

Electroreductive Coupling of Aliphatic Amides. A Useful Method for the Synthesis of α -Amino Ketones¹

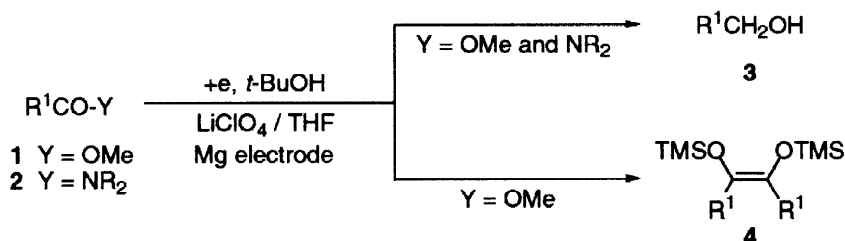
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Abstract: Electroreduction of aliphatic amides ($RCONMe_2$) with Mg electrode in the presence of chlorotrimethylsilane (TMSCl) has been found to give the coupling products $[R(TMSO)C=C(NMe_2)R]$ and hydrolysis of the products affords the corresponding α -amino ketones $[RCOCH(NMe_2)R]$ in excellent yields. © 1998 Elsevier Science Ltd. All rights reserved.

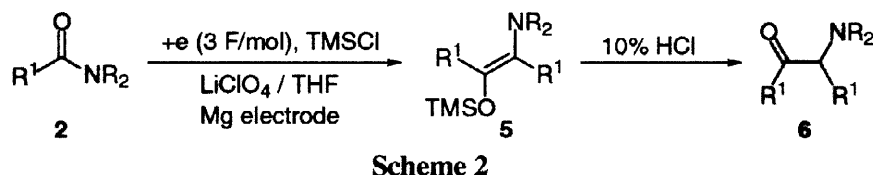
It has been shown in our previous study that the electroreduction of aliphatic ester (1) and aliphatic amide (2) with Mg electrode gives primary alcohol (3) when the reaction is carried out in the presence of a proton donor like *t*-BuOH.⁶ Recently we have also found that the electroreduction of 1 with 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

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.



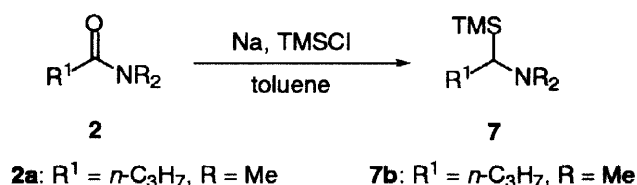
The electroreduction of **2** was carried out as follows: Into an undivided electrolysis cell equipped with Mg (99.9% purity, Rare Metallic Co., LTD) cathode and anode (rod, diameter =1 cm; length =4 cm) were put anhydrous LiClO₄ (1.06 g, 10 mmol), molecular sieve 5A (1.5 g), and anhydrous THF (20 mL, dried over Na-ketyl). After the mixture was stirred overnight under a N₂ 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*-dimethylamides (**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	<i>n</i> -C ₃ H ₇ CONMe ₂ (2a)	70 (5a)	98 (6a)
2	<i>n</i> -C ₄ H ₉ CONMe ₂ (2b)	67 (5b)	100 (6b)
3	CH ₂ =CH(CH ₂) ₃ CONMe ₂ (2c)	65 (5c)	100 (6c)
4	MeCH=CH(CH ₂) ₃ CONMe ₂ (2d)	63 (5d)	100 (6d)
5	<i>n</i> -C ₃ H ₇ CONH ₂ (2e)	0 ^d	
6	<i>n</i> -C ₃ H ₇ CONHMe (2f)	0 ^d	
7	<i>n</i> -C ₃ H ₇ CONMe(TMS) (2g)	28 (5g)	
8	PhCONMe ₂ (2f)	<div style="text-align: center;"> TMS Ph-CH-NMe₂ </div> 64 (7a)	

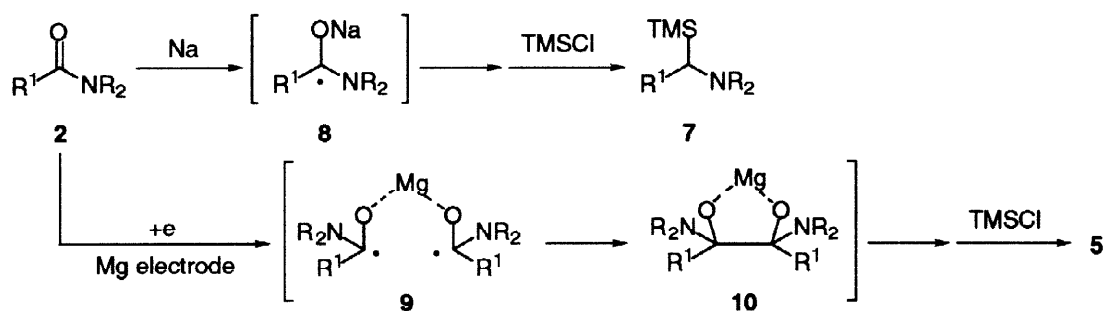
a) Isolated. b) 3 F/mol of electricity based on **2** was passed.
 c) All products gave satisfactory spectroscopic values for the assigned structures. d) Starting material was recovered.

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 condensation¹⁴ 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 Mg²⁺ 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

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References and Notes

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- 9) It has been reported that the reduction of an aliphatic amide with Na metal was unsuccessful¹⁰ 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 (CDCl₃) 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 C₁₃H₂₉NOSi: 243.2020; Found: 243.1995.
5b: IR (neat) 2935, 1240, 835 cm⁻¹; NMR (CDCl₃) 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 C₁₅H₃₃NOSi: 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, 1478 cm⁻¹; NMR (CDCl₃) 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 C₁₀H₂₁NO: 171.1624; Found: 171.1620.
6b: IR (neat) 2970, 1720, 1470, 1040 cm⁻¹; NMR (CDCl₃) 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* = 7.0 Hz), 2.88 (dd 1H, *J* = 6.0, 8.0 Hz); Anal. Calcd for C₁₂H₂₅NO: 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, 910 cm⁻¹; NMR (CDCl₃) 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, 4.2 Hz), 4.89-5.05 (m, 4H), 5.64-5.87 (m, 2H); HRMS Calcd for C₁₄H₂₅NO: 223.1937; Found: 223.1909.
6d: IR (neat) 2950, 1720, 1460, 980 cm⁻¹; NMR (CDCl₃) δ 1.23 (m, 4H), 1.61 (m, 8H), 1.97 (m, 4H), 2.23 (s, 6H), 2.45 (t, 2H, *J* = 7.0 Hz), 2.89 (dd 1H, *J* = 6.0, 7.5 Hz), 5.38 (m, 4H); Anal. Calcd for C₁₆H₂₉NO: 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, 840 cm⁻¹; NMR (CDCl₃) δ 0.03 (s, 9H), 0.71 (t, 3H, *J* = 6.0 Hz), 1.40 (m, 4H), 1.84 (m, 1H), 2.29 (s, 6H); HRMS Calcd for C₉H₂₃NSi: 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/MgI₂ gave **7** (R = C₆H₅).¹¹
- 17) Similar steric effect on the reductive coupling of an aliphatic ester has been reported.¹⁸
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