Pergamon

Tetrahedron Letters 39 (1998) 6199-6202

TETRAHEDRON LETTERS

Electroreductive Coupling of Aliphatic Amides. A Useful Method for the Synthesis of α-Amino Ketones[1]

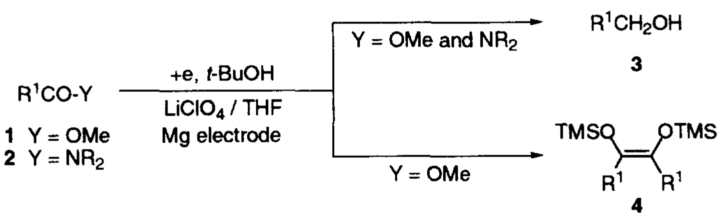
Shigenori Kashimura,[2]* Manabu Ishifune,[2] Yoshihiro Murai,[2] Hiroaki Murase,[3] Masatoshi Shimomura,[4] and Tatsuya Shono[5]*

Kin-Ki University, 3-4-1 Kowakae, Higashi-Osaka, 577-8502, JAPAN

Received 13 May 1998; revised 15 June 1998; accepted 19 June 1998

Abstract: Electroreduction of aliphatic amides ($RCONMe_2$) with Mg electrode in the presence of chlorotrimethylsilane (TMSCl) has been found to give the coupling products [R(TMSO)C=C(NMe_2)R] and hydrolysis of the products affords the corresponding α-amino ketones [RCOCH(NMe_2)R] in excellent yields.

It has been shown in our previous study that the electroreduction of aliphatic ester (**1**) and aliphatic amide (**2**) with Mg electrode gives primary alcohol (**3**) when the reaction is carried out in the presence of a proton donor like *t*-BuOH.[6] Recently we have also found that the electroreduction of **1** with Mg electrode in the presence of chlorotrimethylsilane (TMSCl) gives the corresponding bis(trimethylsiloxy)alkene (**4**) through electrochemical acyloin condensation of **1** (Scheme 1).[7,8] Although the acyloin condensation of **1** to form **4** has been well established by using alkali metal as the reducing agent so far the similar type condensation of aliphatic amide **2** has never been reported.[9]

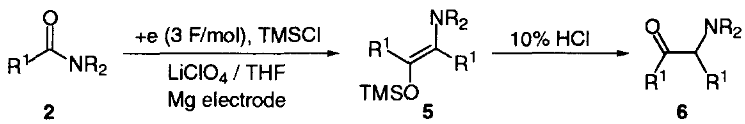


Scheme 1

It has been found in the present study that the electroreduction of aliphatic amide (**2**) with Mg electrode leads to the reductive coupling of **2** to form **5** (Scheme 2). This reaction is not only the first finding of the reductive coupling of aliphatic amides **2** but also useful for the selective synthesis of the enol ethers **5**, which

PII: S0040-4039(98)01274-X

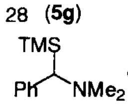
are the versatile intermediates for the organic synthesis. The hydrolysis of **5** with 10 % aqueous solution of HCl, for example, gave α-aminoketones **6** in excellent yield.



Scheme 2

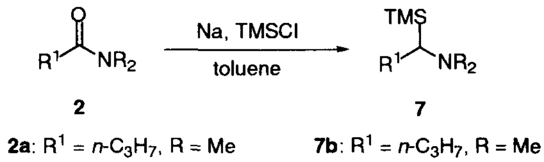
The electroreduction of **2** was carried out as follows: Into an undivided electrolysis cell equipped with Mg (99.9% purity, Rare Metallic Co., LTD) cathode and anode (rod, diameter =1 cm; length =4 cm) were put anhydrous $LiClO_4$ (1.06 g, 10 mmol), molecular sieve 5A (1.5 g), and anhydrous THF (20 mL, dried over Na-ketyl). After the mixture was stirred overnight under a N_2 atmosphere in order to remove the residual water, an aliphatic amide (**2**) (5 mmol) and TMSCl (1.63 g, 15 mmol) were added to the mixture. The constant current (0.05 A) electrolysis was performed at a cathode potential of ca. -2.7 V *vs*. SCE. The cathode and anode were alternated at the interval of 15 sec. during the reaction. After 3 F/mol of electricity (based on **2**) was passed through the cell, product **5** was isolated by alumina column (ICN, Act. I, pentane). The hydrolysis of **5** with 10 % HCl (50 mL) at room temperature gave **6** in a quantitative yield. As some typical results are shown in Table 1, the electroreduction of *N,N*-dimetylamides (**2a**-**2d**) (runs 1-4) gave the coupling products (**5a**-**5d**) in good yields but that of primary amide **2e** and secondary amide **2f** (runs 5 and 6) did not give the coupling products but the starting materials were recovered unchanged.[12] The TMS-protected secondary amide **2g** afforded the desired product **5g** in 28% yield (run 7). The aromatic amide **2f** showed different reactivity, that is, the coupling reaction did not proceed but the trimethylsilylated product **7a** was obtained (run 8). The products (**5a**-**5d** and **6a**-**6d**) gave satisfactory spectroscopic values for the assigned structures.[13]

Table 1. Electroreductive Coupling of Aliphatic Amides

entry	Aliphatic Amides 2		Product Yield (%)[a, b, c] 5	6
1	n-$C_3H_7CONMe_2$	(**2a**)	70 (**5a**)	98 (**6a**)
2	n-$C_4H_9CONMe_2$	(**2b**)	67 (**5b**)	100 (**6b**)
3	CH_2=$CH(CH_2)_3CONMe_2$	(**2c**)	65 (**5c**)	100 (**6c**)
4	MeCH=$CH(CH_2)_3CONMe_2$	(**2d**)	63 (**5d**)	100 (**6d**)
5	n-$C_3H_7CONH_2$	(**2e**)	0[d]	
6	n-$C_3H_7CONHMe$	(**2f**)	0[d]	
7	n-$C_3H_7CONMe(TMS)$	(**2g**)	28 (**5g**)	
8	$PhCONMe_2$	(**2f**)		64 (**7a**)

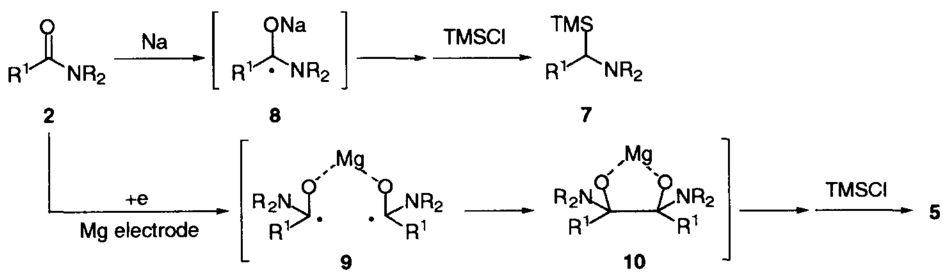
a) Isokated. b) 3 F/mol of electricity based on **2** was passed.
c) All products gave satisfactory spectroscopic values for the assigned structures. d) Starting material was recovered.

Since so far the reductive coupling of aliphatic amide **2** has never been reported, we have examined the reduction of **2** under typical reaction conditions of acyloin condensation[14] and found that the reduction of **2a** with Na metal in the presence of TMSCl did not give the coupling product **5a** but yielded **7b** in 69 % yield (Scheme 3).[15, 16]



Scheme 3

These results indicate that the reaction pathway of the electroreduction of **2** shown in the scheme 2 is different from the reduction of **2** with Na metal (Scheme 3). Although the difference in the reaction pathway is not always clearly explained, the counter cation in the reaction seems to play an important role for the determination of the reaction pathway. Namely, the reduction of **2** with Na metal forms an anion radical intermediate **8** in which the counter cation is Na^+. The dimerization of the tertiary radical **8** to give **5** seems to hardly take place due to its huge bulkiness, as shown in the scheme 4.[17] On the other hand, two molecules of anion radical intermediates are bound by Mg^{2+} in the electroreduction of **2** with Mg electrode, and hence, the coupling of radical **9** leading to **10** takes place much easier than that of **8** since the former is not intermolecular but intramolecular.



Scheme 4

Acknowledgments: The author (S.K) thank the Ministry of Education, Science and Culture Japan for Grant-in Aid for Scientific Research on Priority Areas (No. 9239251).

References and Notes

1) Electroorganic Chemistry 155. For part 154, see *Tetrahedron Lett.* **1997**, *38*, 6717.
2) Faculty of Science and Engineering.
3) Research and Development Department, Osaka Gas Co. Ltd. 1 Chyudoji-Machi, Simogyo, Kyoto 600.
4) Department of Synthetic Chemistry, Kyoto University.

5) Research Institute for Science and Technology.

6) Shono, T.; Masuda, H.; Murase, H.; Shimomura, M.; Kashimura, S. *J. Org. Chem.* **1992**, *57*, 1061.

7) Kashimura, S.;Murai, Y.;Ishifune, M.;Masuda, H.;M.;Murase, H.;Shono, T. *Tetrahedron Lett.* **1995**, *36*, 4805.

8) Kashimura,S.;Muraai,Y.;Ishifune,M.;Washika,C.;Yoshiwara,D.;Kataoka,Y.;Murase,H.;Shono,T. *Tetrahedron Lett.* **1997**, *38*, 6717.

9) It has been reported that the reduction of an aliphatic amide with Na metal was unsuccessful[10] and that of an aromatic amide under similar reduction conditions did not give the coupling product.[11]

10) Lynn,J.W.; English, J. *J. Am. Chem. Soc.* **1951**, *73*, 4284.

11) Bourgeois, P.;Duffaut, N. *J. Organometal. Chem.* **1972**, *35*, 63.

12) The electroreduction of **2e** with Mg electrode gave Mg salt $(RCONH)_2Mg$ and this salt was insoluble in THF and hence, **2e** was not reduced under the conditions of electroreduction.

13) **5a**: IR (neat) 2930, 1240, 840 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.86 (t, 6H, *J* = 6.0 Hz), 1.40 (m, 4H), 1.90 (m, 4H), 2.36 (s, 6H); HRMS Calcd for $C_{13}H_{29}NOSi$: 243.2020; Found: 243.1995.

5b: IR (neat) 2935, 1240, 835 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.88 (t, 6H, *J* = 6.0 Hz), 1.40-1.55 (m, 8H), 1.90 (m, 4H), 2.36 (s, 6H); HRMS Calcd for $C_{15}H_{33}NOSi$: 271.2333; Found: 271.2301.

The products **5c** and **5d** were rather unstable and their structures were determined after their hydrolysis to the corresponding α-aminoketones **6c** and **6d**.

6a: IR (neat) 3430, 2975, 1710, 1478cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 6H, *J* = 6.1 Hz), 1.55 (m, 6H), 2.29 (s, 6H), 2.47 (t, 2H, *J* = 6.3 Hz), 2.93 (t, 1H, *J* = 7.0 Hz); HRMS Calcd for $C_{10}H_{21}NO$: 171.1624; Found: 171.1620.

6b: IR (neat) 2970, 1720, 1470, 1040cm^{-1}; NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 8.0 Hz), 0.88 (t, 3H, *J* = 8.0 Hz), 1.22 (m, 6H), 1.52 (m, 4H), 2.23 (s, 6H), 2.46 (t, 2H, J=7.0Hz), 2.88(dd 1H, J=6.0 8.0Hz) ; Anal. Calcd for $C_{12}H_{25}NO$: C,72.31; H, 12.64; N, 7.03. Found: C,72.26; H, 12.93; N, 6.96.

6c: IR (neat) 2940, 1720, 1640, 1450, 910cm^{-1}; NMR ($CDCl_3$) δ 1.49-1.72 (m, 6H), 1.97-2.10 (m, 4H), 2.23 (s, 6H), 2.48 (m, 2H), 2.90(dd 1H, J=7.3, 4.2Hz), 4.89-5.05(m,4H) , 5.64-5.87(m, 2H); HRMS Calcd for $C_{14}H_{25}NO$: 223.1937; Found: 223.1909.

6d: IR (neat) 2950, 1720, 1460, 980cm^{-1}; NMR ($CDCl_3$) δ 1.23 (m, 4H), 1.61 (m, 8H), 1.97 (m, 4H), 2.23 (s, 6H), 2.45 (t, 2H, J=7.0Hz), 2.89(dd 1H, J=6.0 7.5Hz) , 5.38(m, 4H); Anal. Calcd for $C_{16}H_{29}NO$: C,76.44; H, 11.63; N, 5.57. Found: C,76.34; H, 11.92; N, 5.48.

14) Bloomfield, J.J.;Owsley, D.C. *J. Org. Chem.* **1975**, *40*, 393.

15) **7**: IR (neat) 2970, 2790, 1460, 1260, 840cm^{-1}; NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.71(t, 3H, J=6.0Hz), 1.40 (m, 4H), 1.84(m, 1H), 2.29 (s, 6H); HRMS Calcd for $C_9H_{23}NSi$: 173.1600; Found: 173.1612.

16) Although the mechanism of the formation of **7** is not always clear, it has been reported that the reduction of N,N-dimethylbenzamide with Mg/MgI_2 gave **7** ($R=C_6H_5$) .[11]

17) Similar steric effect on the reductive coupling of an aliphatic ester has been reported.[18]

18) Kuwajima, I,;Sato, T.; Minami, N.; Abe, T. Tetrahedron Lett. **1976**, 1591.