Novel Approach to Lactams *via* (Triisopropylsilyl)azidohydrin Formation and Photoinduced Schmidt Rearrangement

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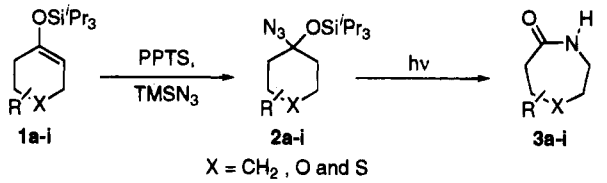
Lactams are particularly important molecules owing to their versatility as synthetic intermediates and widespread occurrence in biologically important compounds.[1,2] They have also proven extremely informative as transition state models in amide reactivity studies.[3] Despite the development of a variety of new methods,[4,5] the Schmidt[6] and Beckmann[7] reactions remain the most convenient and general protocols for their preparation. However, one of the major limitations of the Schmidt rearrangement may be attributed to the severity of the reaction conditions required to effect the ring expansion. Strong protic[6] or Lewis acids[5d] are often required, which accounts for the problematic side reactions observed in acid labile molecules. In this paper, we describe a novel approach to the lactams **3a–i** *via* a photoinduced Schmidt rearrangement of the α-azido triisopropylsilyl ethers **2a–i**, which are prepared by the direct azidonation of the triisopropylsilyl enol ethers **1a–i** (Scheme 1). Triisopropylsilyl enol ethers are useful synthetic intermediates owing to their resistance to hydrolysis, compared to trimethylsilyl enol ethers, which is the result of the increased steric hindrance at silicon created by the isopropyl groups.[8–10]

In the course of an investigation of the electrophilic[10] and oxidative[11] chemistry of triisopropylsilyl enol ethers, we discovered that silyl enol ether **1a** reacts slowly (7 days) with trimethylsilyl azide to afford α-azido triisopropylsilyl ether **2a** in 85% yield.[12,13] The reaction is the result of the formal addition of hydrazoic acid across the silyl enol ether. In an attempt to enhance the rate of the addition, we examined a series of mild acid catalysts which would provide more efficient proton sources. Our preliminary studies indicated that pyridinium *p*-toluenesulfonate (PPTS) was the superior acid catalyst (PPTS > CSA > TsOH), since both camphorsulfonic acid (CSA) and *p*-toluenesulfonic acid (TsOH) lead to significant amounts of hydrolysis, even under anhydrous reaction conditions.[14] This is probably due to the fact that pyridinium *p*-toluenesulfonate is capable of buffering the reaction.

Scheme 1



The photolysis of α-azido alkyl ethers was known from Hassner and co-workers to furnish imino ethers which are then hydrolyzed to amides.[13] The initial reaction presumably involves the formation of a reactive nitrene which then undergoes alkyl migration to form the imino ether. We decided to examine the photochemistry of the azidohydrin **2a** with the aim of forming lactams directly. Photolysis of the α-azido triisopropylsilyl ether **2a** in cyclohexane at 0 °C furnished the lactam **3a** in 89% yield.[15]

Table 1 summarizes the results of the application of the reaction sequence to the cyclohexanone derived triisopropylsilyl enol ethers **1a–i**.[17] The 2-methyl and 3-methyl triisopropylsilyl enol ethers **1b** and **1c** gave the

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(2) For a recent review on medium ring nitrogen heterocycles, see: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.

(3) Lease, T. G.; Shea, K. J. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1992; Vol. 2, pp 79–112.

(4) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron: Asymmetry* **1990**, *1*, 593. Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 857. Evans, P. A.; Holmes, A. B.; Russell, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3397.

(5) (a) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1991**, *32*, 2429. (b) Coates, B.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1991**, *32*, 4199. (c) Kawase, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1076. (d) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635. (e) Vedejs, E.; Sano, H. *Tetrahedron Lett.* **1992**, *33*, 3261. (f) Kim, S.; Joe, G. –H.; Do, J. –Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328. (g) MaGee, D. I.; Ramaseshan, M. *Synlett* **1994**, 743. (h) Suda, K.; Sashima, M.; Izutsu, M.; Hino, F. *J. Chem. Soc., Chem. Commun.* **1994**, 949. (i) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Weller, H. N.; Pan, Y. Y.; Malley, M.; Dimarco, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 2348 and pertinent references cited therein.

(6) Schmidt, Z. *Angew. Chem.* **1923**, *36*, 511. Wolff, H. *Org. React.* **1946**, *3*, 307.

(7) Beckmann, E. *Chem. Ber.* **1886**, *89*, 988.

(8) For a recent review on the triisopropylsilyl enol ethers, see: Rücker, C. *Chem. Rev.* **1995**, *95*, 1009.

(9) Magnus, P.; Roe, M. B.; Hulme, C. *J. Chem. Soc., Chem. Commun.* **1995**, 263 and pertinent references therein.

(10) Evans, P. A.; Longmire, J. M. *Tetrahedron Lett.* **1994**, *35*, 8345.

(11) Evans, P. A.; Longmire, J. M.; Modi, D. P. *Tetrahedron Lett.* **1995**, *36*, 3985.

(12) Trifluoroacetic acid catalyzed addition of HN_3 to silyl enol ethers has been reported by: Kyba, E. P.; John, A. M. *Tetrahedron Lett.* **1977**, 2737.

(13) Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237. Hassner, A.; Fibiger, R.; Amarasekara, A. S. *J. Org. Chem.* **1988**, *53*, 22 and pertinent references therein.

(14) **General Procedure for the Preparation of α-Azido Triisopropylsilyl Ethers.** The triisopropylsilyl enol ether **1a** (0.127 g, 0.499 mmol) was dissolved in anhydrous dichloromethane (5 mL) and stirred at room temperature under an atmosphere of nitrogen. Trimethylsilyl azide (0.66 mL, 4.99 mmol) was added followed by pyridinium *p*-toluenesulfonate (0.256 g, 1.019 mmol) and the resulting homogeneous mixture stirred at ambient temperature for *ca.* 48 h. The reaction mixture was then poured into saturated Na_2HCO_3 solution (25 mL) and extracted with dichloromethane (3 × 20 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with hexane) furnished the azidohydrin **2a** (0.114 g, 77%) as a colorless oil: IR (neat) 2948, 2892, 2865, 2104 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 1.76–1.66 (2H, m), 1.57–1.26 (8H, m), 1.18–1.04 (21H, m); ^{13}C NMR (62.5 MHz, C_6D_6) δ 91.57 (e), 38.50 (e), 25.16 (e), 23.41 (e), 18.45 (o), 13.56 (o); *m/z* 256 (10), 255 (40), 254 (100), 211 (14), 156 (6); HRMS (EI) calcd for $C_{11}H_{24}N_3OSi$ 254.1689, found 254.1674.

(15) **General Procedure for the Conversion of the α-Azido Triisopropylsilyl Ethers to the Lactams.** The azidohydrin **2a** (0.157 g, 0.528 mmol) was dissolved in cyclohexane (20 mL), transferred to a quartz test tube, and degassed with nitrogen for *ca.* 20 min. The quartz tube was then attached to an ultraviolet lamp and cooled to 0 °C. The reaction was photolysed for *ca.* 1 h (the reaction mixture warms up appreciably during the photolysis) and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with 1:1 ethyl acetate/hexane then 10% methanol in ethyl acetate) furnished the lactam **3a** (0.053 g, 89%) as a white crystalline solid: mp 68–69 °C (lit.[16] mp 68–70 °C); IR ($CHCl_3$) 3420, 3293, 3224, 3019, 2937, 2859, 1660 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 8.33 (1H, bs), 2.74–2.68 (2H, m), 2.25–2.21 (2H, m), 1.33–1.14 (6H, m); *m/z* 113 (54), 85 (25), 84 (33), 56 (37), 55 (68), 43 (9), 42 (36), 41 (32), 39 (13), 30 (100); HRMS (EI) calcd for $C_6H_{11}NO$ 113.08413, found 113.0833.

(16) Marvel, C. S.; Eck, J. C. *Organic Syntheses*; Blatt, A. H., Ed.; John Wiley and Sons: New York, 1943; Collect. Vol. 2, p 371.

(17) The reaction sequence has also been successfully applied to other ring sizes. This information will be reported in a full account of this work.

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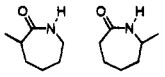
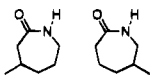
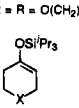
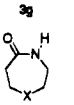
Table 1. Preparation of α-Azido Triisopropylsilyl Ethers 2a–i and Conversion to Azepin-2-ones 3a–i

entry	triisopropylsilyl enol ether[a]	time (days)	α-azido tips ethers[b]	yield (%)[c]	azepin-2-ones[f,g]	yield (%)[c]
1	 1a	2	 2a	77	 3a	89[h]
2	 1b	5	 2b	42[d]	 3b 3b'	75[i]
3	 1c	2	 2c	82[e]	 3c 3c'	87[j]
4	 1d R = Me 1e R = tBu	2 3	 2d 2e	76[e] 74[e]	 3d 3e	89 85
5	 1f R = R = Me 1g R = R = O(CH2)2O	2 3	 2f 2g	70 94	 3f 3g	85 82
6	 1h X = O 1i X = S	4 8	 2h 2i	91 97	 3h 3i	83 64[k]

[a] Azidohydrins were prepared by treating the TIPS enol ether with 10 equiv of $TMSN_3$ and 2 equiv of PPTS in dichloromethane at room temperature on a 0.5 mmol reaction scale. [b] Ratios of inseparable diastereoisomers determined by ^{1}H-NMR integration. [c] Isolated yields. [d] Approximately 1:1 mixture of diastereoisomers. [e] Approximately 2:1 mixture of diastereoisomers. [f] Photolysis with ultraviolet light at 0 °C on a 0.25 mmol reaction scale for *ca.* 1 h. [g] Ratios of inseparable regioisomers determined by ^{1}H-NMR integration. [h] Reaction carried out on a 0.5 mmol reaction scale. [i] 1.6:1 mixture regioisomers. [j] 1:1 mixture of regioisomers. [k] Photolysis for 15 min in order to reduce decomposition.

corresponding azidohydrins **2b** and **2c** as a 1:1 and 2:1 mixture of diastereoisomers, respectively (entries 2 and 3). The 2-methyl silyl enol ether **1b** was particularly sensitive to hydrolysis *via* protodesilylation. Photolysis of α-azido triisopropylsilyl ethers **2b** and **2c** furnished a 1.6:1 and 1:1 mixture of regioisomeric lactams **3b/b'** and **3c/c'**, illustrating the absence of any significant migratory preference in the ring expansion. The 4-methyl (**1d**) and 4-*tert*-butyl (**1e**) derivatives also afforded the azidohydrins **2d** and **2e** as mixtures of diastereoisomers. However, owing to the plane of symmetry in the azidohydrins, photolysis led to the exclusive formation of the lactams **3d** and **3e** (entry 4). Similarly, the 4,4-dimethyl (**2f**) and 4-ethylene ketal (**2g**) derivatives provide the 5,5-disubstituted lactams **3f** and **3g** in excellent yield (entry 5). The reaction was also applied to the heterocyclic derivatives **1h** and **1i** in which the azidohydrins **2h–i** rearrange to afford the oxygen- and sulfur-containing lactams **3h** and **3i** in 83% and 64% yield, respectively (entry 6). The moderate yield of the sulfur-containing lactam **3i** was attributed to decomposition during the photolysis reaction.

In conclusion, we have developed a novel sequence for the conversion of triisopropylsilyl enol ethers, *via* α-azido triisopropylsilyl ethers, to the corresponding caprolactam derivatives. This protocol has two major advantages over current synthetic methodology. The preparation of the α-azido ethers utilizes trimethylsilyl azide, a convenient nonexplosive alternative to hydrazoic acid,[18] and the photolysis provides the lactams directly under essentially neutral reaction conditions, making this methodology particularly attractive for target-directed synthesis. However, owing to the lack of migratory control in the ring expansion, applications will be symmetry driven.[19] We are continuing to explore both the mechanistic and synthetic potential of the novel ring expansion.

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Supporting Information Available: Spectra for compounds **2a–i** and **3a–i** (18 pages).

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(18) Trimethylsilyl azide has been reported to be a nonexplosive alternative to hydrazoic acid: Birkofer, L.; Wegner, P. *Organic Syntheses*; Noland, W. E., Ed.; John Wiley and Sons: New York, 1988; Collect. Vol. 6, p 1030.

(19) For an example of a symmetry-driven synthesis, see: Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009.