

Convenient Synthesis of α -(2-Oxoazetidin-4-yl) Esters and Ketones and Related Systems

Robin P. Attrill,[†] Anthony G. M. Barrett,^{*,†} Peter Quayle, and Jan van der Westhuizen

Department of Chemistry, Imperial College, London SW7 2AY, England, and Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Michael J. Betts

Imperial Chemical Industries PLC, Pharmaceuticals Division, Mereside Alderley Park, Macclesfield, Cheshire SK10 4TG, England

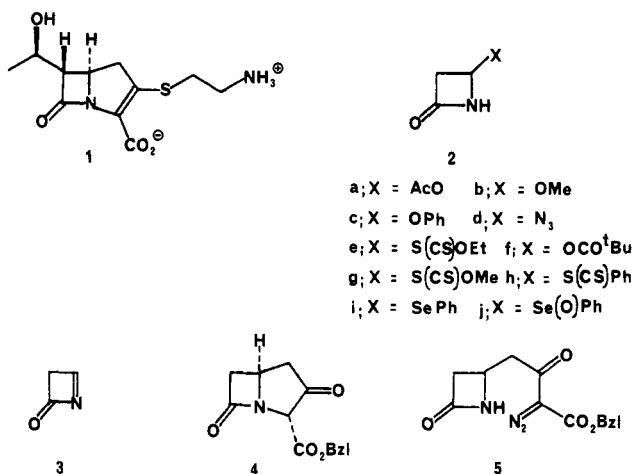
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4-Acetoxy-1-(trimethylsilyl)azetidin-2-one reacted smoothly with the silyl enol ethers $[R^1CH=C(OSiMe_3)R^2]$ $[R^1 = H, Me; R^2 = Ph, C_6H_4-4-Cl, C_6H_4-4-Me, SPh, OCH_2Ph, OEt, CH=C(OMe)OSiMe_3]$ in dichloromethane solution in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst to produce the corresponding α -(2-oxoazetidin-4-yl) esters and ketones. Attempts to intercept 1-azetin-4-one, the intermediate in the nucleophilic displacement reactions of 4-acetoxyazetidin-2-one, with dienes were unsuccessful.

Thienamycin (1) (Chart I) is a third generation β -lactam antibiotic produced by *Streptomyces cattleya*.¹ On account of its excellent broad spectrum activity, 1 and structurally related carbapenems have been the subject of extensive synthetic investigations.² Prior to these studies, Clauss and co-workers at Hoechst described the chemistry of a versatile β -lactam: 4-acetoxyazetidin-2-one (2a).³ Acetate 2a was prepared via the cycloaddition reaction of chlorosulfonyl isocyanate with vinyl acetate. On reaction with diverse oxygen-, nitrogen-, and sulfur-centered nucleophiles, 2a was found to produce the corresponding C-4 substitution products. For example, on reaction with 2a, magnesium methoxide, sodium phenoxide, azide, and *O*-ethyl xanthate gave 2b, 2c, 2d, and 2e, respectively. Clauss also noted that the nucleophilic displacement reaction proceeded with racemization. Thus it is possible that, under the basic reaction conditions, the 1-azetin-4-one (3) is the reactive intermediate. Although 2a has been widely applied for β -lactam synthesis, prior to the start of our investigations, no systematic study of the reaction of 2a with carbon-centered nucleophiles had been reported.⁴ We were confident that the development of such a process would facilitate synthesis of the carbapenems including thienamycin (1). This expectation was based upon the elegant synthesis of the thienamycin precursor 4 via the rhodium acetate catalyzed cyclization of the diazo ester 5.⁵

Reaction of Acetate 2a with Carbon-Centered Nucleophiles. As a potential route to β -lactams 6 (Chart II)

Chart I



we examined the reaction of acetate 2a or pivalate 2f⁵ with malonate anions. We had hoped that the more hindered ester 2f would react more rapidly and would not undergo competitive de-*O*-acylation. Using sodium hydride or potassium *tert*-butoxide as the base in THF or *tert*-butyl

(1) For example, see: Copper, R. D. G. In "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Wiley: New York, 1980; Vol. 3, p 101.

(2) For example, see: Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstein, L. M. *J. Am. Chem. Soc.* 1981, 103, 6765 and references therein.

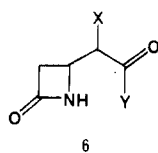
(3) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* 1974, 539.

(4) Onoue, H.; Narisada, M.; Uyeo, S.; Matsumura, H.; Okada, K.; Yano, T.; Nagata, W. *Tetrahedron Lett.* 1979, 3867. Kobayashi, T.; Ishida, N.; Hiraoka, T. *J. Chem. Soc., Chem. Commun.* 1980, 736.

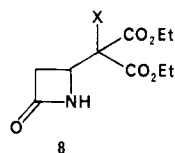
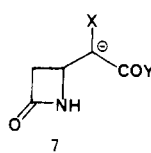
(5) Ratcliffe, R. W.; Saltzman, T. N.; Christensen, B. G. *Tetrahedron Lett.* 1980, 21, 31.

[†]Current address: Department of Chemistry, Northwestern University, Evanston Illinois, 60201.

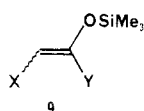
Chart II



- a; X = CO₂Me Y = OMe
 b; X = H Y = OEt
 c; X = H Y = Ph
 d; X = H Y = C₆H₄-4-Cl
 e; X = H Y = C₆H₄-4-Me
 f; X = Me Y = Ph
 g; X = H Y = SPh
 h; X = Me Y = OBzl
 i; X = Me Y = OEt
 j; X = H Y = CH₂CO₂Me
 k; X = Ac Y = OMe



- a; X = Me
 b; X = SPh



- a; X = H Y = Ph
 b; X = H Y = C₆H₄-4-Cl
 c; X = H Y = C₆H₄-4-Me
 d; X = Me Y = Ph
 e; X = H Y = SPh
 f; X = Me Y = OBzl
 g; X = Me Y = OEt

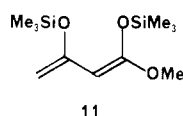
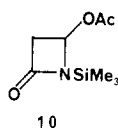
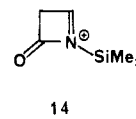
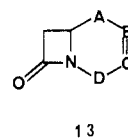
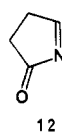


Chart III



methane solution **9a** smoothly condensed with **10** to produce the corresponding β -lactam **6c** (89%) on workup with potassium fluoride. In our hands we found trimethylsilyl trifluoromethanesulfonate¹⁰ to be the optimum Lewis acid for the catalysis of the condensation reaction. In the same way **10** reacted with **9b–9g** to produce the corresponding functionalized β -lactams **6d–6i**, all in excellent yields.¹¹ The products (**6f**, **6h**, and **6i**) were all obtained as mixtures of diastereoisomers. The substituted butadiene **11**¹² condensed with **10** to produce two β -lactams **6j** (56%) and **6k** (30%). Both were readily separated and fully authenticated. An attempt to prepare **6j** from the condensation reaction of **10** with diketene and methoxytrimethylsilane using trimethylsilyl trifluoromethanesulfonate catalysis gave only the β -lactam **2b**. Clearly silyl enol ether chemistry provides a convenient and simple solution to the synthesis of the useful¹³ β -lactams **6**. Independently, Sankyo¹⁴ and Merck¹⁵ chemists have reported the synthesis of **6** using enol aluminate and enol silyl ether chemistry, respectively. In addition, the C-4 allylation and related reactions of the azetidin-2-one ring system have recently been reported.¹⁶

Attempted Trapping of 1-Azetin-4-one (3). The 1-azetidin-4-one (**3**) is widely speculated as the reactive intermediate in the nucleophilic substitution reactions of acetate **2a**. Since the structurally related 1-pyrrolin-5-one **12** and derivatives have been trapped by Diels–Alder reaction,¹⁷ we attempted to capture **3** with 1,3-dienes, 2,4,6-trimethylbenzoxitrone, or 4-(dimethylamino)-3-buten-2-one. If feasible, such a transformation would support the existence of **3** and provide a concise route to the bicyclic β -lactams **13** (Chart III). We studied the generation of **3** from **2a**, **2c**, **2g**, **2h**, **2i**, and **2j** (generated in situ¹⁸) under acidic, basic, thermal, or photochemical conditions. However, none of these experiments gave Diels–Alder adducts **13**. Possibly if **3** is not rapidly captured, its ring opens to produce vinyl isocyanate.¹⁹ It is reasonable to assume, albeit speculatively, that in the condensation of the silyl enol ethers with **2a** to produce **6** that **14** is the reactive intermediate.

alcohol solutions, we were unable to cleanly condense diethyl or di-*tert*-butyl malonate with **2a** or **2f**. Kametani and Shibuya reported that dimethyl lithiomalonate and ethyl lithioacetate and related systems reacted with **2a** to produce **6a** and **6b** albeit in poor yields.⁶ In addition, Kametani demonstrated that these low yields resulted from ring fragmentation, via **7**, taking place subsequent to the production of the crucial carbon–carbon single bond. Thus providing that the deprotonation giving rise to **7** is suppressed, then high yields of the primary adducts **6** should be realized.⁶ On the basis of this tenet, we condensed diethyl methylmalonate with **2a** in the presence of sodium hydride to produce **8a** (66%). Greengrass prepared **8b** and related systems by a similar strategy.⁷ Since the thienamycin precursor **5** was not substituted at C-1', we still required the development of a synthetic method to directly condense simple esters and ketones with **2a**.

Since the β -lactams **6** are unstable under basic conditions, we set out to prepare these derivatives under acidic conditions using trimethylsilyl enol ether chemistry.⁸ The silyl enol ethers **9a–9g** were prepared by using standard procedures.⁹ Acetate **2a** reacted smoothly with chlorotrimethylsilane and triethylamine in diethyl ether solution to produce the *N*-silyl derivative **10** (90%). In dichloro-

(6) Kametani, T.; Hirata, S.; Nemoto, H.; Ihara, M.; Fukumoto, K. *Heterocycles* **1979**, *12*, 523. Shibuya, M.; Kubota, S. *Ibid.* **1979**, *12*, 1315. Kametani, T.; Honda, T.; Sasaki, J.; Terasawa, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1884. Kametani, T.; Honda, T.; Nakayama, A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 1967. Kametani, T.; Honda, T.; Sasaki, J.; Terasawa, H.; Nakayama, Y.; Fukumoto, K. *Ibid.* **1980**, *14*, 575.

(7) Greengrass, C. W.; Hoople, D. W. T. *Tetrahedron Lett.* **1981**, *22*, 1161.

(8) Fleming, I. In "Comprehensive Organic Chemistry", Barton, D. H. R., Ollis, W. D., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, pp 587–592.

(9) Reference 8, p 585–586.

(10) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(11) Preliminary communication: Barrett, A. G. M.; Quayle, P. J. *Chem. Soc. Chem. Commun.* **1981**, 1076.

(12) Chan, T. H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578.

(13) For examples, see: Greengrass, C. W.; Hopple, D. W. T. *Tetrahedron Lett.* **1981**, *22*, 5335. Reider, P. J.; Grabowski, E. J. *J. Ibid.* **1982**, *23*, 2293. Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Machizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2228.

(14) Oida, S.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1980**, *28*, 3494.

(15) Reider, P. J.; Rayford, R.; Grabowski, E. J. *J. Tetrahedron Lett.* **1982**, *23*, 379.

(16) Koher, W.; Linken, A.; Pietsch, H.; Rehlung, H.; Reuschling, D. *Tetrahedron Lett.* **1982**, *23*, 1545. Prasad, K.; Kneussel, P.; Schutz, G.; Stütz, P. *Ibid.* **1982**, *23*, 1247. Aratani, M.; Sawada, K.; Hashimoto, M. *Ibid.* **1982**, *23*, 3921. Nishida, A.; Shibasaki, M.; Ikegami, S. *Ibid.* **1981**, *22*, 4819. Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Heterocycles* **1982**, *19*, 1023. Prasad, K.; Adlgasser, K.; Sharma, R.; Stütz, P. *Ibid.* **1982**, *19*, 2099. Martell, A.; Daris, J.-P.; Bachand, C.; Ménard, M.; Durst, T.; Belleau, B. *Can. J. Chem.* **1983**, *61*, 1899. Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134.

(17) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

(18) Trost, B. M.; Liu, G.-J. *J. Org. Chem.* **1981**, *46*, 4616.

(19) Guillemin, J. C.; Denis, J. M.; Lablanche-Combier, A. *J. Am. Chem. Soc.* **1981**, *103*, 468.

Conclusion

A new synthetic method for the conversion of acetate **2a** into the structurally versatile and important β -lactams **6** has been developed.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot state apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 or 257 grating infrared spectrophotometer. NMR spectra were recorded on a Varian T60 or a Perkin Elmer R32 spectrometer, using tetramethylsilane as an internal reference. Medium-pressure chromatography was carried out on Merck Kieselgel H (type 60) or Kieselgel 60 silica. Solvents were purified as follows: ethyl acetate, hexane, and pentane were redistilled; dichloromethane was dried over and redistilled from phosphorus pentoxide; diethyl ether was redistilled from and dried over sodium wire; tetrahydrofuran (THF) was redistilled from potassium and benzophenone ketyl; triethylamine and diisopropylamine were redistilled from 4-Å molecular sieves and stored over 4-Å molecular sieves; chlorotrimethylsilylsilane was freshly redistilled from calcium hydride under a dry nitrogen atmosphere. Reactions were performed under a dry nitrogen or argon atmosphere. Low reaction temperatures were recorded as internal temperatures. Organic solutions were routinely dried over anhydrous sodium or magnesium sulfate. Solvents were evaporated at reduced pressure using a rotary evaporator at or below 40 °C unless otherwise stated.

4-[1,1-Bis(ethoxycarbonyl)ethyl]azetid-2-one (8a). NaH (57.6 mg) and imidazole (2 mg) were added to diethyl malonate (348 mg) in dry THF (20 mL) at 0 °C. The mixture was stirred at room temperature until hydrogen evolution ceased (2 h). After cooling to -78 °C, 4-acetoxiazetid-2-one (**2a**)³ (258 mg) in dry THF (5 mL) was added. After stirring at -78 °C for 4 h, the mixture was warmed to room temperature and the solvent evaporated. Trituration of the residue with CH₂Cl₂ (2 × 25 mL) gave an extract which was filtered through Celite and concentrated under vacuum. Chromatography on Merck Kieselgel H (8 g) gave (eluant CH₂Cl₂:EtOAc 5:1) **8a** (320 mg, 66%) as an oil: IR (CHCl₃) 3300, 1765, 1730, 1370, 1270, 1115 cm⁻¹; NMR (CDCl₃) δ 1.26 (t, 6 H, *J* = 7 Hz), 1.45 (s, 3 H), 2.71–3.2 (m, 2 H), 4.11–4.38 (m, 5 H), 6.33 (s, 1 H); mass spectrum, *m/e* 244 (M⁺ + 1), 215, 174. Anal. Calcd for C₁₁H₁₇NO₅: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.56; H, 7.13; N, 5.71.

1-(Benzoyloxy)-1-[(trimethylsilyloxy)prop-1-ene (9f). To *i*-Pr₂NH (6.18 mL) in dry THF (50 mL) at 0 °C was slowly added *n*-BuLi (1.4 M, 34.5 mL). After stirring at 0 °C for 30 min, the solution was cooled to -78 °C, and EtCO₂CH₂Ph (6.56 g) in dry THF (10 mL) was slowly added (5 min). After 30 min at -78 °C the mixture was warmed to 0 °C, recooled to -78 °C, and Me₃SiCl (5.62 mL) was added. After 15 min at -78 °C the mixture was warmed to room temperature and the solvent evaporated under reduced pressure. The residue was extracted with dry pentane (2 × 25 mL), filtered, evaporated, and distilled to give **9f** (3.3 g, 34%) as a colorless oil: bp 96–98 °C (1.5 mm); IR (CHCl₃) 1680, 1455, 1380, 1305, 1250, 1200 cm⁻¹; NMR (CDCl₃) δ 1.48, 1.51 (2 d, 3 H, *J* = 7 Hz), 3.48–3.77 (m, 1 H), 4.60, 4.75 (2 s, 2 H), 7.28 (s, 5 H); mass spectrum, *m/e* 237 (M⁺ + 1), 147, 91. Anal. Calcd for C₁₃H₂₀O₂Si: C, 66.05; H, 8.53. Found: C, 66.18; H, 8.48.

1-(Phenylthio)-1-[(trimethylsilyloxy)ethene (9e). To a solution of LiN-*i*-Pr₂ (33 mmol) in dry THF (50 mL) at -78 °C was added PhSAc (4.56 g) in dry THF (5 mL) dropwise over 5 min. After stirring at -78 °C for 15 min, the solution was warmed to 0 °C, recooled to -78 °C, and Me₃SiCl (4.2 mL) added. After 15 min at -78 °C the mixture was warmed up to room temperature, the solvent was evaporated under reduced pressure, and the residue was extracted with dry pentane (2 × 30 mL). Filtration, concentration in vacuo, and distillation gave **9e** (4.71 g, 70%), as an oil: bp 60–63 °C (0.1 mm); IR (CHCl₃) 1600, 1165, 905 cm⁻¹; NMR (CDCl₃) δ 0.13 (s, 9 H), 4.5 (m, 2 H), 7.1–7.5 (m, 5 H); mass spectrum, *m/e* 224 (M⁺), 167, 147, 73. Anal. Calcd for C₁₁H₁₆OSSi: C, 58.93; H, 7.14. Found: C, 59.09; H, 7.37.

4-Acetoxy-1-(trimethylsilyl)azetid-2-one (10). To 4-acetoxiazetid-2-one (**2a**) (6.62 g) in dry Et₂O (100 mL) at 0 °C was added Et₃N (6.18 g) followed by Me₃SiCl (6.08 g). After stirring at 0 °C for 2 h, the solvent was removed in vacuo and

the residue extracted with dry pentane (4 × 60 mL). The extract was filtered, concentrated in vacuo, and distilled to give **10** (9.8 g, 90%) as a colorless oil: bp 80–81 °C (0.5 mm); IR (CCl₄) 1755, 1310, 1250, 1230, 1200, 1175, 1140, 1110, 840, 740 cm⁻¹; NMR (CDCl₃) δ 0.28 (s, 9 H), 2.06 (s, 3 H), 2.92 (dd, 1 H, *J* = 16, 1 H), 3.37 (dd, 1 H, *J* = 16, 4 Hz), 5.92 (dd, 1 H, *J* = 4, 1 Hz); mass spectrum, *m/e* 202 (M⁺ + H), 158, 117, 86, 75. Anal. Calcd for C₈H₁₅NO₃Si: C, 47.73; H, 7.51; N, 6.96; (M⁺ + 1), 202.0899. Found: C, 47.20; H, 7.50; N, 7.20; (M⁺ + 1), 202.0896.

4-(Benzoylmethyl)azetid-2-one (6c). Me₃SiOSO₂CF₃ in CH₂Cl₂ (1% v/v, 1 mL) was added to β -lactam **10** (402 mg) and silyl enol ether **9a**²⁰ (422 mg) in dry CH₂Cl₂ (10 mL) at -78 °C. After 15 min stirring, the reaction mixture was allowed to warm to room temperature (20 min) and stirred for 30 min. The lime green colored solution was quenched with aqueous KF (5% w/v, 20 mL) and the aqueous layer extracted with CH₂Cl₂ (2 × 25 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo and the residue chromatographed on Kieselgel H (10 g) to give (eluant:CH₂Cl₂:pentane 0:1:1) **6c** (338 mg, 89%) as a white crystalline solid: mp 141–143 °C (from CH₂Cl₂:pentane) (lit.¹⁴ 141–143 °C); IR (CH₂Cl₂) 3410, 1755, 1680 cm⁻¹; NMR (CDCl₃) δ 2.7 (dd, 1 H, *J* = 15, 3 Hz), 3.04–3.33 (m, 2 H), 3.49 (dd, 1 H, *J* = 15, 5 Hz), 4.0–4.29 (m, 1 H), 6.35 (s, 1 H), 7.25–8.09 (m, 5 H); mass spectrum, *m/e* 189 (M⁺), 161, 120, 105, 77. Anal. Calcd for C₁₁H₁₁NO₂: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.85; N, 7.40.

4-[(4-Chlorobenzoyl)methyl]azetid-2-one (6d). β -Lactam **6d** (363 mg, 81%), prepared from **9b**²⁰ in the same way, was obtained as a white crystalline solid: mp 130–133 °C (from CH₂Cl₂:pentane); IR (CH₂Cl₂) 3400, 1755, 1675, cm⁻¹; NMR (CDCl₃) δ 2.64 (dd, 1 H, *J* = 15, 2 Hz), 2.93–3.2 (m, 2 H), 3.35 (dd, 1 H, *J* = 19, 5 Hz), 3.88–4.15 (m, 1 H), 6.4 (s, 1 H), 7.37 (d, 2 H, *J* = 9 Hz), 7.8 (d, 2 H, *J* = 9 Hz); mass spectrum, *m/e* 223, 225 (M⁺ + 1), 195, 154, 139. Anal. Calcd for C₁₁H₁₀ClNO₂: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.02; H, 4.49; N, 6.23.

4-[(4-Methylbenzoyl)methyl]azetid-2-one (6e). β -Lactam **6e** (306 mg, 75%), prepared from **9c**²⁰ in the same way, was obtained as a white crystalline solid: mp 135.5–137 °C (from CH₂Cl₂:pentane); IR (CH₂Cl₂) 3410, 1755, 1670 cm⁻¹; NMR (CDCl₃) δ 2.42 (s, 3 H), 2.66 (dd, 1 H, *J* = 15, 3 Hz), 2.97–3.58 (m, 3 H), 3.98–4.26 (m, 1 H), 6.29 (s, 1 H), 7.31 (d, 2 H, *J* = 8 Hz), 7.81 (d, 2 H, *J* = 8 Hz); mass spectrum, *m/e* 203 (M⁺), 175. Anal. Calcd for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.96; H, 6.46; N, 6.89.

4-(1-Benzoyloxyethyl)azetid-2-one (6f). β -Lactam **6f** (289 mg, 71%), prepared from **9d**²⁰ was obtained as a white crystalline solid: mp 125–129 °C (from CH₂Cl₂:pentane); IR (CH₂Cl₂) 3410, 1755, 1675 cm⁻¹; NMR (CDCl₃) δ 1.31 (d, 3 H, *J* = 7 Hz), 2.62 (dd, 1 H, *J* = 15, 3 Hz), 3.08 (ddd, 1 H, *J* = 15, 5, 2 Hz), 3.44–3.58 (m, 1 H), 3.91–4.11 (m, 1 H), 6.5 (s, 1 H), 7.44–8.0 (m, 5 H); mass spectrum, *m/e* 203 (M⁺), 175, 134, 105, 77. Anal. Calcd for C₁₂H₁₃NO₂: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.47; N, 6.92.

4-[(Phenylthio)carbonyl]methylazetid-2-one (6g). β -Lactam **6g** (1.27 g, 76%), prepared from **9e**, was obtained as a white crystalline solid: mp 60–61 °C (from Et₂O:pentane); IR (CH₂Cl₂) 3400, 1770, 1690 cm⁻¹; NMR (CDCl₃) δ 2.62 (dd, 1 H, *J* = 15, 2 Hz), 2.82–3.26 (m, 3 H), 3.77–4.07 (m, 1 H), 6.68 (s, 1 H), 7.4 (s, 5 H); mass spectrum, *m/e* 221 (M⁺), 112, 110, 109, 70. Anal. Calcd for C₁₁H₁₁NO₂S: C, 59.42; H, 5.01; N, 6.33. Found: C, 59.42; H, 4.96; N, 6.29.

4-[1-(Benzoyloxy)carbonyl]ethylazetid-2-one (6h). β -Lactam **6h** (271 mg, 58%), prepared from **9f**, was obtained as viscous oil (contaminated with a trace of **2a**): IR (CH₂Cl₂) 3410, 1755, 1730, 1610 cm⁻¹; NMR (CDCl₃) δ 1.18, 1.25 (2d, 3 H, *J* = 7 Hz), 2.48–3.2 (m, 3 H), 3.58–3.91 (m, 1 H), 5.13 (s, 2 H), 6.38 (br s, 1 H), 7.35 (s, 5 H); calcd for C₁₃H₁₅NO₃ (M⁺), 233.1047; found, 233.1052.

4-[1-(Ethoxycarbonyl)ethyl]azetid-2-one (6i). β -Lactam **6i** (326 mg, 95%), prepared from **9g**²⁰ was obtained as an oil: bp 120 °C (0.1 mm) (Kugelrohr distillation); IR (CH₂Cl₂) 3400, 1760, 1720, 1120 cm⁻¹; NMR (CDCl₃) δ 1.8, 1.26 (2 d, 3 H, *J* = 6 Hz),

(20) Chang, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* 1979, 4029. Wada, M. *Chem. Lett.* 1981, 153. Seyferth, D.; Murphy, G. J.; Mauzé, B. *J. Am. Chem. Soc.* 1977, 99, 5317.

2.38–2.90 (m, 2 H), 3.09 (ddd, 1 H, $J = 17, 5, 1$ Hz), 3.64–3.91 (m, 1 H), 4.18, 4.19, (2 q, 2 H, $J = 6$ Hz), 6.73, 7.0 (2 s, 1 H); mass spectrum, m/e 171 (M^+), 143. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.10; H, 7.80; N, 8.02.

Preparation of 4-(4-Methoxy-2,4-dioxobutyl)azetididin-2-one (6j) and 4-(1-Methoxy-1,3-dioxo-2-butyl)azetididin-2-one (6k). As in the foregoing examples, reaction of diene 11¹² and β -lactam 10 and chromatography on Kieselgel H (eluant EtOAc–pentane) gave 6j¹⁴ (524 mg, 56%) as a colorless oil: IR (CH_2Cl_2) 3400, 1750, 1715 cm^{-1} ; NMR ($CDCl_3$) δ 2.62 (ddd, 1 H, $J = 15, 2.5, 1$ H), 2.85 (dd, 1 H, $J = 18, 8.5$ Hz), 3.06 (dd, 1 H, $J = 18, 4$ Hz), 3.17 (ddd, 1 H, $J = 15, 5, 2.5$ Hz), 3.5 (s, 2 H), 3.73 (s, 3 H), 3.96 (m, 1 H), 6.40 (br s, 1 H). 6k¹⁴ (281 mg, 30%) as a colorless oil: IR (CH_2Cl_2) 3400, 1770, 1740, 1715 cm^{-1} ; NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.68 (dt, 1 H, $J = 15, 3$ Hz), 3.18 (ddd, 1 H, $J = 15, 5, 3$ Hz), 3.7 (m, 1 H), 3.8 (s, 3 H), 4.15 (m, 1 H), 6.2 (br s, 1 H).

Attempted Preparation of 4-(4-Methoxy-2,4-dioxobutyl)azetididin-2-one (6j) from Diketene. Me_3SiOMe (490 mg) and $Me_3SiOSO_2CF_3$ (0.1 g) were added to β -lactam 10 (1.005 g) and diketene (420 mg) in dry CH_2Cl_2 (20 mL) at $-78^\circ C$. After stirring for 1 h at $-78^\circ C$ the mixture was added to KF in MeOH (5% w/v, 100 mL) and stirred for 0.5 h. After evaporation in vacuo the residue was extracted with CH_2Cl_2 (4×40 mL), filtered, and concentrated in vacuo. Chromatography on Kieselgel H (15 g) gave (eluant EtOAc–pentane) methyl acetoacetate (522 mg, 90%) and 4-methoxyazetididin-2-one (2b)³ (450 mg, 89%) both identical with authentic samples.

4-[[Methoxy(thiocarbonyl)]thio]azetididin-2-one (2g). Carbon disulfide (760 mg) was added dropwise to NaOMe [from Na (0.23 g) in dry MeOH (5 mL)]. The resulting solution was added to β -lactam (2a)³ (1.29 g) in dry THF (30 mL) at $-40^\circ C$. The mixture was subsequently stirred at room temperature for 1 h, added to ice, and extracted with EtOAc (3×50 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on Kieselgel H to give (eluant EtOAc:hexane 1:9) β -lactam 2g (965 mg, 54%) as colorless needles: mp $54-55^\circ C$ (from Et₂O–i-Pr₂O); NMR ($CDCl_3$) δ 2.97 (ddd, 1 H, $J = 15, 3, 1$ Hz), 3.49 (ddd, 1 H, $J = 15, 6, 2$ Hz), 4.2 (s, 3 H), 5.41 (dd, 1 H, $J = 6, 3$ Hz), 7.18 (br s, 1 H); mass spectrum, m/e 177 (M^+), 149, 117, 108. Anal. Calcd for $C_5H_7NO_2S_2$: C, 33.86; H, 3.98; N, 7.90; S, 36.18. Found: C, 34.16; H, 4.01; N, 7.62; S, 35.89.

4-[(Thiobenzoyl)thio]azetididin-2-one (2h). Zinc bis(dithiobenzoate)²¹ (2 g) and β -lactam 2a (1.29 g) in dry PhH (70 mL) were stirred for 24 h at room temperature. Evaporation in vacuo and chromatography on the residue on Kieselgel H gave (eluant hexane:EtOAc 9:1) 2h (940 mg, 42%) as red plates: mp $89-90^\circ C$ (from Me_2CO); IR 3410, 1770 cm^{-1} ; NMR ($CDCl_3$) δ 3.12 (ddd, 1 H, $J = 15, 3, 1$ Hz), 3.56 (ddd, 1 H, $J = 15, 6, 2$ Hz), 5.5 (dd, 1 H, $J = 6, 3$ Hz), 6.9 (br s, 1 H), 7.2–8.1 (m, 5 H); mass spectrum, m/e M^+ absent, 176, 105, 85, 83. Anal. Calcd for $C_{10}H_9NOS_2$: C, 53.79; H, 4.06; N, 6.27; S, 28.71. Found: C, 53.67; H, 4.0; N, 6.3; S, 28.76.

4-(Phenylseleno)azetididin-2-one (2i). $NaBH_4$ (400 mg) was added in portions to $PhSeSePh$ (1.56 g) in dry EtOH (24 mL) and the mixture was stirred at room temperature for 30 min. β -Lactam 2a (1.29 g) in EtOH (4 mL) was added and stirring continued for 1 h. After filtration through Kieselgel H, the solution was evaporated and the residue chromatographed on Kieselgel H to give (eluant hexane:EtOAc 9:1) 2i (1.80 g, 79%) as colorless needles: mp $59-60^\circ C$ (from CCl_4); IR (CH_2Cl_2) 3400, 1770, 1340, 960, 940 cm^{-1} ; NMR ($CDCl_3$) δ 3.02 (dt, 1 H, $J = 17, 2$ Hz), 3.49 (ddd, 1 H, $J = 17, 6, 2$ Hz), 5.2 (dd, 1 H, $J = 6, 2$ Hz), 6.96 (br s, 1 H), 7.4–7.75 (m, 5 H); mass spectrum, m/e 226 (M^+), 157. Anal. Calcd for C_9H_9NOSe : C, 47.8; H, 4.0; N, 6.2. Found: C, 47.51; H, 3.96; N, 6.26.

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Registry No. 2a, 28562-53-0; 2g, 77705-30-7; 2h, 89691-17-8; 2i, 89691-18-9; 6c, 76127-62-3; 6d, 80675-57-6; 6e, 80675-56-5; 6f, 89691-19-0; 6g, 76127-66-7; 6h, 79260-92-7; 6i, 79261-32-8; 6j, 77960-47-5; 6k, 77960-48-6; 8a, 89691-20-3; 9a, 13735-81-4; 9h, 58518-76-6; 9c, 54731-27-0; 9d, 37471-46-8; 9e, 80675-54-3; 9f, 86593-93-3; 9g, 80675-53-2; 10, 80675-59-8; 11, 67609-52-3; $EtCO_2CH_2Ph$, 122-63-4; $PhSAc$, 934-87-2; diethyl malonate, 105-53-3.

(21) Houben, J. *Chem. Ber.* 1906, 39, 3219.

Cationic Cyclizations of Ketene Dithioacetals. A General Synthesis of Pyrrolizidine, Indolizidine, and Quinolizidine Alkaloid Ring Systems

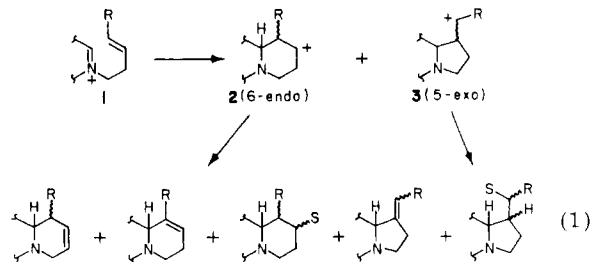
A. Richard Chamberlin,* Hoa D. Nguyen, and John Y. L. Chung

Department of Chemistry, University of California, Irvine, California 92717

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Cyclizations of ketene dithioacetals have been applied to the synthesis of pyrrolizidine, indolizidine, and quinolizidine alkaloid ring systems. This new cationic cyclization terminator allows the efficient formation of 5-, 6-, and 7-membered heterocyclic rings, as illustrated by the preparation of 10a–e. Several of these products, available in three steps, have been converted into the known alkaloids (\pm)-supinidine, (\pm)-trachelanthamide, (\pm)-elaeokanine A, and (\pm)-*epi*-lupinine.

Cationic cyclization is a common method of ring closure in alkaloid synthesis. Simple iminium ions, formed in any number of ways,¹ often initiate this process, although acyl iminium ions can prove to be superior because of their greater reactivity and ease of formation.² In planning such cyclizations one must give careful consideration not only



(1) (a) Rapoport, H. *Lect. Heterocycl. Chem.* 1978, 4, 47. (b) Faling, S. N.; Rapoport, H. *J. Org. Chem.* 1980, 45, 1260 and references therein. (c) See also: Cook, A. G., Ed. "Enamines"; M. Dekker: New York, 1968.

(2) Acyliminium cyclizations in alkaloid synthesis have been reviewed: Speckamp, W. N. *Recl. Trav. Chem. Pays-Bas* 1981, 100, 345.

to the initiator but also to the internal nucleophile (terminator) for the reaction. The choice of a terminator can