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ELECTROOXIDATIVE CYCLIZATION OF HYDROQUINOLYL ALCOHOLS

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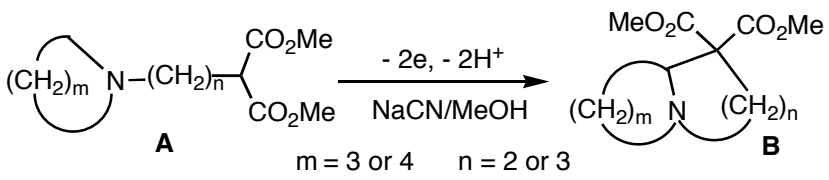
Abstract – Several hydroquinolyl, hydroisoquinolyl, and indolinyl alcohols were electrochemically oxidized in methanol in the presence of sodium methoxide and potassium iodide. The hydroquinolyl and hydroisoquinolyl alcohols afforded the corresponding intramolecular cyclization products through the bond formation between the α-carbon of the nitrogen atom and the oxygen atom of the hydroxy group. In contrast, the indolinyl alcohols underwent dehydrogenation to give the corresponding indolyl alcohols. Presumably, in all cases, the electrooxidation involves a two-electron oxidation process.

INTRODUCTION

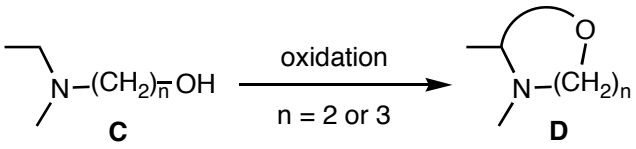
In our most recent study, we reported the electrochemical cyclization of dimethyl aminomalonates **A** to afford the corresponding heterobicyclic compounds **B**, as illustrated in Scheme 1.[1, 2]



Scheme 1 Electrochemical cyclization of dimethyl aminomalonates

In a basic media, the α-carbon of the nitrogen atom of **A** is subjected to a nucleophilic attack by the

carbanion of the dimethyl malonate moiety to give **B**. Moreover, the electrooxidative cyanation of tertiary aliphatic amines, in which the reaction mechanism is similar to that of Scheme 1, was previously reported.[3] The beginning of this study, we reasoned that the oxygen atom of the intramolecular hydroxy group of tertiary amine **C** would initiate a similar nucleophilic attack to form the corresponding cyclization product **D**, as illustrated in Scheme 2.



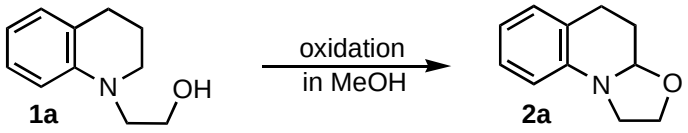
Scheme 2 Electrochemical cyclization of amino alcohols

Due to the simple synthetic procedures, and because the corresponding products (cyclic *N, O*-acetal) are presumably stable against methanolysis and hydrolysis, hydroquinolyl alcohol (**1**), hydroisoquinolyl alcohol (**3**), and indolinyl alcohol (**5**) were chosen as the starting substrates. As expected, **1** and **3** afforded heterocyclic **2** and **4**, respectively, through the formation of an intramoleclar carbon-oxygen bond (Table 2). Schneider and co-worker first reported the formation of **4a** using 3,4-dihydroquinoline as the starting substrate.[4] The conversion of **4a** into several derivatives were investigated.[5] Lohray and co-workers were able to obtain **2a** in a yield of 56% by reduction of the amide esters.[6] On the other hand, Shono and co-workers reported the cyclization of carbamates that employ similar electrochemical techniques.[7] To the best of our knowledge, however, the systematic electrochemical preparation of this class of compounds using **1**, **3**, or **5** as the starting substrate has yet to be reported.

RESULTS AND DISCUSSION

To determine the optimal reaction conditions, the electrooxidation reaction of a model substrate, hydroquinolyl ethanol (**1a**), to yield the corresponding fused-ring heterocyclic compound (**2a**), was examined. The reactions were carried in the presence of various supporting electrolytes, as listed in Table 1. The presence of basic electrolytes, such as NaOAc, NaCN, NaOH, and NaOMe (Runs 1-4) afforded **2a** in yields of 25 to 80%. In contrast, the use of neutral electrolytes, such as $LiClO_4$, tetraethylammonium *p*-toluenesulfonate, KBr, and KI (Runs 5-8) gave **2a** in poor yields; in these cases, the purification procedures resulted in the recovery of unreacted **1a** and/or the deposit of considerable amounts of dark brownish material on the silica gel column (see general procedure section). It is noteworthy that, although the presence of NaOMe or KI afforded **2a** with yields of 80 and 23% (Runs 4 and 8, respectively), the concurrent use of both electrolytes resulted in an improved yield of 93% (Run 9) – in contrast, the concurrent use of KBr or KCl did not exhibit such improvements.

Table 1 Influence of supporting electrolytes[a]



Runs	Supporting Electrolyte	(mmol)	Recovery of **1a**	Yield (%)[b] of **2a**
1	NaOAc	10	37	25
2	NaCN	10	14	50
3	NaOH	10	4	70
4	NaOMe	10	17	80
5	$LiClO_4$	10	59	1
6	*p*-TsON(Et)$_4$	8	15	2
7	KBr	10	23	7
8	KI	10	22	23
9	KI + NaOMe	5 + 5	4	93

[a]Reaction conditions: **1a** (5 mmol), MeOH (40 mL), current passed (2.0 F/mol), constant current (0.3 A), temperature (ca. 15 ˚C).

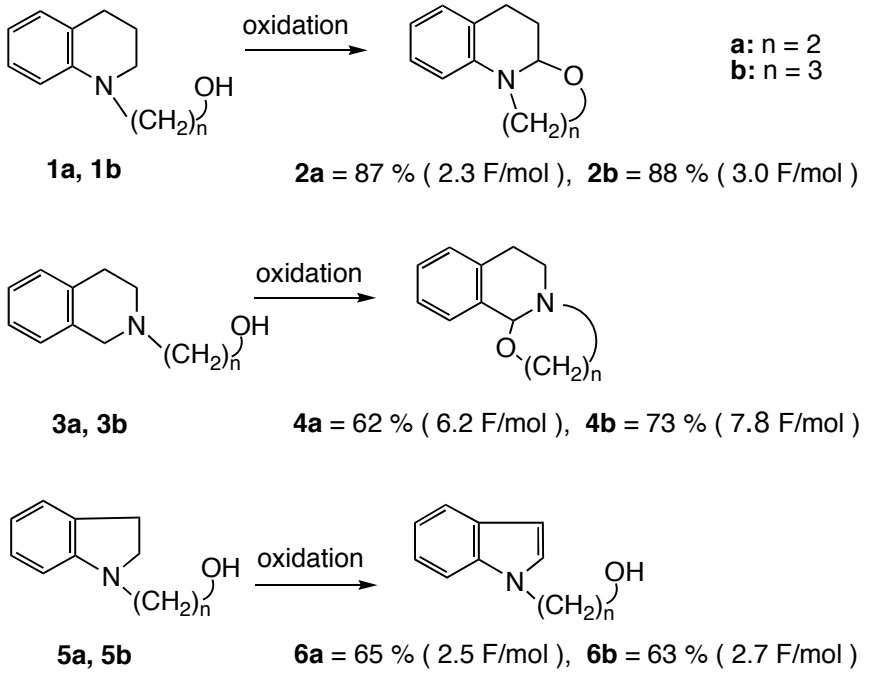
[b]Recovery of **1a** and yields of **2a** were determined by GC analysis.

Our studies showed that the amount of KI, over a range of 2 to 10 mmol, did not affect the yield of **2a** (90 and 91%, respectively), whereas an excessive amount of NaOMe (20 vs. 5 mmol) decreased the yield of **2a** (73 vs. 93%, respectively). Because halide ion sources such as KBr (Run 7) and KI (Run 8), which can act as electron carriers (indirect oxidation), did not affect the yield of the product, it can be assumed that the electrooxidation proceeds via direct electron transfer from the substrate to the anode.

Preliminary electrooxidations revealed that the formation of **2a** was in proportion almost quantitatively to the current passed (24%, 0.5 F/mol; 49%, 1.0 F/mol; 93%, 2.0 F/mol). The maximum yield of 96% was obtained after passage of 2.3 F/mol (reaction time, 62 min; current efficiency, 83%), at which point, the

majority of **1a** was consumed. Subsequently, using the optimal reaction conditions as described above, the electrooxidation reactions were carried out using hydroquinolyl alcohol (**1b**), hydroisoquinolyl alcohols (**3a** and **3b**), and indolinyl alcohols (**5a** and **5b**), as shown in Table 2.

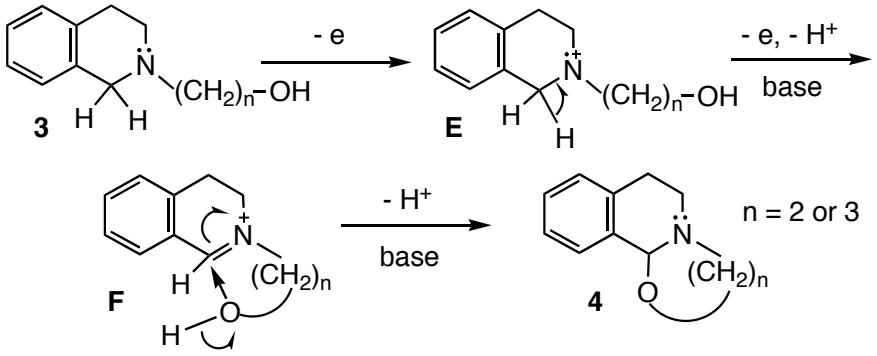
Table 2 Electrooxidation of tetrahydroquinolyl alcohols, tetrahydroisoquinolyl alcohols, and indolinyl alcohols[a]



[a]Reaction conditions: substrate (5 mmol), NaOMe (5 mmol), KI (5 mmol), MeOH (40 mL), constant current (0.3 A), temperature (ca. 15 ˚C). Isolated yields are shown.

The substrates required significantly different amounts of electrical current – for example, substrates (**1a** and **1b**) required electric currents of 2.3 and 3.0 F/mol, respectively, to form the corresponding heterocyclic products in good yields (**2a**, 87% and **2b**, 88%, respectively), whereas substrates (**3a** and **3b**) required currents of 6.2 and 7.8 F/mol, respectively, to form the products in moderate yields (**4a**, 62% and **4b**, 73%, respectively). In the cases of **3a** and **3b**, the oxygen atom on the hydroxy group carried out the nucleophilic attack only on the benzylic carbon, presumably due to the stable molecular structure of the radical and/or cationic intermediate which forms conjugate system (Scheme 3). The products were obtained as a slightly yellow viscous oily liquid; in the cases of **2b** and **4a**, the viscous oil solidified upon

storage in a refrigerator for several days. Under similar reaction conditions, the electrooxidation of indolinyl alcohols (**5a** and **5b**) resulted in the dehydrogenation products (**6a**, 65% and **6b**, 63%, respectively) instead of the expected cyclized products. Apparently, the electrooxidation of **5** favor aromatization over cyclization to afford the corresponding indolyl alcohol (**6**).[8] As a note, purification of **6a** and **6b** by distillation resulted in considerable amounts of tar-like material that remained in the distilling flask. Although details of the reaction mechanism remain unclear, a reasonable reaction pathway (as shown in Scheme 3) describes the cyclization of tetrahydroisoquinoline (**3**) to **4** as: 1) the loss of one electron from the lone electron pair of the nitrogen of substrate (**3**) to the anode to form cationic radical **E**, 2) the further one-electron oxidation and deprotonation to form immonium ion **F**, then 3) the subsequent nucleophilic attack by the oxygen of the hydroxy group. Essentially, substrate **3** loses two protons and two electrons during the course of the reaction. During these steps, NaOMe would serve as the base in facilitating the deprotonation of both cation radical **E** and the hydroxy group of **F**.



Scheme 3 Proposed scheme of the oxidative cyclization

In conclusion, our studies have demonstrated the electrooxidation of hydroquinolyl alcohols, hydroisoquinolyl alcohols, and indolinyl alcohols toward the synthesis of several heterocyclic compounds. Although the yields depend upon the structure of the substrate, our methodology is advantageous due to: 1) the absence of oxidants and/or special reagents, 2) the mild reaction conditions, 3) the availability of the substrates, and 4) the simple, one-pot procedure. Further investigations using substrates having various carbon chain lengths of the alcohol moiety and /or substituted aromatic moiety are currently underway in our laboratories.

EXPERIMENTAL

Preparative-scale electrooxidations were carried out in a tall 50-mL beaker equipped with a fine frit cup (porosity, *ca.* 100 μm) as the cathode compartment with nickel or stainless steel coil (diameter, 0.8 mm;

length, 250 mm) as the cathode, and an insert cylindrical platinum net (diameter, 32 mm; height, 35 mm; 55 mesh) as the anode. Electrooxidations of the substrates (**1**, **3**, or **5**) (5 mmol) were carried in a solution of powdered KI (0.83 g, 5 mmol) in MeOH (40 mL) containing NaOMe (5 mmol) under a constant current (0.3 A). During the course of the electrooxidation, the anolyte was magnetically stirred and the temperature of the cell was maintained at approximately 15 ˚C. Upon passage of electricity, the reaction mixture was concentrated *in vacuo* at approximately 40 ˚C to remove most of the methanol. The residue was treated with water (*ca*. 15 mL), and the resulting oily layer was extracted with diethyl ether (4 x 60 mL), which were combined, and dried over magnesium sulfate. Following the removal of the solvent, the product was isolated by silica gel column chromatography (diameter, 20 mm; length, 400 mm; diethyl ether as the elution solvent) or by distillation under reduced pressure.

2a bp 108–110 ˚C /2 mmHg. IR (neat) : 2939, 2864, 1605, 1504, 1460, 1346, 1312, 1061, 1053, 1001, 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ =1.4–1.9 (m, 1H), 2.1–2.4 (m, 1H), 2.6–2.9 (m, 2H), 3.2–3.6 (m, 2H), 3.8–4.3 (m, 2H), 4.7–4.9 (m, 1H), 6.4–6.8 (m, 2H, Arom), 6.9–7.3 (m, 2H, Arom). ^{13}C NMR ($CDCl_3$): δ =24.76 (CH_2), 26.18 (CH_2), 47.36 (CH_2), 65.68 (CH_2), 87.96 (CH), 111.90 (CH), 116.99 (CH), 122.33 (C), 127.37 (CH), 128.07 (CH), 143.87 (C). MS m/z (%) : 175 (M^+, 87), 174 (100), 145 (26), 144 (25), 132 (21), 130 (17), 118 (14), 117 (27), 91 (18), 77 (13). HRMS m/z found : 175.0993 (M^+), calcd. for $C_{11}H_{13}NO$: 175.0997.

2b bp 110–112 ˚C /1.5 mmHg. mp 39~41˚C (recrystallized from EtOH). IR (neat) : 2953, 2845, 1603, 1495, 1458, 1315, 1263, 1171, 1076, 1061, 748 cm^{-1}. ^1H NMR ($CDCl_3$) : δ =1.2–1.5 (m, 1H), 1.7–2.1 (m, 3H), 2.4–3.4 (m, 3H), 3.7–4.3 (m, 3H), 4.6–4.8 (m, 1H), 6.4–6.8 (m, 2H, Arom), 6.9–7.3 (m, 2H, Arom). ^{13}C NMR ($CDCl_3$) : δ = 23.67 (CH_2), 24.43 (CH_2), 28.38 (CH_2), 46.91 (CH_2), 67.84 (CH_2), 85.96 (CH), 112.84 (CH), 118.13 (CH), 125.62 (C), 127.09 (CH), 128.68 (CH), 143.91 (C). MS m/z (%) : 189 (M^+, 100), 188 (50), 170 (13), 158 (26), 146 (29), 132 (36), 131 (72), 130 (52), 91 (13), 77 (11). HRMS m/z found : 189.1179 (M^+), calcd. for $C_{12}H_{15}NO$: 189.1154.

4a mp 50~52˚C (recrystallized from EtOH). IR (neat) : 1464, 1394, 1290, 1078, 1057, 1016, 991, 889, 777, 746 cm^{-1}. ^1H NMR ($CDCl_3$) : δ = 2.5–4.0 (m, 8H), 5.19 (s, 1H), 6.8–7.5 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ = 29.73 (CH_2), 45.65 (CH_2), 54.73 (CH_2), 62.18 (CH_2), 90.40 (CH), 126.28 (CH), 128.07 (CH), 128.23 (CH), 128.84 (CH), 132.14 (C), 134.95 (C). MS m/z (%) : 175 (M^+, 69), 174 (100), 145 (53), 130 (25), 117 (53), 115 (26), 103 (15), 91 (21), 77 (17), 56 (16). HRMS m/z found : 175.0973 (M^+), calcd. for $C_{11}H_{13}NO$: 175.0997.

4b bp 114–116 ˚C /1.5 mmHg. IR (neat) : 2947, 2839, 1464, 1393, 1371, 1294, 1142, 1086, 964, 885, 745 cm^{-1}. ^1H NMR ($CDCl_3$) : δ = 1.2–1.5 (m, 1H), 1.8–3.4 (m, 7H), 3.7–4.3 (m, 2H), 4.87 (s, 1H), 7.0–7.4 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ = 22.97 (CH_2), 29.08 (CH_2), 46.22 (CH_2), 53.22 (CH_2), 68.33 (CH_2), 89.95 (CH), 125.95 (CH), 127.29 (CH), 127.78 (CH), 128.31 (CH), 132.20 (C), 134.83 (C). MS m/z (%) : 189 (M^+, 38), 188 (77), 158 (37), 146 (100), 145 (31), 133 (46), 132 (66), 131 (42), 130 (35), 104 (79). HRMS m/z found : 189.1174 (M^+), calcd. for $C_{12}H_{15}NO$: 189.1154.

6a bp 141–142 ˚C /2.5 mmHg. IR (neat) : 3380, 1510, 1481, 1464, 1362, 1337, 1315, 1063, 764, 743 cm^{-1}. ^1H NMR ($CDCl_3$) : δ = 1.94 (bs, 1H), 3.69 (t, *J* = 7Hz, 2H), 4.07 (t, *J* = 7Hz, 2H), 6.4–6.5 (m, 1H), 6.9–7.3 (m, 4H), 7.5–7.7 (m, 1H). ^{13}C NMR ($CDCl_3$) : δ = 48.54 (CH_2), 61.61 (CH_2), 101.31 (CH), 109.34 (CH), 119.51 (CH), 120.98 (CH), 121.59 (CH), 128.35 (CH), 128.68 (C), 136.09 (C). MS m/z (%) : 161 (M^+, 38), 131 (10), 130 (100), 103 (7), 77 (8). HRMS m/z found : 161.0841 (M^+), calcd. for $C_{10}H_{11}NO$: 161.0841.

6b bp 148–150 ˚C /2 mmHg. IR (neat): 3380, 2941, 1510, 1485, 1464, 1337, 1315, 1065, 1015, 743 cm^{-1}. ^1H NMR ($CDCl_3$) : δ =1.87 (quint, *J* = 7Hz, 2H), 2.7 (bs, 1H), 3.38 (t, *J* = 7Hz, 2H), 4.09 (t, *J* = 7Hz, 2H), 6.6–6.7 (m, 1H), 7.1–7.6 (m, 4H), 7.8–7.9 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 32.58 (CH_2), 42.51 (CH_2), 59.29 (CH_2), 101.07 (CH), 109.34 (CH), 119.23 (CH), 120.90 (CH), 121.39 (CH), 127.90 (CH), 128.56 (C), 135.97 (C). MS m/z (%) : 175 (M^+, 45), 131 (36), 130 (100), 117 (7), 103 (7), 89 (7), 77 (8). HRMS m/z found : 175.0993 (M^+), calcd. for $C_{11}H_{13}NO$: 175.0997.

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