

An Efficient and Regioselective Preparation of 4-Oxyazetid-2-ones from 4-Trimethylsilylazetid-2-ones by Use of Anodic Oxidation

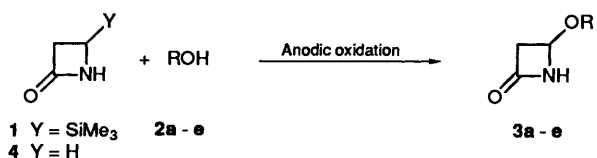
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Anodic oxidations of 4-trimethylsilylazetid-2-one and 1-benzyl-4-trimethylsilylazetid-2-one in the presence of alcohols or acetic acid regioselectively provide the corresponding 4-oxyazetid-2-ones in good yields.

Azetidin-2-ones possessing a 4-substituent replaceable with a variety of nucleophiles are recognized as synthetically useful in β -lactam chemistry.¹ Electrochemical oxidation is an attractive means of inducing nucleophilic attack at the carbon (*i.e.* α -carbon) adjacent to the nitrogen of amides,² and was recently used to convert azetid-2-ones³ and 4-carboxyazetid-2-ones⁴ into 4-oxyazetid-2-ones. Although valuable, these methods still have limitations:^{3,4} (1) the oxidation potential of β -lactams is usually high; (2) the yields are greatly dependent on the structure of the substrates; (3) the oxidation lacks regioselectivity in the case of *N*-substituted lactams, nucleophiles being introduced into both carbons α to the nitrogen. We, therefore, expected that 4-silylation of azetid-2-ones would lower the oxidation potential, thus enhancing the reactivity and regioselectivity of nucleophiles in the electrochemical process.† Here we report preliminary results for an efficient electrochemical preparation of 4-oxyazetid-2-ones **3** from 4-trimethylsilylazetid-2-one **1** ‡ (Scheme 1).



Scheme 1 a, R = Me; b, R = CH₂CHMe₂; c, R = (CH₂)₂CH=CH₂; d, R = CH₂Ph; e, R = CH₂CH=CH₂

We first compared the oxidation potentials of azetid-2-one **4** and **1**, using cyclic voltammetry. As expected, the oxidation of **1** took place at a low potential and the first oxidation wave appeared at a peak potential of 1.75 V *vs.* Ag/AgCl in acetonitrile, whereas the peak potential of **4** was 2.38 V. This large decrease in the oxidation potential, caused by the silylation, suggests that there is in the rigid β -lactam ring of **1** effective overlap between the lone pair of the nitrogen atom and the neighbouring carbon-silicon σ bond. †

Constant current electrolysis (15 mA cm⁻²) of **1** (1 mmol) was carried out in methanol (10 cm³) containing Et₄NOTs (0.2 mol dm⁻³) as a supporting electrolyte with a graphite plate anode-graphite plate cathode in an undivided cell. After passage of 2.5 F mol⁻¹ of electricity **1** had completely been consumed and 4-methoxyazetid-2-one **3a** was obtained (60%); in contrast, almost all of **4** was recovered even after passage of 10 F mol⁻¹ of electricity. Extension of the anodic oxidation to the synthesis of

† Studies on electrochemical oxidation of organosilicon compounds bearing a silicon and hetero atoms on the same carbon have extensively expanded (see ref. 5).

‡ Several synthetic methods for 4-trimethylsilylazetid-2-one **1** have been reported (see ref. 6).

Table 1 Electrochemical transformation of **1** to **3**

Alcohols 2	Products 3	Electricity (F mol ⁻¹ of 1)	Yields ^a (%)
2a	3a	2.5	78
2b	3b	2.2	74
2c	3c	2.4	72
2d	3d	3.0	78
2e	3e	2.5	51 ^b

^a Isolated yields based on **1** used. ^b The recovery of **1** was 28%.

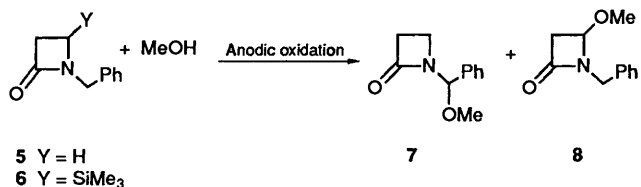
Table 2 Electrochemical methoxylation of **5** and **6**

Run	Substrate	Solvent	Electricity (F mol ⁻¹)	Yield of 7 (%)	Yield of 8 (%)
1	5	MeOH	10.0	45	8
2	5	MeCN ^a	15.0	43	22
3	6	MeOH	2.5	~0	75
4	6	MeCN ^a	2.2	~0	80

^a MeOH (10 mmol) was added as a nucleophile.

other 4-alkoxyazetid-2-ones necessitated a change of solvent. Acetonitrile was found to be an efficient solvent and in it, with an excess of the appropriate alcohol (5–10 equiv. mol⁻¹ of **1**), the trimethylsilyl group of **1** underwent smooth displacement by various alkoxy groups under electrolysis conditions similar to those described above (Table 1).§ The yield of **3a** in acetonitrile was much better than that in methanol. The method described can also be applied to alcohols such as benzyl and allyl alcohols the oxidation potentials of which are lower than that of **4**.

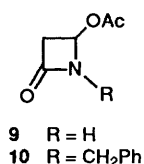
As a model approach for the regioselective alkoxylation of *N*-substituted lactams we investigated the anodic oxidations of 1-benzyl-**5** and 1-benzyl-4-trimethylsilyl-azetid-2-one **6** in methanol and in acetonitrile. Although, **5** gave a mixture of 1-(α -methoxybenzyl)-**7** and 1-benzyl-4-methoxy-azetid-2-one **8** in both the solvents, **6** exclusively gave **8** (80%) (Scheme 2 and Table 2).



Scheme 2

§ Replacements of trimethylsilyl group of **1** were attempted by several groups but have failed (see ref. 6b).

4-Acetoxyazetid-2-one **9** is known as a versatile intermediate for the synthesis of bicyclic β -lactams because the acetoxy group is readily displaced by various nucleophiles.^{1a,e} The anodic oxidation of **1** in acetonitrile containing acetic acid (10 equiv. mol⁻¹ of **1**) and Et₄NOTs (0.2 mol dm⁻³) gave **9** (89% isolated yield) after passage of 4 F mol⁻¹ of electricity. A similar acetoxylation of **6** is completely regioselective, and gave 1-benzyl-4-acetoxyazetid-2-one **10** (84%). Since 4-trimethylsilylazetid-2-ones can be prepared by the reaction of 4-acetoxy-



azetid-2-ones with a silyl cuprate [(Me₃Si)₂CuLi],^{6b} the two functional groups, 4-acetoxy and 4-trimethylsilyl in β -lactams, are now ones convertible each to the other, if necessary. We are extending the anodic oxidation of 4-silylazetid-2-ones to reactions with other nucleophiles.

Experimental

General Procedure.—A mixture of **1** (1 mmol) and an alcohol or AcOH (5–10 mmol) in acetonitrile (10 cm³) containing Et₄NOTs (0.2 mol dm⁻³) in an undivided electrolysis cell equipped with a graphite anode and a graphite cathode was subjected to constant current electrolysis (50 mA; current density, 15 mA cm⁻²) at ambient temperature. After passage of 2–4 F mol⁻¹ **1** had been consumed and the electrolysed solution was poured into water (20 cm³) and extracted with CH₂Cl₂ (10 cm³ × 3). The organic layer was dried (MgSO₄) and concentrated under a reduced pressure and the residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) as an eluent to give the product **3** or **9**. The same procedure was essentially applied to the electrochemical acetoxylation and methoxylation of **6**. All the products have been characterized on the basis of IR, NMR and high resolution mass spectrometries; δ_{H} (270 MHz, CDCl₃) data of **7**, **8** and **10** are as follows: **7** δ 2.88–3.04 (m, 3 H), 3.23–3.28 (m, 1 H), 3.49 (s, 3 H, OCH₃), 5.86

(s, 1 H, CHPh) and 7.26–7.40 (m, 5 H); **8** δ 2.84–2.99 (m, 2 H), 3.25 (s, 3 H, OCH₃), 4.60 and 4.19 (each d, *J* 15.2, each 1 H, CH₂Ph), 4.83 (dd, *J* 3.6 and 1.7, 1 H, CHOMe) and 7.26–7.39 (m, 5 H). **10** δ 1.93 (s, 3 H, OCOCH₃), 2.94–3.28 (m, 2 H), 4.45 and 4.31 (each d, *J* 15.2, each 1 H, CH₂Ph), 5.95 (dd, *J* 4.0 and 1.3, 1 H, CHOAc) and 7.01–7.38 (m, 5 H).

References

- (a) S. Mickel, *Aldrichimica Acta*, 1985, **18**, 95; (b) T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura and T. Miyadera, *Tetrahedron Lett.*, 1982, **23**, 1075; (c) T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura and T. Miyadera, *J. Chem. Soc., Chem. Commun.*, 1982, 713; (d) N. Daniels, G. Johnson and B. C. Ross, *J. Chem. Soc., Chem. Commun.*, 1983, 1006; (e) A. Sheppard and M. J. Miller, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2519; (f) Y. Kita, N. Shibata, N. Yoshida and T. Tohjo, *Tetrahedron Lett.*, 1991, **32**, 2375; and references cited therein.
- (a) T. Shono, *Electroorganic Synthesis*, Academic Press, London, 1991, p. 67; (b) M. Okita, T. Wakamatsu and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 1979, 749; and references cited therein.
- (a) M. Mori, *Recent Advances in Electroorganic Synthesis*, ed. S. Torii, Elsevier, Amsterdam, Kodansha, Tokyo, 1987, p. 89; (b) M. Mori, Y. Higuchi, K. Kagechika and M. Shibasaki, *Heterocycles*, 1989, **29**, 853; (c) M. Okita, M. Mori, T. Wakamatsu and Y. Ban, *Heterocycles*, 1985, **23**, 247; (d) M. Mori and Y. Ban, *Heterocycles*, 1985, **23**, 317.
- (a) M. Mori, K. Kagechika, H. Sasai and M. Shibasaki, *Tetrahedron*, 1991, **47**, 531; (b) M. Mori, K. Kagechika, K. Tohjima and M. Shibasaki, *Tetrahedron Lett.*, 1988, **29**, 1409; (c) M. Mori, *Yakugaku Zasshi*, 1990, **110**, 463 (*Chem. Abstr.*, 1990, **113**, 140666y).
- (a) J. Yoshida and S. Isoe, *Tetrahedron Lett.*, 1987, **28**, 6621; (b) J. Yoshida, T. Maekawa, T. Murata, S. Matsunaga and S. Isoe, *J. Am. Chem. Soc.*, 1990, **112**, 1962; (c) T. Koizumi, T. Fuchigami and T. Nonaka, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 219; and references cited therein.
- (a) G. S. Zaitseva, G. S. Krylova, O. P. Perelygina, Y. I. Baukov and I. F. Lutsenko, *Zh. Obshch. Khim.*, 1981, **51**, 2252 (*Chem. Abstr.*, 1982, **96**, 35384n); (b) C. Nativi, A. Ricci and M. Taddei, *Tetrahedron Lett.*, 1990, **31**, 2637; (c) D. MacLeod, P. Quayle and G. M. Davies, *Tetrahedron Lett.*, 1990, **31**, 4927.

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