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Electroreductive Coupling of Aromatic Imines with Electrophiles in the Presence of Chlorotrimethylsilane[1]

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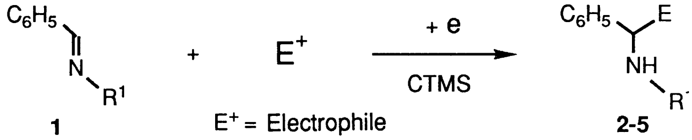
Electroreduction of aromatic imines in the presence of electrophiles gave the corresponding inter- and intramolecular coupling products when the reaction was carried out with the use of chlorotrimethylsilane (CTMS) as the trapping agent of an anion intermediate.

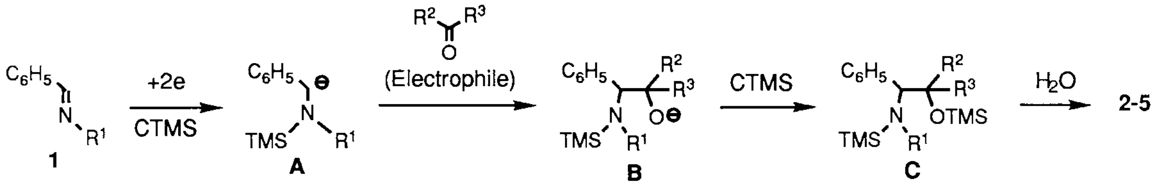
Reductive cross coupling of imines with electrophiles is one of the useful methods for the synthesis of amino compounds. Recently, reductive intermolecular coupling of aromatic imines with aldehydes or ketones was reported to be promoted by $NbCl_3$(DME) and to provide a convenient route for preparation of 2-amino alcohols.[2] On the other hand, electroreduction has been known as an effective method for reduction of aromatic imines.[3] Electroreductive coupling of aromatic imines with electrophiles has, however, scarcely been known[4] with the exception of alkylation with alkyl halides[6] and of carboxylation with carbon dioxide.[7] We wish to report herein that chlorotrimethylsilane (CTMS) effectively promoted the electroreductive intermolecular coupling of aromatic imines **1** with a variety of electrophiles. In addition, it was also found that the electroreduction of iminoesters in the presence of CTMS gave intramolecular coupling products.



A typical procedure for the electroreduction of **1** with an electrophile is as follows: A solution of Et_4NOTs (4 g) in DMF (40 mL) was put into a divided cell (50 mL beaker) equipped with a lead cathode (5 X 10 cm^2), a carbon rod anode, and a ceramic diaphragm. To the catholyte were added an aromatic imine **1** (5 mmol), an aldehyde or a ketone (15 mmol), CTMS (15 mmol), and Et_3N (15 mmol).[8] Electricity was passed at a constant current of 0.2 A until almost all of **1** were consumed (4-5 F/mol). The catholyte was poured into water (200 mL) and the aqueous solution was extracted with ether. After evaporation of ether, amino alcohol **2** and its trimethylsilyl ether were isolated by column chromatography on silica gel (AcOEt-hexane). The silyl ether was easily converted to alcohol by treatment with Bu_4NF in THF (room temp, 30 min).

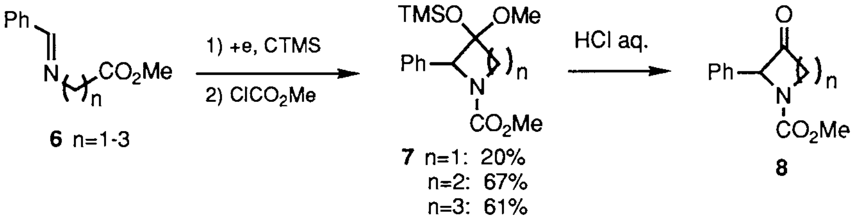
The results of the electroreduction of **1** in the presence of a variety of electrophiles are summarized in Table 1. 2-Amino alcohols **2** were obtained effectively by the use of aldehydes or ketones as electrophiles (runs 1-7). The present electroreductive method is also useful for the acylation of **1**. Namely, the reaction of **1** with acid anhydrides or *N*-acylimidazoles gave α-amino ketones **3** (runs 8-10) and that with *N*-methoxycarbonylimidazole afforded α-amino esters **4** (runs 11-13). Furthermore, the electroreductive intermolecular coupling of **1** with α,β-unsaturated esters effectively yielded γ-amino esters **5** (runs 14 and 15). Unfortunately, aliphatic imines were not reduced under the same conditions.

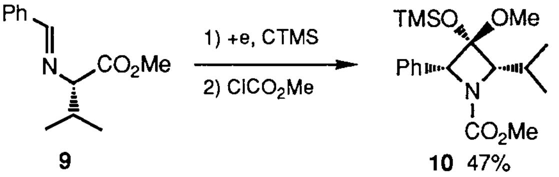
When electroreduction of a mixture of **1** and an electrophile was carried out in the absence of CTMS, only simply reduced amine (E = H) was formed (>90% yield) but no coupling product was obtained.[9] This result shows that the presence of CTMS is essential to the present electroreductive coupling. Although the role of CTMS is not always clearly explainable, the reaction mechanism may be depicted as shown in Scheme 1. It seems reasonable that CTMS promotes the reaction of anion intermediate **A** with an electrophile (carbonyl compound) through trapping the resultant alkoxy anion **B** as the corresponding silyl ether **C**.



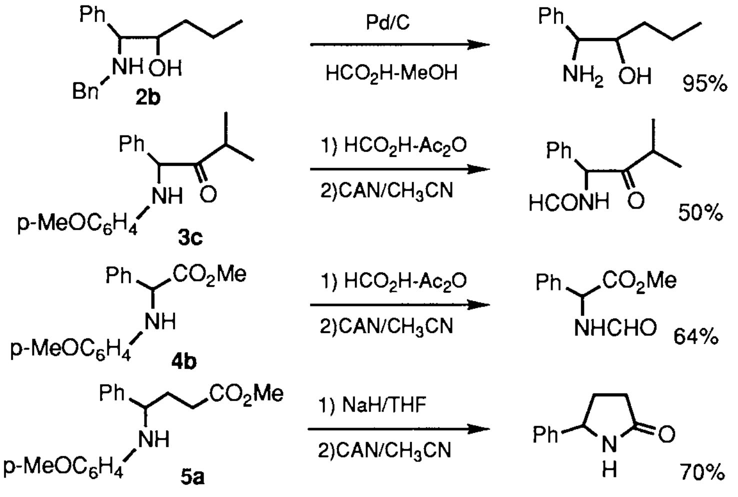
Scheme 1.

The electroreduction of imino esters **6** carried out in the presence of CTMS gave intramolecularly coupled products **7** which were easily hydrolyzed to the corresponding ketones **8**. An imino ester **9** prepared from L-valine methyl ester was similarly electroreduced to give the cyclized product **10** stereoselectively.[10]



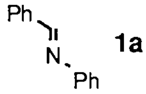
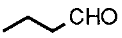
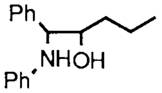
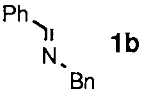
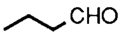
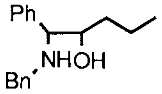
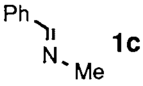
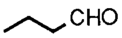
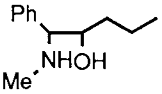
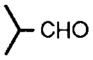
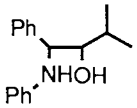
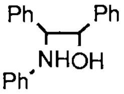
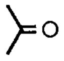
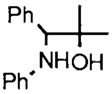
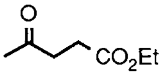
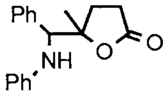
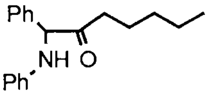
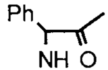
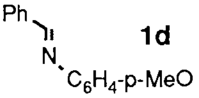
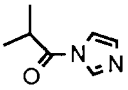
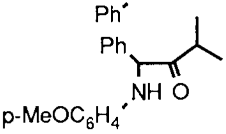
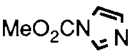
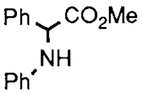
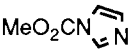
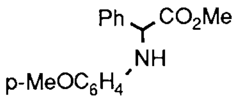
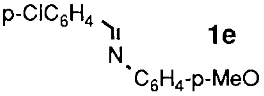
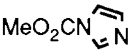
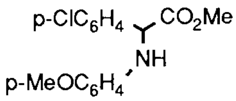
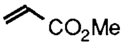
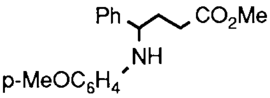
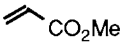
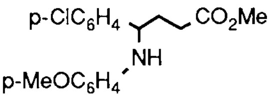


N-Benzyl and *N*-p-methoxyphenyl substituents in the coupling products (R^1 in **2**-**5**) are readily removed by hydrogenolysis or oxidation with CAN, respectively (Scheme 2). These results show that the present electroreductive coupling of aromatic imines is also useful for the synthesis of primary amines.



Scheme 2.

Table 1. Electroreductive Intermolecular Coupling of Aromatic Imines **1** with Electrophiles

Run	Aromatic imine	Electrophile	Product and yield[a] (ds)[b]
1	 **1a**		 **2a** 90 (5:5)
2[c]	 **1b**		 **2b** 81 (6:4)
3[c]	 **1c**		 **2c** 79 (5:5)
4	**1a**		 **2d** 81 (5:5)
5	**1a**	PhCHO	 **2e** 50 (5:5)
6	**1a**		 **2f** 80
7	**1a**		 **2g** 50 (5:5)
8	**1a**	$(n\text{-}C_5H_{11}CO)_2O$	 **3a** 73
9	**1a**		 **3b** 60
10	 **1d**		 **3c** 60
11	**1a**		 **4a** 58
12	**1d**		 **4b** 62
13	 **1e**		 **4c** 71
14	**1d**		 **5a** 63
15	**1e**		 **5b** 65

a) Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained for all of the products.
b) Diastereomeric ratios determined by 200 MHz ^{1}H NMR ($CDCl_3$). c) THF was used as solvent.

References

1) Electroorganic Chemistry. 136.

2) E. J. Roskamp and S. F. Pedersen, *J. Am. Chem. Soc.*, **109**, 6551 (1987).

3) A. J. Fry, "Synthetic Organic Electrochemistry," Harper & Row, New York (1972), p. 216; M. R. Rifi and F. H. Covitz, "Introduction to Organic Electrochemistry," Marcel Dekker, New York (1974), p. 236; "Technique of Electroorganic Synthesis," ed by N. L. Weinberg, John Wiley & Sons, New York (1975), p. 227.

4) It has been reported that the electroreduction of a methanolic solution of *N*-methylbenzylideneamine and benzaldehyde gave a cross-coupled product though its yield was low (22%).5)

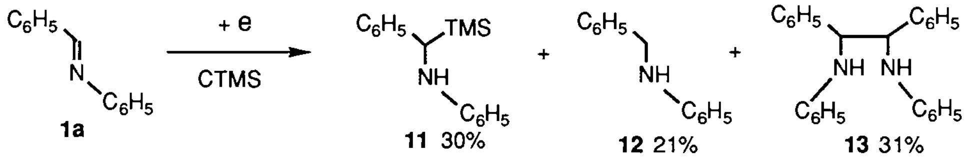
5) L. Horner and D. H. Shaletz, *Justus Liebig Ann. Chem.*, **1975**, 1210.

6) C. Degrand, P. L. Compagnon, G. Belot, and D. Jacquin, *J. Org. Chem.*, **45**, 1189 (1980).

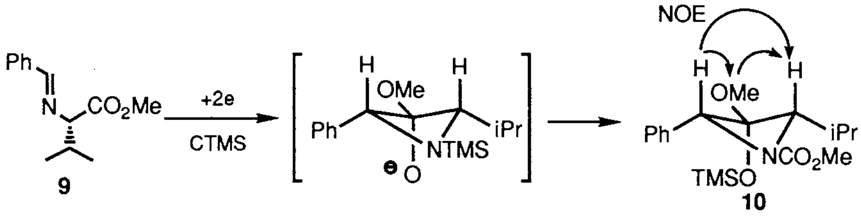
7) N. L. Weinberg, A. K. Hoffmann, and T. B. Reddy, *Tetrahedron Lett.*, **1971**, 2274; U. Hess, P. Fuchs, E. Jacob, and H. Lund, *Z. Chem.*, **20**, 64 (1980); D. K. Root and W. H. Smith, *J. Electrochem. Soc.*, **129**, 1231 (1982).

8) When the electroreduction was carried out in the absence of Et$_3$N, a considerable amount of homo-coupled product was formed and yield of the cross-coupled product decreased.

9) When the electroreduction of **1a** was carried out in the absence of the electrophile, α-trimethylsilyl amine **11** was obtained together with simply reduced amine **12** and homo-coupled product **13**.



10) **10**: $[\alpha]^{20}_{D}$ +2.2 (c 1.0, CHCl$_3$). The enantiomeric excess of **10** was determined to be 85% by ^{1}H NMR using Eu(hfc)$_3$. The stereo-structure was confirmed by NOE enhancements in its ^{1}H NMR. The high stereo-selectivity may be explained by the fact that both phenyl and isopropyl groups are located at the equatorial position in the most stable intermediate.



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