Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3133–3136

TETRAHEDRON LETTERS

Anodic methoxylation and acetoxylation of imines and imidates

Daisuke Baba and Toshio Fuchigami*

Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8502, Japan

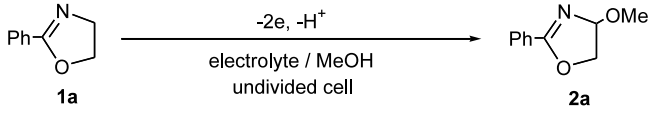
Received 4 December 2002; revised 21 February 2003; accepted 21 February 2003

Abstract—Anodic oxidation of cyclic imidates, 2-aryl-2-oxazolines, in methanol provided the corresponding 4-methoxylated products. Anodic α-methoxylation and α-acetoxylation of open-chain imines derived from glycine esters and benzophenone were also achieved using a bromide ion mediator. On the other hand, anodic α-acetoxylation of CF_3-containing imine and imidate was successful without use of the bromine mediator. This is the first example of successful anodic α-substitution of imines and imidates.

Although anodic α-substitution reactions of amines and carbamates are well established,[1] there has been no report on anodic substitutions at the α-position of the nitrogen atom of imines. Anodic oxidation of imines, such as *N*-benzylidene-*p*-anisidines, has been studied in detail:[2] nucleophiles such as water in a solvent reacted with the radical cation generated from the imine double bond to cause cleavage of the C–N bond. It is known that imines, derived from benzophenone and glycine esters, reacted with *N*-bromosuccinimide in NaOAc–DMF solution to give the corresponding α-acetoxy derivatives.[3] In this paper we wish to report the first example of successful anodic α-methoxylation and α-acetoxylation of imines and imidates.

A 2-oxazoline ring system has vast synthetic potential.[4] Firstly, anodic methoxylation of a cyclic imidate like 2-phenyl-2-oxazoline was carried out under various conditions for the optimization of the conditions (Table 1). Electrolysis was performed at a constant current using an undivided cell. As shown in Table 1, anodic methoxylation proceeded and a methoxy group was introduced to the position α to the nitrogen atom predominantly. When the anodic methoxylation was carried out using a neutral supporting electrolyte such as Et_4NBF_4, the yield was low and a large excess amount of electricity was required until the reaction was completed (runs 1–3). On the other hand, the use of an acidic electrolyte such as $Et_4NF{\cdot}4HF$ increased both the yield and current efficiency (run 4). The best result was obtained by the use of both Et_4NBF_4 and $(NH_4)_2SO_4$ (run 5).[5] The detailed role of $(NH_4)_2SO_4$ is not clear: however, the presence of $(NH_4)_2SO_4$ seems to keep the electrolytic solution almost neutral, which

Table 1. Anodic methoxylation of 2-phenyl-2-oxazoline (**1a**)



1a **2a**

Run	Temp.	Anode	Electrolyte	Electricity (F/mol)	Yield (%)[a]
1	rt	Pt	Et_4NBF_4	12	40
2	0°C	Pt	Et_4NBF_4	15	41
3	rt	Graphite	Et_4NBF_4	15	41
4	rt	Pt	$Et_4NF{\cdot}4HF$	5	69
5	rt	Pt	$Et_4NBF_4+(NH_4)_2SO_4$[b]	5	80

[a] Isolated yields.
[b] 3 equiv. of $(NH_4)_2SO_4$ (suspension).

* Corresponding author. Tel./fax: +81 45 924 5406; e-mail: fuchi@echem.titech.ac.jp

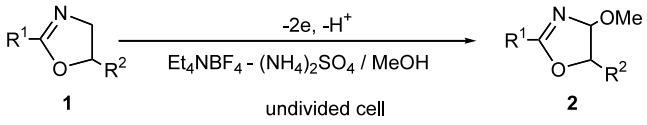
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00548-3

suppresses simultaneous oxidation of cathodically generated methoxide ions during the electrolysis.

Anodic methoxylation of various 2-substituted-2-oxazolines was carried out under the optimized conditions as shown in Table 2. Methoxylation reaction proceeded smoothly to provide the corresponding α-methoylated products in good yields, except for 2-(*p*-methoxyphenyl)-2-oxazoline (**1c**) and 2-nonyl-2-oxazoline (**1g**). Since the *p*-methoxyphenyl moiety of **1c** is more easily oxidized than the imine moiety,[6] the desired reaction did not proceed. In the anodic methoxylation of **1b**, a stereoisomeric mixture was obtained with moderate stereoselectivity (*trans*/*cis* = 4.8). In the case of 2-(*p*-nitrophenyl)-2-oxazoline (**1f**), polymerized products were formed mainly under the same conditions as above. The nitro group of **1f** possesses a more positive reduction potential than methanol, and **1f** was reduced at the cathode to give polymeric products. On the other hand, anodic methoxylation of **1f** was successfully carried out in a divided cell. In this case, 10 equiv. of pyridine as the acid scavenger was added to the anolyte. In the case of 2-nonyl-2-oxazoline (**1g**), the methoxylated product was not obtained at all, but a considerable amount of decanoic acid was formed. In this case, methanol was predominantly oxidized at the anode due to the much higher oxidation potential of **1g** (2.8 V versus SCE) compared with methanol, therefore, acids generated anodically from methanol (EGA) seem to cause decomposition of **1g**.

1,3-Oxazole derivatives are found in a variety of natural products.[7] The methoxylated products **2** thus obtained were found to be readily converted to the corresponding 1,3-oxazole derivatives **3** in good yields by the treatment of **2** with acid catalysts (Table 3). Among the acid catalysts used, $BF_3{\cdot}OEt_2$ gave the best result under reflux in toluene for 1 h. On the other hand, other weaker acids such as *p*-toluenesulfonic acid and camphorsulfonic acid gave poor yield.[8] Several methods have been reported for the synthesis of 1,3-oxazoles by the dehydrogenation of 2-oxazolines using a nickel peroxide,[9] DDQ,[10] NBS,[11] $CuBr_2$–HMPA–DBU,[12] and selenium-mediated olefination.[7] However, these chemical oxidation processes incur waste problems after use.

Table 2. Anodic methoxylation of **1**

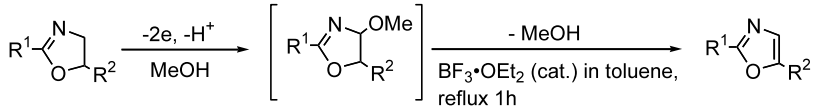


1 **2**

2-Oxazoline			E_p^{ox} (V versus SCE)[a]	Electricity (F/mol)	Yield (%)[b]
No.	R^1	R^2			
1a	Ph	H	2.3	5	**2a** 80
1b	Ph	Me	2.3	6	**2b** 80 (*trans*/*cis*) = 4.8[c]
1c	4-$MeOC_6H_4$	H	1.9	5	
1d	4-ClC_6H_4	H	2.3	7	**2d** 65
1e	4-MeC_6H_4	H	2.1	6	**2e** 42
1f[d]	4-$NO_2C_6H_4$	H	2.4	7	**2f** 65
1g	$^nC_9H_{19}$	H	2.8	10	[e]

[a] Oxidation peak potentials measured by CV using Pt electrode in 0.1 M Et_4NBF_4–MeCN (sweep rate 0.1 V/s).
[b] Isolated yields.
[c] Complex mixture.
[d] A divided cell was used.
[e] $^nC_9H_{19}COOH$ was obtained in 24% yield.

Table 3. Synthesis of 1,3-oxazoles **3** from 2-oxazolines **1**

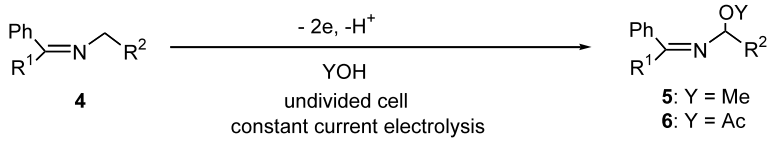


1 **2** **3**

Run	R^1	R^2	Yield (%)[a]
1	Ph	H	61
2	Ph	Me	42
3	4-ClC_6H_4	H	55
4	4-$NO_2C_6H_4$	H	53

[a] Isolated yields from 2-oxazoline **1**.

Table 4. Anodic methoxylation and acetoxylation of imines and imidate



4

5: Y = Me
6: Y = Ac

4			Electrolyte	Solvent	Electricity (F/mol)	Yield (%)
No.	R^1	R^2				
4a	Ph	CO_2Me	Et_4NBr	MeOH	2.5	**5a** 84
4a	Ph	CO_2Me	Et_4NBF_4	MeOH	10	**5a** trace
4a	Ph	CO_2Me	Et_4NBr	MeCN/AcOH (100/1)	5	**6a** 60
4b	Ph	CO_2Et	Et_4NBr	MeCN/AcOH (9/1)	7	**6b** 66
4b	Ph	CO_2Et	Et_4NBF_4	MeCN/AcOH (9/1)	7	**6b** 0
4c	Ph	CF_3	Et_4NBr	MeCN/AcOH (9/1)	7	**6c** 0
4c	Ph	CF_3	Et_4NBF_4	MeCN/AcOH (9/1)	7	**6c** 40
4d	OMe	CF_3	Et_4NBF_4	MeCN/AcOH (9/1)	4	**6d** 55

Furthermore, we attempted anodic methoxylation and acetoxylation of open-chain imines **4a** and **4b** which are readily prepared from glycine esters and benzophenone (Table 4).[13] Anodic oxidation using Et_4NBF_4 as supporting salt did not give any α-methoxylated or α-acetoxylated product. It was found that the use of Et_4NBr as the supporting electrolyte was effective to provide α-methoxylated and α-acetoxylated products, **5a**, **6a** and **6b**. Since bromide ions are much more easily oxidized than **4a** and **4b** ($E_p^{ox} = 2.0$ V versus SCE), they seem to act as the mediator.[3] In sharp contrast, anodic acetoxylation of trifluoromethyl derivatives **4c** using a bromide supporting salt failed. However, direct anodic oxidation using Et_4NBF_4 as the supporting electrolyte provided the desired α-acetoxylated product **6c**[14] in moderate yield. Anodic α-acetoylation of CF_3-containing imidate **4d** was similarly achieved. It is well known that a trifluoromethyl group is very strongly electron-withdrawing: therefore, the generation of carbocations α to the CF_3 group is generally difficult. However, notably, trifluoromethylated imine derivatives **4c** and **4d** provided the desired α-acetoxylated products **6c** and **6d**.

In conclusion, we have successfully carried out for the first time anodic α-substitution reactions of imines and imidates.

Acknowledgements

This work is supported by a Grant-in Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecule' from the Ministry of Education, Science, Sports, Culture and Technology of Japan.

References

1. (a) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1984**, *63*, 206; (b) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, *59*, 607; (c) Yoshida, J.; Suga, S.; Suzuki, S.; Yamamoto, A.; Fujisawa, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546; (d) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527; (e) Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735.
2. Masui, M.; Ohmori, H. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1882.
3. O'Donnell, M. J.; Bennett, W. D.; Polt, R. B. *Tetrahedron Lett.* **1985**, *26*, 695.
4. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
5. Electrolysis was carried out at a platinum anode and cathode (2×2 cm^2, each) in MeOH (10 mL) containing 0.3 mmol of Et_4NBF_4, 3 mmol of $(NH_4)_2SO_4$ and 1 mmol of **1** using an undivided glass cell. Constant current (50 mA) was passed until the starting material was consumed. After the electrolysis, the resulting electrolytic solution was mixed with water. The resulting solution was extracted with ethyl acetate and the extracts were washed with brine, and then were dried over $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel using a mixture of appropriate ratio of hexane/ethyl acetate as an eluent to give **2**. **2a**: ^{1}H NMR δ 3.54 (3H, s), 4.25 (1H, dd, $J = 10$ Hz, 4.6 Hz), 4.41 (1H, dd, $J = 10$ Hz, 7.8 Hz), 5.55 (1H, dd, $J = 7.8$ Hz, 4.6 Hz), 7.39–7.51 (3H, m), 7.99–8.02 (2H, m); ^{13}C NMR δ 55.36, 72.39, 97.79, 127.19, 128.20, 128.57, 131.79, 166.86; HRMS *m*/*z*: calcd for $C_{10}H_{11}NO_2$: 177.0790, found: 177.0763; **2b**: ^{1}H NMR δ 1.40 (3H, d, $J = 6.5$ Hz, *trans*), 1.43 (3H, d, $J = 6.8$ Hz, *cis*), 3.52 (3H, s, *trans*), 3.55 (3H, s, *cis*), 4.49–4.58 (1H, dq, $J = 6.5$ Hz, 4.6 Hz, *trans*), 4.67–4.73 (1H, dq, $J = 7.0$ Hz, 6.8 Hz, *cis*), 5.03 (1H, d, $J = 4.6$ Hz, *trans*), 5.27 (1H, d, $J = 7.0$ Hz, *cis*), 7.37–7.51 (3H, m), 7.96–8.00 (2H, m); HRMS *m*/*z*: calcd for $C_{11}H_{13}NO_2$: 191.0946, found 191.1946; **2d**: ^{1}H NMR δ 3.54 (3H, s), 4.26 (1H, dd, $J = 10.2$ Hz, 4.6 Hz), 4.41 (1H, dd, $J = 10.2$ Hz, 6.8 Hz), 5.52 (1H, dd, 6.8 Hz, 4.6 Hz), 7.40 (2H, d, $J = 8.4$ Hz), 7.94 (2H, d, $J = 8.4$ Hz); ^{13}C NMR δ 55.54, 72.59, 97.90, 125.74, 128.57, 129.93, 138.07, 165.92. Anal. calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.55; H, 4.69; N, 6.39; **2e**: ^{1}H NMR δ 2.37 (3H, s), 3.51 (3H, s), 4.23 (1H, dd, $J = 10.3$ Hz, 4.2 Hz), 4.36 (1H, dd,

$J=10.3$ Hz, 7.3 Hz), 5.49 (1H, dd, $J=7.3$ Hz, 4.2 Hz), 7.19 (2H, d, $J=8.3$ Hz), 7.86 (2H, d, $J=8.3$ Hz); ^{13}C NMR δ 21.65, 55.30, 72.29, 97.82, 124.39, 128.55, 128.93, 142.26, 166.98; HRMS m/z: calcd for $C_{11}H_{13}NO_2$: 191.0946, found 191.0959; **2f**: ^{1}H NMR δ 3.54 (3H, s), 4.29 (1H, dd, $J=10.0$ Hz, 4.3 Hz), 4.46 (1H, dd, 10.0 Hz, 7.3 Hz), 5.54 (1H, dd, 7.3 Hz, 4.3 Hz), 8.15 (2H, d, 8.9 Hz), 8.25 (2H, d, 8.9 Hz); ^{13}C NMR δ 55.86, 72.96, 97.97, 123.44, 129.65, 133.06, 149.73, 164.81. HRMS m/z: calcd for $C_{10}H_{10}N_2O_4$: 222.0641, found 222.0649.

6. Corley, E. G.; Karady, S.; Abramson, N. L.; Ellison, D.; Weinstock, L. M. *Tetrahedron Lett*. **1988**, *29*, 1497.
7. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc*. **1992**, *114*, 9434.
8. Cardwell, K. S.; Hermitage, S. A.; Sjolin, S. *Tetrahedron Lett*. **2000**, *41*, 4239.
9. Evans, D. L.; Minster, D. K.; Jordis, S. M.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem*. **1979**, *44*, 497.
10. McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett*. **1992**, *33*, 2641.
11. Mayer, A. I.; Tavares, F. X. *J. Org. Chem*. **1996**, *61*, 8207.
12. Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem*. **1998**, *63*, 92.
13. **5a**: ^{1}H NMR δ 3.36 (3H, s), 3.76 (3H, s), 5.02 (1H, s), 7.25–7.73 (10H, m); ^{13}C NMR δ 52.48, 55.07, 90.05, 127.75, 127.95, 128.33, 128.95, 129.01, 130.97, 135.43, 138.45, 168.72, 172.99. HRMS m/z: calcd for $C_{17}H_{17}NO_3$ 283.1208, found 283.1198.
14. **6c**: ^{1}H NMR δ 2.01 (3H, s), 6.20 (1H, q, $J=4.3$ Hz), 7.37–7.48 (10H, m); ^{13}C NMR δ 20.73, 81.60 (q, $J=35$ Hz), 122.07 (q, $J=280$ Hz), 127.52, 128.09, 128.38, 129.22, 129.43, 131.71, 135.05, 138.11, 168.63, 176.92; ^{19}F NMR δ −1.77 (d, $J=4.3$ Hz); HRMS m/z: calcd for $C_{17}H_{14}F_3NO_2$ 321.0977, found 321.0977. **6d**: ^{1}H NMR δ 2.07 (3H, s), 3.90 (3H, s), 6.11 (1H, q, 4.3 Hz), 7.37–7.48 (5H, m); ^{13}C NMR δ 20.83, 54.63, 80.38 (q, $J=35$ Hz), 122.26 (q, $J=279$ Hz), 127.44, 128.46, 130.36, 131.09, 168.85, 169.79; ^{19}F NMR δ −3.10 (d, $J=4.3$ Hz). HRMS m/z: calcd for M^+–OAc 216.0637, found 216.0636.