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Electroreductive Acylation of Aromatic Ketones with Acylimidazoles

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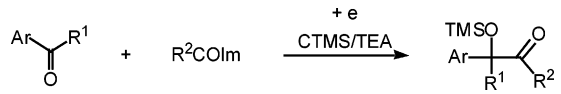
Received July 19, 2005

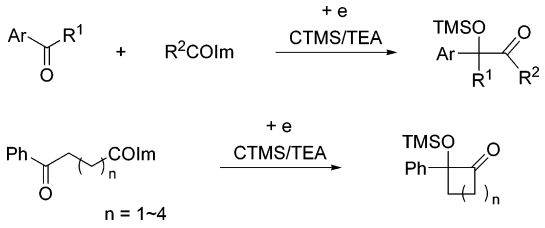


The intermolecular reductive coupling of aromatic ketones with acylimidazoles was effected by electroreduction in the presence of chlorotrimethylsilane and gave α-trimethylsiloxy ketones and esters. The best result was obtained using Bu_4NPF_6 as a supporting electrolyte and a Pb cathode in THF. The α-trimethylsiloxy-containing products were transformed to the corresponding α-hydroxy ketones and esters by treatment with TBAF in THF. This method was also effective for the intramolecular reductive coupling of δ- and ϵ-keto acylimidazoles.

Introduction

Reductive cross-coupling of ketones with carboxylic acid derivatives provides a useful method for the synthesis of α-hydroxy ketones. This type of intra- and intermolecular cross-coupling has been achieved between ketones and nitriles with Zn−chlorotrimethylsilane (CTMS),[1] Yb,[2] electroreduction,[3] Li−naphthalene,[4] SmI_2,[5] or low-valent titanium.[6] Reductive intramolecular coupling of keto esters has also been realized with low-valent titanium[7] or SmI_2.[8] In addition, reductive intermolecular cross-coupling of aromatic aldehydes and ketones with aliphatic acid chlorides has been achieved with Mg as a reducing agent.[9] We have recently reported that the electroreduction in the presence of CTMS is a useful method for the reductive intramolecular coupling of aromatic δ- and ϵ-keto esters.[10] However, this reaction was limited to intramolecular coupling to give five- and six-membered cyclized products. Therefore, we attempted intermolecular coupling of aromatic ketones with carboxylic acid derivatives more reactive than esters. In this context, we wish to report that the electroreduction of aromatic ketones with acylimidazoles in the presence of chlorotrimethylsilane (CTMS) and triethylamine (TEA) effected inter- and intramolecular reductive acylation of aromatic ketones (Scheme 1). This electroreduction provides a useful method for the synthesis of aryl α-hydroxy ketones and esters.

SCHEME 1



Results and Discussion

Intermolecular Electroreductive Acylation of Aromatic Ketones with Acylimidazoles. Conditions for the electroreductive acetylation of aromatic ketones were surveyed with acetophenone (**1a**) as an aromatic ketone and *N*-acetylimidazole (5 equiv) as an acetylating agent using a divided cell (Table 1). The acetylated product was isolated as α-trimethylsiloxy ketone **2a′**. In the absence of CTMS, the acetylated product was not obtained, and simply reduced alcohol, 1-phenylethanol, was formed as the only product (run 1). The presence of CTMS was crucial for the reductive acetylation of **1a** (run 2). The addition of 5 equiv of CTMS to **1a** was the optimal condition (1 equiv of CTMS, 32% yield of **2a′**; 3 equiv, 56%; 7 equiv, 63%). The addition of triethylamine (5

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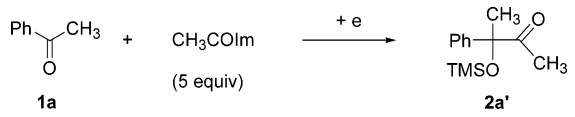
10.1021/jo051498w CCC: $30.25
Published on Web 10/11/2005

TABLE 1. Electroreduction of Acetophenone with Acetylimidazole



1a **2a'**

run	solvent of catholyte[a]	additive[b]	cathode material	yield[c] (%) of **2a′**
1	Bu_4NPF_6/THF	none	Pb	0
2	Bu_4NPF_6/THF	CTMS	Pb	65
3	Bu_4NPF_6/THF	CTMS/TEA	Pb	76
4	Bu_4NBr/THF	CTMS/TEA	Pb	67
5	Bu_4NClO_4/THF	CTMS/TEA	Pb	70
6	Bu_4NPF_6/THF	CTMS/TEA	Pt	72
7	Bu_4NPF_6/THF	CTMS/TEA	Au	68
8	Bu_4NPF_6/THF	CTMS/TEA	Ag	69
9	Bu_4NPF_6/THF	CTMS/TEA	Zn	65
10	Bu_4NPF_6/THF	CTMS/TEA	Sn	67
11	Bu_4NPF_6/THF	CTMS/TEA	Cu	60

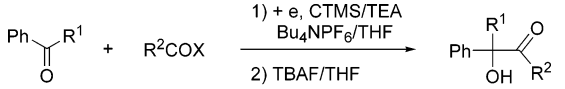
[a] 0.3 M electrolyte in solvent. [b] 5 equiv. [c] Isolated yields.

equiv) to the catholyte improved the yield of **2a′** to some extent (run 3), although it was not essential.[11] As a supporting electrolyte, tetrabutylammonium salts were suitable. Among them, Bu_4NPF_6 gave better yield of **2a′** than Bu_4NBr and Bu_4NClO_4 (runs 3−5). Although this reductive acetylation seemed to proceed irrespective of the cathode material, Pb brought about slightly better results than the other cathode materials such as Pt, Au, Ag, Zn, Sn, and Cu (runs 3, 6−11). Consequently, the best yield of **2a′** was obtained using Bu_4NPF_6 as a supporting electrolyte and a Pb cathode (run 3). One of us previously reported that the electroreduction of acylimidazoles in the presence of CTMS formed acylsilanes.[12] In the present reactions, it was difficult to detect the formation of acetylsilane, since it is volatile. In the case of octanoylimidazole as described later (Table 2, run 7), a small amount of octanoylsilane was obtained as a byproduct (>5% yield). The product α-trimethylsiloxy ketone **2a′** could be easily desilylated by treatment with Bu_4NF in THF to give the corresponding α-hydroxy ketone **2a** in 95% yield (Scheme 2).

The electroreduction of acetophenone and benzophenone (**1b**) with a number of acylating agents was carried out under the same conditions as run 3 in Table 1. The resulting α-trimethylsiloxy ketones were successively desilylated to the corresponding α-hydroxy ketones with Bu_4NF in THF. The results exhibited in Table 2 show that acylimidazoles are better acylating agents than acid anhydrides and afford the corresponding α-hydroxy ketones **2a**−**e** and **3a**−**e** in good to excellent yields. Next, a variety of aromatic ketones were subjected to the reductive acetylation with acetylimidazole (Table 3). In the case of isobutyrophenone, the yield of α-hydroxy ketone **2h** decreased, presumably due to steric hindrance (run 3). Aromatic substitution of either the electron-donating or electron-withdrawing group lowered the yields of α-hydroxy ketones (**2i**−**m**) (runs 4−8). In addition, when the electroreduction of aromatic ketones was carried out with methoxycarbonylimidazole as an acylating agent, the corresponding α-hydroxy esters **4** were formed in moderate to good yields (Table 4).

Under the present conditions, intermolecular coupling of aromatic ketones with esters did not proceed com-

TABLE 2. Electroreduction of Acetophenone and Benzophenone with Acylating Agents

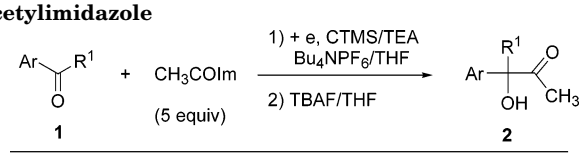


1a (R^1 = CH_3) **2** (R^1 = CH_3)
1b (R^1 = Ph) **3** (R^1 = Ph)

run	R^1	R^2COX[a]	yield[b] (%) of **2** and **3**
1	CH_3	CH_3COIm	**2a**, 72
2	CH_3	$(CH_3CO)_2O$	**2a**, 58
3	CH_3	C_2H_5COIm	**2b**, 76
4	CH_3	$(C_2H_5CO)_2O$	**2b**, 65
5	CH_3	*n*-C_3H_7COIm	**2c**, 74
6	CH_3	*i*-C_3H_7COIm	**2d**, 83
7	CH_3	*n*-$C_7H_{15}COIm$	**2e**, 86
8	Ph	CH_3COIm	**3a**, 68
9	Ph	$(CH_3CO)_2O$	**3a**, 70
10	Ph	C_2H_5COIm	**3b**, 86
11	Ph	$(C_2H_5CO)_2O$	**3b**, 67
12	Ph	*n*-C_3H_7COIm	**3c**, 92
13	Ph	*i*-C_3H_7COIm	**3d**, 87
14	Ph	*n*-$C_7H_{15}COIm$	**3e**, 82

[a] 5 equiv. [b] Isolated yields.

TABLE 3. Electroreduction of Aromatic Ketones with Acetylimidazole

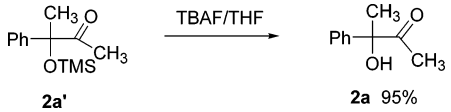


1 **2**

Run	Ar	R^1	Yield[a] (%) of **2**
1	Ph	C_2H_5	**2f** 72
2	Ph	*n*-C_3H_7	**2g** 63
3	Ph	*i*-C_3H_7	**2h** 35
4	*p*-$MeOC_6H_4$	CH_3	**2i** 33
5	*m*-$MeOC_6H_4$	CH_3	**2j** 63
6	*o*-$MeOC_6H_4$	CH_3	**2k** 61
7	*p*-FC_6H_4	CH_3	**2l** 48
8	3,4-$(MeO)_2C_6H_3$	CH_3	**2m** 48
9	1-Naphthyl	CH_3	**2n** 67
10	2-Naphthyl	CH_3	**2o** 73
11			**2p** 70
12			**2q** 50

[a] Isolated yields.

SCHEME 2



2a' **2a** 95%

(11) When TEA was added to the THF solution of acetophenone and CTMS, the solution became clouded. The silyl enol ether of acetophenone did not form, even if the solution was stirred at room temperature for 1 h prior to adding current.

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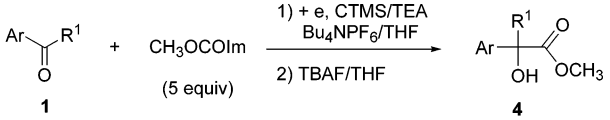
TABLE 4. Electroreduction of Aromatic Ketones with Methoxycarbonylimidazole

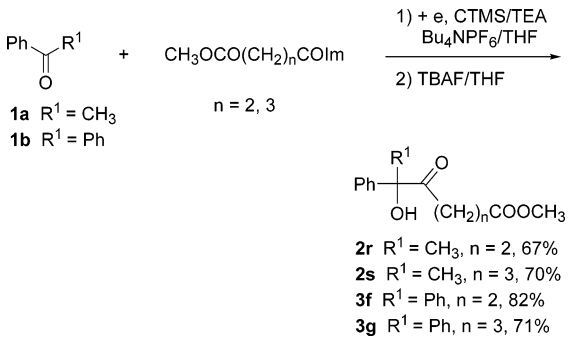


1 **4**

Run	Ar	R^1	Yield[a] (%) of **4**
1	Ph	CH_3	**4a** 64
2	Ph	Ph	**4b** 66
3	*p*-$MeOC_6H_4$	CH_3	**4c** 61
4	*m*-$MeOC_6H_4$	CH_3	**4d** 60
5	*o*-$MeOC_6H_4$	CH_3	**4e** 55
6	*p*-FC_6H_4	CH_3	**4f** 50
7	3,4-$(MeO)_2C_6H_3$	CH_3	**4g** 58
8			**4h** 64

[a] Isolated yields.

SCHEME 3

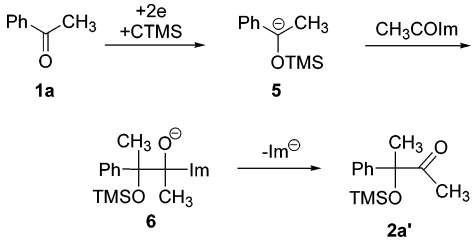


pletely. For example, the electroreduction of acetophenone with methyl acetate (5 equiv) in the presence of CTMS−TEA gave no cross-coupling product. Accordingly, it would be expected that the reaction of aromatic ketones with acylimidazoles possessing an ester group gave the products reacted only with the acylimidazole moiety chemoselectively. In fact, the electroreduction of **1a**,**b** with acylimidazoles derived from succinic acid and glutaric acid monomethyl esters afforded the chemoselectively coupled products **2r**, **2s**, **3f**, and **3g** as shown in Scheme 3.

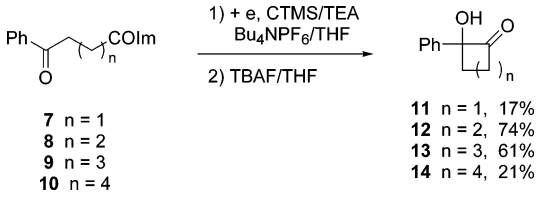
One of the authors reported that the addition of CTMS shifted the reduction potential of octanoylimidazole from −2.34 to −1.38 V vs SCE.[12] In the same manner, we observed that the addition of CTMS also shifted the reduction potential of acetophenone from −2.00 to −1.04 V vs SCE. These results suggest that acetophenone is more reducible than acylimidazoles. Therefore, the reaction mechanism of the electroreductive acylation of aromatic ketones with acylimidazoles can be speculated to be as shown in Scheme 4. Anion **5** is formed from acetophenone by a two-electron transfer and subsequent *O*-silylation. The anion **5** attacks the carbonyl group of acetyl imidazole to give **6**. Elimination of the imidazole anion from **6** leads to α-trimethylsiloxy ketone **2a′**.

Intramolecular Electroreductive Acylation of Aromatic Ketones with Acylimidazoles. We have already reported the electroreductive intramolecular coupling of aromatic δ- and ϵ-keto esters.[10] We also

SCHEME 4



SCHEME 5



attempted the electroreduction of several keto acylimidazoles **7**−**10** under the same conditions as described above (Scheme 5). The reactions of δ- and ϵ-keto acylimidazoles **8** and **9** gave the five- and six-membered cyclized products **12** (74%) and **13** (61%), respectively. The yields of these products were slightly better than those obtained from the corresponding δ- and ϵ-keto esters (63% and 53%, respectively). On the other hand, the electroreduction of γ- and ζ-keto acylimidazoles **7** and **10** afforded the four- and seven-membered cyclized products **11** (17%) and **14** (21%), although the yields of these products were low. The electroreduction of the corresponding γ- and ζ-keto esters did not give any cyclized product; the alcohols resulting from a simple reduction were formed as the main products from these esters.

Conclusion

This paper describes the electroreductive intermolecular coupling of aromatic ketones with acylimidazoles in the presence of CTMS and TEA followed by desilylation with TBAF in THF to produce α-hydroxy ketones and esters. The presence of CTMS in the catholyte is essential to promote the electroreductive coupling. This method is also effective for the intramolecular reductive coupling of δ- and ϵ-keto acylimidazoles to form five- and six-membered cyclized products. Four- and seven-membered cyclized products were obtained from the electroreduction of γ- and ζ-keto acylimidazoles, although the yields were low.

Experimental Section

General Methods. Column chromatography was performed on silica gel 60. THF was distilled from sodium benzophenone ketyl. CTMS and TEA were distilled from CaH_2. Acetylimidazole and the aromatic ketones employed are commercially available. The other acylimidazoles, shown in Table 2 and Scheme 3, and methoxycarbonylimidazole were prepared from the corresponding acid chlorides and imidazole (2 equiv) by stirring in THF. Keto acylimidazoles **7**−**10** were prepared from the corresponding keto acids by treatment with 1,1′-carbonyldiimidazole in THF, and the THF solutions were subjected to electroreduction directly.

Typical Procedure for Electroreduction (Table 1, Run 3). A 0.3 M solution of Bu_4NPF_6 in THF (15 mL) was placed

in the cathodic chamber of a divided cell (40-mL beaker, 3-cm diameter, 6-cm height) equipped with a lead cathode (5 × 5 cm^2), a platinum anode (2 × 1 cm^2), and a ceramic cylindrical diaphragm (1.5-cm diameter). A 0.3 M solution of Bu_4NClO_4 in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). Acetophenone (**1a**) (120 mg, 1 mmol), acetylimidazole (550 mg, 5 mmol), CTMS (0.64 mL, 5 mmol), and triethylamine (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300 C of electricity was passed at a constant current of 100 mA at room temperature, the catholyte was evaporated in vacuo. The residue was diluted with Et_2O (30 mL), and insoluble Bu_4NPF_6 was filtered off. The filtrate was evaporated in vacuo. The crude mixture was purified by column chromatography on silica gel (hexanes−ethyl acetate, 50:1) to give **2a′** in 76% yield.

Typical Procedure of Successive Electrolysis and Desilylation (Table 2, Run 1). After the electroreduction was carried out as described above, the catholyte was evaporated in vacuo. The residue was diluted with Et_2O (30 mL), and insoluble Bu_4NPF_6 was filtered off. The filtrate was evaporated in vacuo. The residue was diluted with THF (10 mL). To the solution was added 1 M TBAF in THF (1 mL, 1 mmol) in an ice bath, and then the mixture was stirred at this temperature for 30 min. After addition of acetic acid (60 mg, 1 mmol), the solvent was removed in vacuo. The crude mixture was purified by column chromatography on silica gel (hexanes−ethyl acetate, 10:1) to give **2a** in 72% yield. All the known compounds, **2a**,[13] **2b**,[13] **2c**,[14] **2f**,[13] **2g**,[15] **2q**,[16] **3a**,[2] **3d**,[2] **4a**,[17] **4b**,[18] **12**,[19] and **13**,[19] gave the spectral data in accordance with those reported in the literature. The other products were identified by spectroscopic and elemental analyses (Supporting Information).

Supporting Information Available: A drawing of the electrolysis cell and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051498W

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