO_3$: C, 43.04; H, 3.62; N, 6.28. Found: C, 42.97; H, 3.63; N, 6.27.

6-Methyl-8-(trifluoroacetyl)-8-aza-2-oxabicyclo[4.2.0]-7-octanone (20b). Reaction of trifluoroacetyl isocyanate[11] (0.14 g) and 5-methyl-3,4-dihydro-2*H*-pyran (**19a**)[23] (0.10 g) in $CHCl_3$ (4 mL) for 24 h at room temperature gave, on evaporation, crude **20b** (0.23 g, 96%) as an oil: IR ($CHCl_3$) 1810, 1730 cm^{-1}; NMR ^1H ($CDCl_3$) (inter alia) δ 1.40 (s, 3 H), 1.5–2.3 (m, 4 H), 3.85 (t, 2 H, *J* = 5 Hz), 5.45 (s, 1 H).

6-Methyl-8-aza-2-oxabicyclo[4.2.0]-7-octanone (20c). Method 1. Crude **20b** (0.24 g) was chromatographed on Florisil (10 g) with Et_2O (400 mL). Evaporation and rechromatography on silica (eluant hexane–CH_2Cl_2 gradient) gave β-lactam **20c** (87 mg, 61%): mp 45–48 °C; IR (CH_2Cl_2) 3280, 1750 cm^{-1}; NMR ^1H

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($CDCl_3$) δ 1.25 (s, 3 H), 1.5–2.0 (m, 4 H), 3.8 (m, 2 H), 4.85 (s, 1 H), 6.3–7.0 (br s, 1 H); mass spectrum, *m/e* 142 ($M^+ + 1$), 98, 83. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.54; H, 7.86; N, 9.92. Found: C, 59.77; H, 7.80; N, 9.85. **Method 2.** Reaction of crude β-lactam **20b** (0.24 g) with $PhCH_2NH_2$ (0.12 g) in CH_2Cl_2 (10 mL) at −78 °C for 1 h and chromatography on silica gave **18c** (58 mg, 41%).

3-Benzyltetrahydropyran-2-one.[32] Ethyl 3-phenylpropanoate (11.4 mL) was added dropwise over 1 h to lithium diisopropylamine solution [from *n*-BuLi in hexane (3.0 M, 21.7 mL), *i*-Pr_2NH (9 mL), and THF (92 mL)] and HMPA (23 mL) at −78 °C. After a further 1 h, 1-iodo-3-[(trimethylsilyl)oxy]propane (13.7 g) was added rapidly. After 1 h at −78 °C the mixture was warmed up to room temperature over 30 min, recooled to −78 °C, and added to hydrochloric acid (10%, 100 mL). The mixture was extracted with Et_2O (500 mL), and the extract washed with saturated aqueous $Na_2S_2O_7$ and H_2O, dried ($MgSO_4$), and evaporated. The residue (17.1 g) and $TsOH·H_2O$ (0.12 g) in PhMe (800 mL) was refluxed for 2 h. Evaporation and chromatography of the residue on silica (eluant hexane:CH_2Cl_2:Et_2O 4:4:1) gave 3-benzyltetrahydropyran-2-one (8.3 g, 83%) as an oil: IR (film) 1730, 1245, 1150, 1070, 965, 740, 700 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.3–2.05 (m, 4 H), 2.5, 2.78 (m, 2 H), 3.23 (m, 1 H), 4.2 (t, 2 H, *J* = 6 Hz), 7.2 (s, 5 H); mass spectrum, *m/e* 190 (M^+·), 147, 118, 91. The product was used crude without further purification.

3-Benzyl-2-methoxytetrahydro-2*H*-pyran. Diisobutylaluminium hydride in PhMe (34% w/w, 27 mL) was added over 1 h to 3-benzyltetrahydropyran-2-one (8.3 g) in PhMe (100 mL) at −78 °C. After 1 h the hydrochloric acid (10%, 100 mL) and ice (100 g) were added. The mixture was extracted with Et_2O and the organic phase washed with saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated. The resultant oil (6.5 g), MeOH (200 mL), and Amberlyst IR 120H resin (5 g) were stirred overnight at room temperature. Filtration, evaporation, reevaporation from toluene, and chromatography on silica gave 3-benzyl-2-methoxytetrahydro-2*H*-pyran (4.77 g, 53%) as an oil: IR (film) 1120, 1050, 960, 750, 700 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.3–1.7 (m, 4 H), 2.5 (m, 2 H), 3.28 (m, 1 H), 3.3 (s, 3 H), 3.5 (m, 2 H), 4.26 (d, 1 H, *J* = 3 Hz), 7.16 (s, 5 H); mass spectrum, *m/e* 206 (M^+·), 174, 118, 91. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found: C, 75.90; 8.93.

5-Benzyl-3,4-dihydro-2*H*-pyran (19b). PhMe (300 mL), 3-benzyl-2-methoxytetrahydro-2*H*-pyran (4.77 g), and Amberlyst IR 120H (10 g) were refluxed for 4 h and distilled to small volume over a further 3 h. Filtration, evaporation, and chromatography on silica gave **19b** (1.6 g, 40%): mp 120–121 °C; IR ($CHCl_3$) 1665, 1130 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.76 (m, 4 H), 3.1 (s, 2 H), 3.8 (t, 2 H, *J* = 3 Hz), 6.23 (s, 1 H), 7.15 (s, 5 H); mass spectrum, *m/e* 174 (M^+·), 173, 131, 91, 83.

6-Benzyl-8-aza-2-oxabicyclo[4.2.0]-7-octanone (20e). Trifluoroacetyl isocyanate (0.16 g) and **19b** (0.18 g) in $CHCl_3$ (2 mL) were allowed to react for 3 weeks at room temperature. Evaporation gave crude **20d** (0.31 g) as a yellow oil: IR ($CDCl_3$) 1820, 1740, 1230, 1170 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.2–2.1 (m, 4 H), 2.78, 3.08 (ABq, 2 H, *J* = 14 Hz), 3.76 (t, 2 H, *J* = 6 Hz), 5.53 (s, 1 H), 7.23 (s, 5 H). Chromatography of the crude product on Florisil [eluant Et_2O (500 mL)] and rechromatography on silica (eluant hexane–CH_2Cl_2 gradient) gave the β-lactam **20e** (88 mg, 40%): mp 95–99 °C; IR ($CHCl_3$) 3410, 1765 cm^{-1}; NMR ^1H ($CDCl_3$) δ 1.3–2.2 (m, 4 H), 2.72, 3.05 (ABq, 2 H, *J* = 14 Hz), 3.76 (m, 2 H), 5.0 (s, 1 H), 6.5 (br s, 1 H), 7.3 (s, 5 H); mass spectrum, *m/e* 218 ($M^+ + 1$), 174, 129, 115, 91. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.52; H, 6.96; N, 6.47.

8-[(2,2,2-Trichloroethoxy)sulfonyl]-8-aza-6-methyl-2-oxabicyclo[4.2.0]-7-octanone (20a). Isocyanate **11a** (0.25) and **19a** (0.10 g) in $CHCl_3$ (4 mL) were allowed to stand at room temperature for 2 days. Evaporation gave crude **20a** (0.34 g) as an oil: IR ($CDCl_3$) 1800, 1400, 1130 cm^{-1}; NMR ^1H ($CDCl_3$) δ (inter alia) 1.4 (s, 3 H), 1.5–2.4 (m, 4 H), 3.9 (m, 2 H), 4.8 (s, 2 H), 5.42 (s, 1 H).

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Wharton Fragmentation of Monosulfonates of Methylhexahydroindandiols[1]

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(*Z*)-5-Methylcyclonon-5-en-1-one (**5**) was obtained by treatment of an 85:15 mixture of 4α- (**4a**) and 4β-(tosyloxy)-7aβ-hydroxy-3aβ-methyl-3a,4,5,6,7,7a-hexahydroindan (**4e**) with potassium *tert*-butoxide in *tert*-butyl alcohol. The corresponding *E* isomer (**6**) was also produced in a small quantity in this experiment and in reasonable yield when 4β-(mesyloxy)-7aβ-hydroxy-3aβ-methyl-3a,4,5,6,7,7a-hexahydroindan (**4b**) was reacted under similar conditions. However, the *E* enone was not isolated in pure form. The hexahydroindandiols which were used to prepare the monosulfonates were obtained by reduction of 3a,7a-epoxy-3a,4,5,6,7,7a-hexahydro-4-indanone (**7**) with lithium and liquid ammonia followed by addition of methyl iodide to give 7aβ-hydroxy-3aβ-methyl-3a,4,5,6,7,7a-hexahydro-4-indanone (**8**) and then reduction of the carbonyl group in **8** with metal hydrides or lithium in liquid ammonia.

In connection with our investigation toward a total synthesis of the antileukemic diterpene jatrophatrione (**1**),[3] we became interested in the fragmentation reactions of 6/5 fused ring systems as a method of producing functionalized cyclononane derivatives. Recently, Patel and Dev[4] reported that the Wharton fragmentation procedure[5] can be used to convert the hydroxy tosylate **2** into (*Z*)-5-methylcyclonon-4-en-1-one (**3**). We now wish to describe our studies on the Wharton fragmentation of hydroxy sulfonates such as **4**, which are related to **2** but contain the leaving group in the six-membered ring, to yield (*Z*)-5-methylcyclonon-5-en-1-one (**5**) and its *E* isomer **6**.

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