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Electrochemical Oxidation of Benzylic Amines into the Corresponding Imines in the Presence of Catalytic Amounts of KI

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Abstract: Oxidation of various benzylic amines using an indirect electrochemical method was successfully carried out under very mild conditions to afford the corresponding imines in good yields. Our results show that, for this electrolytic system, the iodide ions play an important role as electron carriers.

Mild and efficient oxidation of amines is an important synthetic reaction in affording the corresponding imines, which are useful organic compounds that can introduce a new substituent at the β-position of the amine functionality.[1] Although several oxidative methods for this transformation have been developed to date, most require environmentally undesirable oxidants,[2] expensive catalysts,[3] and/or long reaction periods. Our studies, in contrast, involve the oxidation of various organic compounds using an electrochemical method, in both the presence[4] and absence[5] of halide ions. It is well known that the use of electric current is one of the cleanest method for the oxidation of organic compounds.[6] Previously, electrooxidative transformation of amines to corresponding nitriles had been reported by Shono and coworkers.[7] However,

to the best of our knowledge, the electrolytic method of the oxidation of amines into the corresponding imines, from a synthetic viewpoint, has yet to be reported. Herein, we describe the oxidation of several benzylic amines using our electrochemical procedure in the presence of iodide ions as the electron carrier—this is typically referred as the indirect electrochemical oxidation.

Initially, to optimize the reaction conditions, electrooxidations were carried out in the presence of various halide-ion sources and supporting electrolytes, using 1,2,3,4-tetrahydroisoquinoline (1a) as the model substrate. The yields of product 3,4-dihydroisoquinoline (2a) are listed in Table 1.

When NaOMe was used as the lone supporting electrolyte, the yield of 2a was merely 39% (Run 1). However, the addition of a catalytic amount of KI (3 mmol for 10 mmol of substrate) along with a strong base such as NaOMe afforded higher yields of 2a (Runs 4–7). In the cases where KCl or KBr was used instead of KI, 2a was obtained with yields of 66% (Run 2) and 59% (Run 3), respectively. Substituting NaI for KI as the iodide ion source did not decrease the yield of 2a (Run 8). Detailed information on the optimal amounts of KI and NaOMe for this electrooxidation was separately determined, using 1a as the substrate. The yield of 2a increased with increasing amounts of current; at nearly 3 F/mol, the yield reached a maximum of 90%. Excessive amounts of current (more than 3 F/mol), however, resulted in a gradual decrease in the yield of 2a. Because most of 1a was oxidized at the point where 2.5 F/mol of electricity was consumed, the electrooxidation presumably proceeds through a two-electron oxidation process. In the reaction

Table 1. Electrooxidation of 1,2,3,4-tetrahydroisoquinoline[a]
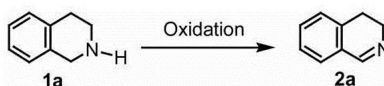
Run	Halogen ion source (3 mmol)	Supporting electrolyte (5 mmol)	Yield of 2a[b] (%)
1	None	NaOMe	39
2	KCl	NaOMe	66
3	KBr	NaOMe	59
4	KI	p-TsON(Et)$_4$	65
5	KI	NaOAc	76
6	KI	NaOH	87
7	KI	NaOMe	90
8	NaI	NaOMe	88

[a]1a: 10 mmol, MeOH: 40 mL, constant current: 0.3 A, current passed: 3.0 F/mol, rt: ca. 15°C.
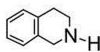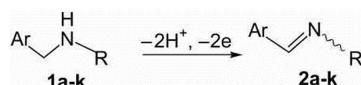[b]Determind by GC analysis.

temperature range of -5 to $55°C$, favorable results were obtained at a convenient temperature of roughly $15°C$.

Subsequently, several benzylic amines **1a–1k** were oxidized using the optimal reaction conditions based on the yields shown in Table 1, and the results are listed in Table 2.

In each case, the course of the electrooxidation was monitored by carefully measuring the composition of the reaction mixture using silica gel TLC (ether/hexane 1:1) and GC analyses. It is important to note that the amount of electric current necessary to complete the reaction was different for each substrate. For example, in the cases of **1a** and N-propylbenzylamine (**1b**), 3.0 F/mol of electric current was sufficient to complete the reaction. In contrast, N-cyclopentylbenzylamine (**1e**) required an excessive amount of current (5.2 F/mol). Moreover, the ease of electrooxidizing alicyclic benzylic amines **1e**, **1f**, and **1j** was influenced by the alkyl group moiety, in the order of cyclohexyl (3.7 F/mol) > cyclooctyl (4.5 F/mol) > cyclopentyl (5.2 F/mol). In the cases of **1f**, **1g**, and **1h**, based on the current passed and the yield of products, significant substituent effects of the phenyl group were not observed. In most cases, the corresponding imines were successfully obtained in yields of 62 to 86%. In the case of N-(4-*tert*-butylcyclohexyl)benzylamine (**1i**), which afforded the product

Table 2. Electrooxidative conversion of benzylic amines into the corresponding imines[a]

Substrate	Ar	R	Current passed (F/mol)	Yield[b] of **2** (%)
1a		(tetrahydroisoquinoline structure) N–H	3.0	86
1b	Ph	*n*-Pr	3.0	62
1c	Ph	*iso*-Pr	4.5	74
1d	Ph	*tert*-Bu	4.0	75
1e	Ph	Cyclopentyl	5.2	71
1f	Ph	Cyclohexyl	3.7	81
1g	4-MeO-C_6H_4	Cyclohexyl	3.7	83
1h	4-Cl-C_6H_4	Cyclohexyl	3.7	76
1i	Ph	4-*tert*-Bu-Cyclohexyl	4.5	66
1j	Ph	Cyclooctyl	4.5	82
1k	Ph	Bn	3.2	75

[a]Substrate: 10 mmol, KI: 3 mmol, NaOMe: 5 mmol, MeOH: 40 mL, constant current: 0.3 A, rt: ca. $15°C$.
[b]Isolated yield.

(66% yield) as a mixture of *cis/trans* isomers (ca. 1:1). In each case, the corresponding benzylidene-type imines were exclusively formed and alkylidene-type imines were not detected.

Unexpectedly, attempts to electrooxidize dialkylamines were less successful than that of the benzylic amines. For example, the electrooxidation of butylcyclohexylamine afforded the only corresponding *N*-cyclohexylbuthylideneamine in 53% yield (determined using GC), whereas corresponding *N*-cyclohexylidenebuthylamine was not detected. Furthermore, the electrooxidation of dicyclohexylamine was not yield the corresponding imines; in fact, small amount of substrates were recovered from the resulting tar-like material, which was difficult to purify and analyze.

Although details of the reaction mechanism remain unclear, we propose that the iodide ion plays an important role as an electron carrier in this electrochemical system. Specifically, the iodide ion undergoes a two-electron oxidation process to form an iodonium ion, which then reacts with the substrate to give an intermediate as illustrated in Scheme 1 (structure within the bracket). The intermediate, which was not isolated, is presumably unstable and can immediately undergo subsequent oxidation to form the imine. In this electrochemical system, the presence of a base such as NaOMe presumably facilitates the deprotonation of both the substrate and the intermediate to form the final product.

The base can also function as an efficient supporting electrolyte to prevent the increase of the terminal voltage. Moreover, the base (NaOMe) must be produced continuously as the results of cathodic reaction, as illustrated in
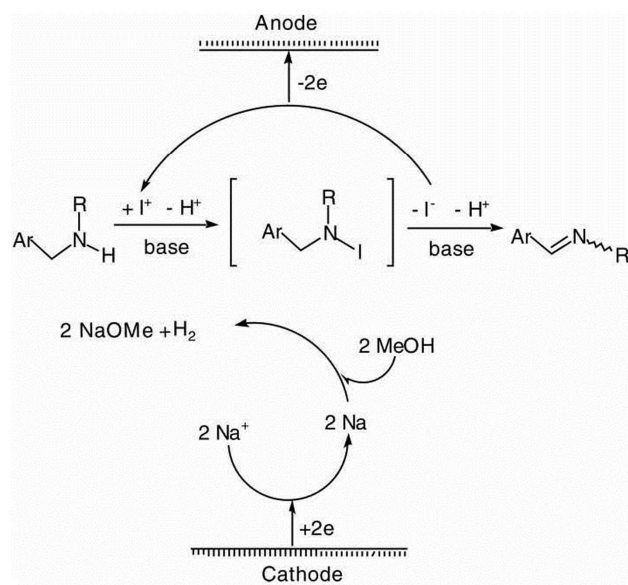
Scheme 1.

the lower pathway of Scheme 1. Accordingly, significant increases in the terminal voltage were observed when KI was used as the only electrolyte. If an excessive amount of current was passed after the completion of the reaction, the color of the electrolytic solution turned from slightly yellow to red brown, which suggests the formation of iodine in the reaction mixture.

In conclusion, oxidations of several benzylic amines were achieved under very mild conditions and without the use of any environmentally undesirable reagents by means of an electrochemical method. The corresponding imines were obtained in good to high yields, with relatively simple isolation procedures. In these electrochemical systems, the presence of iodide ions functioned as electron carriers. Based on our results, we believe that our electrochemical procedure can be applied to the oxidation of a wide variety of benzylic amines to the corresponding imines.

EXPERIMENTAL

All electrooxidation products were identified using their physical and spectral data. Substrates were prepared by means of usual alkylation of amines with alkyl halide except for **1a**, **1d**, and **1f**. **1a**, **1d**, and **1f** were obtained from commercial suppliers and were used without further purifications. Preparative-scale electrooxidations were carried out in a tall, 50-mL beaker, equipped with a fine frit cup as the cathode compartment, an insert cylindrical platinum net (diameter: 32 mm, height: 35 mm, 55 mesh) as the anode, and a nickel-coil cathode. Amines **1a–k** were oxidized as follows: a solution of substrate **1a–k** (10 mmol), KI (3 mmol), and NaOMe (5 mmol) in MeOH (40 mL) was electrooxidized under a constant current (0.3 A). During the course of the electrooxidation, the anolyte was magnetically stirred while the temperature of the cell was maintained at approximately 15°C. GC analyses were performed with stainless steel column (length: 2.0 m, diameter: 5 mm) packed with 20% Apeazon L and 10% of KOH on Chromosorb WAW. The gas chromatograph was equipped with a flame-ionization detector. After completion of the electrooxidation, the reaction mixture was concentrated in vacuo at approximately 40°C to roughly one fifth of its original volume, and the resulting residue was treated with water (30 mL) and then extracted with ether (3 × 40 mL). The combined ether extracts were washed with an aqueous sodium thiosulfate solution (20% w/w, 20 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by distillation under reduced pressure or recrystallization from EtOH (the case of **1h**).

N-**Benzylidenepropylamine** (**2b**): Bp 95–97°C/17 hPa. IR (neat): 2961, 2932, 2874, 2831, 1647, 1450, 968, 754, 694 cm^1. ^{1}H NMR (CDCl$_3$): $\delta = 0.95$ (t, 3 H, $J = 7$ Hz, CH$_3$), 1.72 (sex, 2 H, $J = 7$ Hz, CH$_2$), 3.55 (t, 2 H, $J = 7$ Hz, CH$_2$), 7.2–7.8 (m, 5 H, Ar), 8.23 (s, 1 H, N═CH).

^{13}C NMR (CDCl$_3$): δ = 11.85 (CH$_3$), 24.11 (CH$_2$), 63.52 (CH$_2$), 128.07 (CH), 128.56 (CH), 130.43 (CH), 136.50 (C), 160.68 (CH=N). MS: m/z (%) = 147 (M$^+$, 18), 146 (41), 119 (28), 118 (100), 104 (21), 91 (81), 77 (13), 51 (8). HRMS m/z found: 147.1019 (M$^+$), calcd. for C$_{10}$ H$_{13}$ N: 147.1048.

N-Benzylidenecyclopentylamine (2e): Bp 128–130°C/19 hPa. IR (neat): 2957, 2866, 1643, 1582, 1450, 1383, 1308, 754, 694 cm^1. ^{1}H NMR (CDCl$_3$): δ = 1.4–2.2 [m, 8 H, -(CH$_2$)$_4$-], 3.74 (bs, 1 H, N-CH), 7.2–7.8 (m, 5 H, Ar), 8.21 (s, 1 H, N=CH). ^{13}C NMR (CDCl$_3$): δ = 24.76 (CH$_2$), 34.53 (CH$_2$), 71.75 (CH), 127.98 (CH), 128.43 (CH), 130.14 (CH), 136.66 (C), 158.24 (CH=N). MS: m/z (%) = 173 (M$^+$, 68), 172 (100), 144 (50), 130 (51), 117 (38), 104 (82), 90 (38), 89 (27), 77 (22), 41 (33). HRMS m/z found: 173.1214 (M$^+$), calcd. for C$_{12}$ H$_{15}$ N: 173.1204.

N-(4-Methoxybenzylidene)cyclohexylamine (2 g): Bp 140–142°C/2.6 hPa. IR (neat): 2928, 2853, 1643, 1607, 1512, 1448, 1302, 1248, 1167, 1034, 831 cm^1. ^{1}H NMR (CDCl$_3$): δ = 1.0–2.0 [m, 10 H, -(CH$_2$)$_5$-], 3.26 (bs, 1 H, N-CH), 3.76 (s, 3 H, CH$_3$O), 6.86 (d, 2 H, J = 9 Hz, Ar), 7.64 (d, 2 H, J = 9 Hz, Ar), 8.20 (s, 1 H, N=CH). ^{13}C NMR (CDCl$_3$): δ = 24.88 (CH$_2$), 25.74 (CH$_2$), 34.53 (CH$_2$), 55.18 (CH$_3$O), 69.76 (CH), 113.90 (CH), 129.53 (CH), 129.73 (C), 157.71 (CH=N), 161.42 (C). MS: m/z (%) = 217 (M$^+$, 69), 216 (62), 188 (56), 174 (64), 162 (31), 135 (34), 134 (100), 121 (31), 91 (25), 77 (24). HRMS m/z found: 217.1441 (M$^+$), calcd. for C$_{14}$ H$_{19}$ NO: 217.1467.

N-(4-Chlorobenzylidene)cyclohexylamine (2h): Mp 53–55°C. IR (KBr): 2930, 2853, 1641, 1591, 1487, 1454, 1074, 1011, 827 cm^1. ^{1}H NMR (CDCl$_3$): δ = 1.2–2.0 [m, 10 H, -(CH$_2$)$_5$-], 3.44 (bs, 1 H, N-CH), 7.32 (d, 2 H, J = 9 Hz, Ar), 7.64 (d, 2 H, J = 9 Hz, Ar), 8.23 (s, 1 H, N=CH). ^{13}C NMR (CDCl$_3$): δ = 24.74 (CH$_2$), 25.70 (CH$_2$), 34.37 (CH$_2$), 69.80 (CH), 128.72 (CH), 129.25 (CH), 135.23 (C), 136.21 (C), 157.02 (CH=N). MS: m/z (%) = 221 (M$^+$, 85), 220 (39), 192 (93), 178 (84), 166 (51), 140 (58), 138 (100), 89 (65), 55 (75). HRMS m/z found: 221.0960 (M$^+$), calcd. for C$_{13}$ H$_{16}$ NCl: 221.0971.

N-Benzylidene-4-*tert*-Butylcyclohexylamine (2i): Bp 141–145°C/2.6 hPa (mixture of *cis* and *trans*, ca. 1:1). IR (neat): 2856, 1647, 1580, 1477, 1448, 1393, 1366, 1310, 1061, 754, 692 cm ^{1}. ^{1}H NMR (CDCl$_3$): δ = 0.88, 0.90 (s, s, 9 H, *tert*-Bu), 1.4–2.0 (m, 9 H, -(CH$_2$)$_2$- × 2, CH), 3.5 (bs, 1 H, N-CH), 7.2–7.9 (m, 5 H, Ar), 8.3 (bs, 1 H, N=CH). ^{13}C NMR (CDCl$_3$): δ = 22.11 (CH$_2$), 25.86 (CH$_2$), 27.61 (CH$_3$), 32.37 (C), 32.66 (C), 34.45 (CH$_2$), 34.65 (CH$_2$), 47.28 (CH), 48.58 (CH), 64.58 (CH), 70.33 (CH), 128.07 (CH), 128.43 (CH), 130.02 (CH), 130.23 (CH), 136.70 (C), 137.11 (C), 157.51 (CH=N), 158.57 (CH=N). (*cis* form) MS: m/z (%) = 243 (M$^+$, 11), 187 (18), 186 (100), 144 (33), 106 (33), 104 (26), 57 (24). (*trans* form) MS: m/z (%) = 243 (M$^+$, 100), 228 (90), 214 (41), 186 (44),

144 (47), 133 (72), 106 (87), 104 (78), 91 (40), 57 (63). HRMS m/z found: 243.1958 (M$^+$), 243.1975 (M$^+$), calcd. for $C_{17}H_{25}$ N: 243.1987.

***N*-Benzylidenecyclooctylamine (2j)**: Bp 132–134°C/2.6 hPa. IR (neat): 2922, 2851, 1643, 1580, 1472, 1448, 1385, 1292, 1059, 752, 692 cm^1. ^{1}H NMR (CDCl$_3$): $\delta = 1.1$–2.0 [m, 14 H, -(CH$_2$)$_7$-], 3.38 (bs, 1 H, N-CH), 7.2–7.8 (m, 5 H, Ar), 8.19 (s, 1 H, N=CH). ^{13}C NMR (CDCl$_3$): $\delta = 24.11$ (CH$_2$), 25.78 (CH$_2$), 27.41 (CH$_2$), 34.04 (CH$_2$), 71.51 (CH), 128.03 (CH), 128.39 (CH), 130.10 (CH), 136.82 (C), 157.35 (CH=N). MS: m/z (%) = 215 (M$^+$, 51), 214 (23), 172 (51), 158 (48), 144 (45), 132 (42), 106 (72), 104 (100), 91 (56), 41 (65). HRMS m/z found: 215.1647 (M$^+$), calcd. for $C_{15}H_{21}$ N: 215.1674.

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