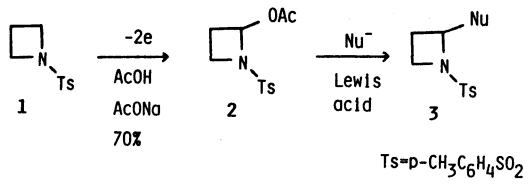
A Facile Syntehsis of 2-Substituted Azetidines[1)]

Tatsuya SHONO,* Yoshihiro MATSUMURA, Kenshi UCHIDA, and Fumihiko NAKATANI
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida Sakyo, Kyoto 606
(Received March 7, 1988)

Synopsis. A new method for the synthesis of 2-substituted azetidines has been exploited. The method consists of (1) anodic acetoxylation of 1-(*p*-tolylsulfonyl)azetidine at the 2-position and (2) subsequent nucleophilic substitution of the acetoxyl group with nucleophiles such as trimethylsilyl cyanide, allyltrimethylsilane, 2-acetoxyfuran, and trimethyl phosphite.

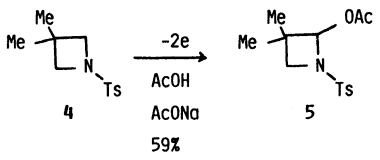
Although formation of 2-carbanions of azetidines followed by introduction of electrophiles to the 2-position has been recently reported,[2)] the opposite methods introducing nucleophiles (Nu^-) to the 2-position of azetidines have been unknown so far. We wish to report a new method for introducing Nu^- to the 2-position of azetidines. Our method consists of (1) anodic acetoxylation of 1-(*p*-tolylsulfonyl)azetidines **1** at the 2-position and (2) subsequent nucleophilic substitution of the acetoxyl group with a variety of Nu^- (Eq. 1).[3)]



(1)

The advantages of this method are (i) the starting compound **1** is easily available, and (ii) a variety of substituents can be introduced to the 2-position of the azetidine skeleton.

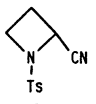
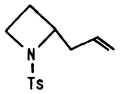
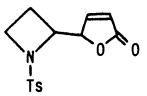
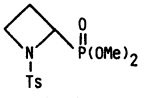
The procedure of anodic oxidation is simple as described in the experimental section. The yield of **2** was 70%. The anodic oxidation of **4** under similar conditions gave **5** in 59% yield (Eq. 2).



(2)

Although anodic oxidation of 1-formylazetidine and 1-(methoxycarbonyl)azetidine under similar conditions also gave the 2-acetoxylated products in 42 and 20% yields, respectively, compound **1** seems to be the most useful intermediate to the preparation of 2-substituted azetidines, since the synthesis of 1-formylazetidine and 1-(methoxycarbonyl)azetidine requires azetidine itself as the precursor, while **1** can easily be prepared from 3-amino-1-propanol.[6)] The anodic oxidation of **1** may proceed with direct electron transfer from **1** to anode, since the oxidation peak of **1**

Table 1. Reaction of **2** with Nucleophiles

Nucleophiles (equiv)		Lewis acid (equiv)		Condition	Product (Yield/%)
Me_3SiCN	(1.2)	$TiCl_4$	(1)	−70 °C, 2 h then r.t., 1 h	 **3a** (68)
	(1.5)	$TiCl_4$	(1)	−70 °C to r.t., 2.5 h	 **3b** (62)
 **6**[a)]	(1.2)	$TiCl_4$	(1)	−70 °C, 5 h	 **3c** (38)
6[a)]	(1.2)	BF_3OEt_2	(1)	−18 °C, 15 min then r.t., 4 h	**3c** (36)
$P(OMe)_3$ **7**	(1.2)	$TiCl_4$	(1)	−70 °C, 2h	 **3d** (34)
7	(1.2)	BF_3OEt_2	(1)	−18 °C, 10 min then r.t., 23 h	**3d** (43)

a) See Ref. 7.

was observed at 2.60 V vs. SCE in acetonitrile.

The reaction of **2** with various Nu^- in the presence of Lewis acid catalysts gave **3a—d** in the yields shown in Table 1. In conclusion, this method provides a new synthetic route to various 2-substituted azetidines.

Experimental

Proton nuclear magnetic resonance spectra were measured on a Varian Associates EM-360 or EM-390 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Hitachi 260-10 spectrometer. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Electrooxidation was carried out using a DC power supply (GD 050-2) of Takasago Seisakusho. Ltd. 1-(*p*-Tolylsulfonyl)azetizine (**1**)[6] and 1-formylazetidine[8] were synthesized according to the reported methods.

1-(Methoxycarbonyl)azetidine was prepared similarly to the synthesis of 1-(ethoxycarbonyl)azetidine[8] (73% yield): bp 80 °C (20 mmHg (1 mmHg≈133.322 Pa), bulb-to-bulb); IR(neat) 2970, 2900, 1715, 1455, 1392, 1200, 1145, 1000, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.16 (quint, 2H, J=7.0 Hz), 3.55 (s, 3H), 3.89 (t, 4H, J=7.0 Hz); MS, m/z 115(M^+), 100, 59, 56, 41(base); Found: C, 52.01; H, 7.93; N, 11.97%. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17%.

1-(*p*-Tolylsulfonyl)-3,3-dimethylazetidine (4) was prepared from 2,2-dimethyl-3-amino-1-propanol similarly according to the synthesis of **1**[6] (77% yield in two steps): mp 60—62 °C; IR(KBr) 2950, 2860, 1595, 1453, 1340, 1232, 1168, 1090, 1060, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.70 (s, 6H), 2.47 (s, 3H), 3.49 (s, 4H), 7.47 (d, 2H, J=9.0 Hz), 7.82 (d, 2H, J=9.0 Hz); Found: C, 60.25; H, 7.07; N, 5.71; S. 13.32%. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40%.

Anodic Oxidation of 1. Into a cell equipped with a carbon rod cathode (8 mmϕ) and a platinum anode (2 cm×2 cm) was placed a solution of **1** (422 mg, 2 mmol) and sodium acetate (1g, 12 mmol) in acetic acid (20 mL). After having been passed 40 F mol^{-1} of electricity at room temperature (current density; 50 mA cm^{-2}, terminal voltage; 40 V), the mixture was poured into water and the organic portion was extracted with CH_2Cl_2. The solvent was removed in vacuo and the residue was subjected to preparative TLC (silica gel, AcOEt : hexane=1 : 2) to yield **2** (376 mg, 1.4 mmol, 70% yield): IR (KBr) 2950 (br), 1745, 1605, 1360, 1240, 1175, 1160, 1115, 1060, 850, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.93—2.67 (m, 2H), 2.10 (s, 3H), 2.48 (s, 3H), 3.22—4.00 (m, 2H), 6.16 (t, 1H, J=6.0 Hz), 7.41 (d, 2H, J=9.0 Hz), 7.86 (d, 2H, J=9.0 Hz); Found: C, 53.55; H, 5.57; N, 4.91; S, 11.87%. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.90%.

Anodic oxidation of 4, 1-formylazetidine, and **1-(methoxycarbonyl)azetidine** in a similar manner to the anodic oxidation of **1** gave the corresponding 2-acetoxylated products.

5: 59% yield at 180 F mol^{-1} of electricity; IR (KBr) 2980, 1750, 1604, 1360, 1228, 1169, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.94 (s, 3H),1.16 (s, 3H), 2.12 (s, 3H), 2.49 (s, 3H), 3.16 (d, 1H, J=7.0 Hz), 3.41 (d, 1H, J=7.0 Hz), 5.75 (s, 1H), 7.45 (d, 2H, J=9.0 Hz), 7.85 (d, 2H, J=9.0 Hz); Found: C, 56.60; H, 6.62; N, 4.71; S, 10.50%. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78%.

2-Acetoxy-1-formylazetidine: 42% yield at 200 F mol^{-1} of electricity; IR (neat) 2980, 2900, 1745, 1675, 1460, 1405, 1228, 1100, 859 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.17 (s, 3H), 2.20—3.00 (m, 2H), 3.80—4.20 (m, 2H), 6.31—6.51 (m, 1H), 8.33—8.56 (br, 1 H); Found: C, 50.71; H, 6.30; N, 9.60%. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79%.

2-Acetoxy-1-(methoxycarbonyl)azetidine; 20% yield at 180 F mol^{-1} of electricity; ^1H NMR ($CDCl_3$) δ=2.00—2.90 (m, 2H), 2.13 (s, 3H), 3.73 (s, 3H), 3.70—4.10 (m, 2H), 6.25—6.43 (m, 1H); Found: C, 48.90; H, 6.31; N, 8.01%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%.

Reaction of 2 with Nucleophiles. A typical procedure is exemplified by the synthesis of 2-cyano-1-(*p*-tolylsulfonyl)-azetidine (**3a**): To a stirred solution of **2** (200 mg, 1.86 mmol) and trimethylsilyl cyanide (222 mg, 2.24 mmol) in CH_2Cl_2 was added dropwise $TiCl_4$ (0.2 mL, 1.86 mmol) at −70 °C under an atmosphere of nitrogen. The mixture was stirred at the temperature for 2 h and warmed to room temperature. Then, the reaction mixture was poured into water, and extracted with CH_2Cl_2. Drying and evaporation of the solvent gave a residue, which was subjected to a silica-gel chromatography (AcOEt : hexane=1 : 5) to yield **3a** (299 mg, 1.265 mmol, 68% yield): mp 106—108 °C; IR (neat) 2250, 1600, 1350, 1165, 1100, 820, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.87—2.97 (m, 2H), 2.50 (s, 3H), 3.64—4.15 (m, 2H), 4.69 (t, 1H, J=9.5 Hz), 7.43 (d, 2H, J=8.3 Hz), 7.86 (d, 2H, J=8.3 Hz); MS, m/z 236 (M^+), 155, 91 (base), 81; Found: C, 55.75; H, 5.14; N, 11.54; S, 13.33%. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.92; H, 5.13; N, 11.86; S, 13.57%.

Data for new compounds **3b—d** are shown below.

3b: IR (neat) 3080, 2985, 1645, 1600, 1500, 1455 (br), 1345, 1305, 1295, 1240, 1163, 1100, 1000, 925, 820, 780, 735, 715, 670 cm^{-1}; ^1H NMR ($CDCl_3$); δ=1.59—2.12 (m, 2H), 2.28—2.60 (m, 2H), 2.41 (s, 3H), 3.18—4.13 (m, 3H), 4.72—5.15 (m, 2H), 5.37—6.06 (m, 1H), 7.23 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz); MS, m/z 251 (M^+), 210 (base), 155, 91; Found: C, 62.24; H, 6.89; N, 5.65; S, 12.51%. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; S, 12.76%.

3c: Mp 130—133 °C; IR (KBr) 1795, 1760, 1610, 1600, 1343, 1315, 1252, 1168, 1101, 1028, 900, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.90—2.41 (m, 2H), 2.51 (s, 3H), 3.67 (t, 2H, J=8.0 Hz), 4.48—4.73 (m, 1H), 5.29—5.44 (m, 1H), 6.29—6.43 (m, 1H), 7.57 (d, 2H, J=9.0 Hz), 7.81—7.96 (m, 1H), 7.92 (d, 2H, J=9.0 Hz); Found: C, 57.49; H, 5.33; N, 4.77; S, 10.70%. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.78; S, 10.93%.

3d: Isolated by alumina chromatography; mp 86—87 °C; IR (KBr) 2960 (br), 1600, 1460 (br), 1355, 1250, 1170, 1100, 1075, 1030, 850, 825, 775, 720, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.86—2.97 (m, 2H), 2.48 (s, 3H), 3.70 and 3.76 (2s, 3H), 3.89 and 3.94 (2s, 3H), 3.57—4.53 (m, 3H), 7.44 (d, 2H, J=9.0 Hz), 7.85 (d, 2H, J=9.0 Hz); Found: C, 45.20; H, 5.67; N, 4.28; P, 9.41%. Calcd for $C_{12}H_{18}NO_5SP$: C, 45.14; H, 5.86; N, 4.39; P, 9.70%.

Oxidation Potentials. Oxidation peak potential of **1** was measured at room temperature by using an H-type cell, a potentiostat HA-104 and function generator HB-107A (Hokuto Denko Ltd.) under the following conditions; scan rate: 100 mV s^{-1}; electrordes: platinum anode and cathode; E_p, 2.60 V vs. SCE (4.74×10^{-3} M (1M=1 mol dm^{-3})), 2.70 V vs. SCE (9.50×10^{-3} M) in CH_3CN-0.1 M $LiClO_4$.

References

1) Electroorganic Chemistry 97.

2) W. Wykypiel, J. J. Lohmann, and D. Seebach, *Helv. Chim. Acta*, **64**, 1337 (1981).

3) Anodic α-methoxylation of *N*-protected amines and a variety of reactions of the α-methoxylated products with nucleophiles have already been reported by us.[4] However, anodic methoxylation of **1**, 1-formylazetidine, and 1-(methoxycarbonyl)azetidine under conditions of the α-methoxylation did not always give satisfactory results, though the anodic 2-methoxylation of 1-formyl-2,2-dimethylazetidine has been reported as the only example.[5]

4) T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1172 (1981); T. Shono, Y. Matsumura, K.

Tsubata, K. Uchida, T. Kanazawa, and K. Tsuda, *J. Org. Chem.*, **49**, 3711 (1984); T. Shono, Y. Matsumura, and K. Tsubata, *Tetrahedron Lett.*, **22**, 2411 (1981); T. Shono, Y. Matsumura, and K. Tsubata, *ibid.*, **22**, 3249, (1981); T. Shono, Y. Matsumura, K. Tsubata, and J. Takata, *Chem. Lett.*, **1981**, 1121; T. Shono, Y. Matsumura, K. Uchida, and H. Kobayashi, *J. Org. Chem.*, **50**, 3243, (1985).

5) K. Warning, M. Mitzlaff, and H. Jensen, *Liebigs Ann. Chem.*, **1978**, 1713.

6) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

7) The preparation of 2-acetoxyfuran: T. Shono, Y. Matsumura, and S. Yamane, *Tetrahedron Lett.*, **22**, 3269 (1981).

8) J. C. Sheehan, and R. W. Tulis, *J. Org. Chem.*, **39**, 2264 (1974).