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NOVEL APPLICATION OF AN ELECTROOXIDATIVE METHOD FOR THE FORMATION OF A TETRAHYDROFURAN RING FROM 5-HYDROXY-2-PENTANONE PHENYLHYDRAZONE

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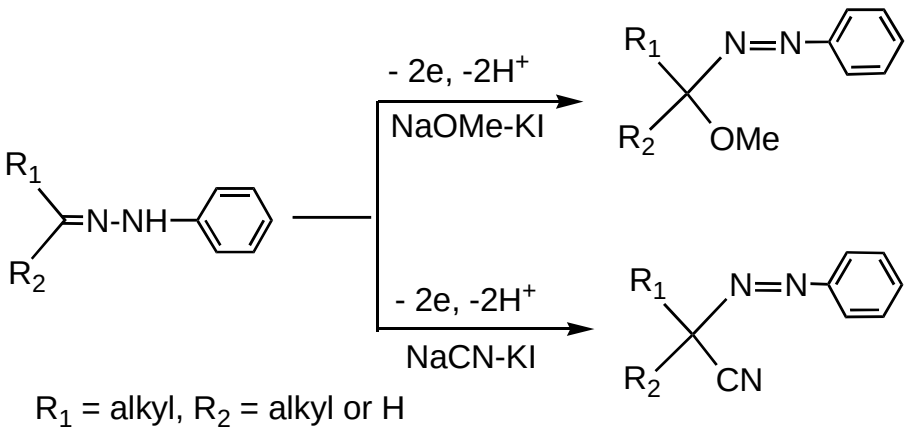
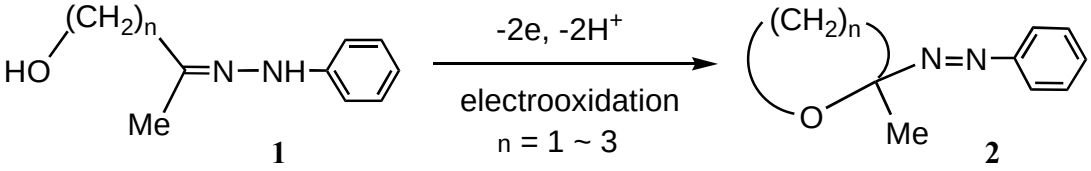
Abstract - Various ketone phenylhydrazones that possess a hydroxy group on the parent ketone moiety were subjected to electrooxidation in methanol in the presence of KI and NaOMe. In the case of 4-hydroxy-2-butanone phenylhydrazone, the nucleophilic attack of the azomethine carbon by a methoxide ion affording the corresponding methoxy(phenylazo)alcohol was dominant. Interestingly, however, in the case of 5-hydroxy-2-pentanone phenylhydrazone, similar reaction conditions favored the intramolecular cyclization to afford a (phenylazo)tetrahydrofuran derivative.

Our investigations towards novel synthetic methodologies have involved the electrooxidations of various aldehyde and ketone hydrazones, which afford the corresponding oxidized products that relatively difficult to prepare using typical methods.[1] Our recent focus on hydrazone derivatives have resulted in the successful electrooxidation of several ketone phenylhydrazones. As shown in Scheme 1, using a methanol solution containing NaOMe and KI, the reaction afforded the corresponding methoxy(phenylazo)alkanes.[2] Using NaCN instead of NaOMe as an electrolyte,[3] the electrooxidation afforded the corresponding cyano(phenylazo)alkanes. In both cases of the electrooxidations, the azomethine carbon of the phenylhydrazones underwent nucleophilic attack by the anionic methoxide or cyanide ions. Based on these results, we reasoned that the electrooxidation of hydroxyketone phenylhydrazone (**1**) may undergo intramolecular cyclization between the azomethine carbon atom and the oxygen atom, as illustrated in Scheme 2, to afford the corresponding heterocyclic compound (**2**).

First, to investigate the starting substrate, we carried out the electrooxidations of hydroxyketone



Scheme 1 Methoxylation and cyanation of ketone phenylhydrazones

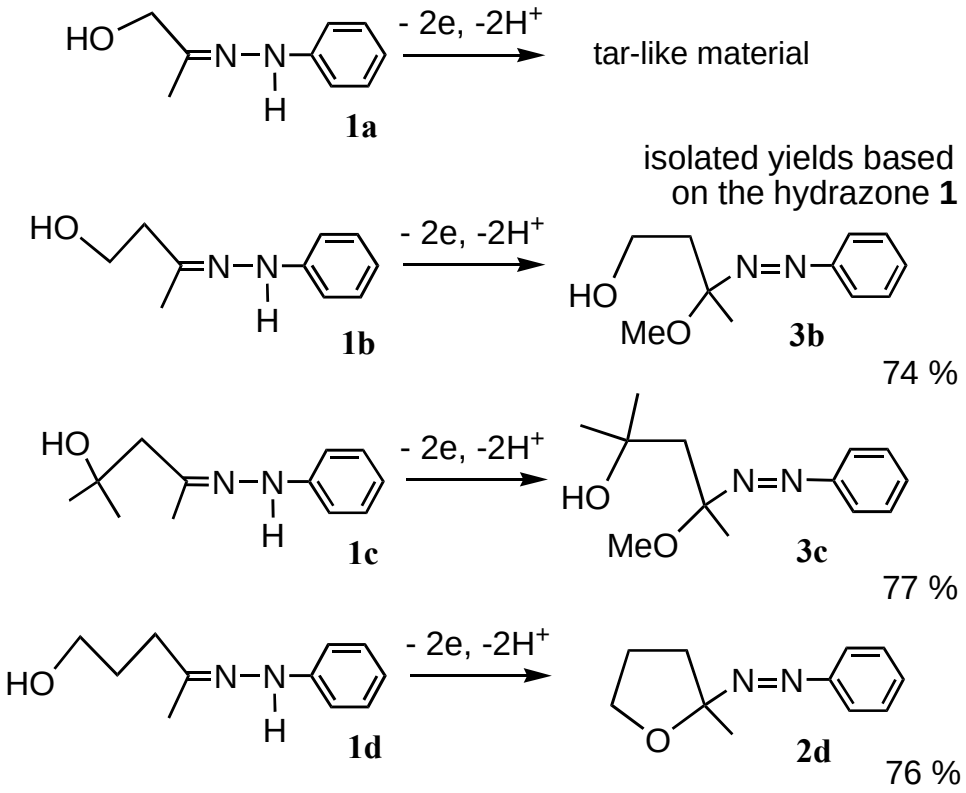


1 **2**

Scheme 2 Intramolecular cyclization of hydroxyketone phenylhydrazones

phenylhydrazones (**1a** ~ **1d**) (Scheme 3), which were derived from the corresponding commercially available hydroxyketones. In the case of 5-hydroxy-2-pentanone phenylhydrazone (**1d**), the electrooxidation proceeded smoothly to afford the corresponding heterocyclic compound (**2d)** (76% yield),[4] without any formation of the methoxylation product. In contrast, however, the electrooxidation of 4-hydroxy-2-butanone phenylhydrazone (**1b**) and 4-hydroxy-4-methyl-2-pentanone phenylhydrazone (**1c**) afforded the corresponding methoxylated compounds (**3b)** (74%) and (**3c)** (77%), without any formation of the corresponding four-membered cyclic products (**2b)** and (**2c)**. In the case of hydroxyacetone phenylhydrazone (**1a**), although the substrate was nearly completely consumed by passing 2.5 $Fmol^{-1}$ of electricity, the principal product was not observed. Gas chromatography analysis (SE-30, 1.5 m) of the reaction mixture revealed a mixture of at least six by-products, all with shorter retention time than that of substrate **1a**. Even after ether extraction, followed by concentration resulting in a viscous dark brown tar-like material, the identity of the by-products remained difficult to identify. The differences among the reactions using substrates **1b** ~ **1d** can be attributed to the dissimilar amount of strain between the four- and five-membered ring structures. In the cases of **1b** and **1c**, the methoxylation reaction was favored over the formation of the four-membered ring.

Next, the effects of the supporting electrolytes were investigated using substrate **1d**. As listed in Table 1,

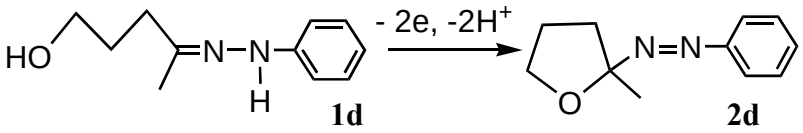


Scheme 3 Electrooxidation of hydroxyketone phenylhydrazones

the combination of KI and NaOMe as the supporting electrolytes (Runs 1) resulted the formation of **2d** with a yield of 84%. Increasing the amounts of KI and NaOMe (Run 2) did not improve the yield of **2d**. In contrast, the use of either KI (Run 3) or NaOMe (Run 4) alone resulted in lower yields of **2d**. Lower yields of **2d** were also observed when using KBr (Run 5) or KCl (Run 6) instead of KI. Furthermore, neutral salts such as *p*-TsON(Et)$_4$ (Run 7) and $LiClO_4$ (Run 8) gave poor yields, in which most of the substrate remained unreacted. Because the presence of catalytic amounts of KI dramatically increases the yield of **2d**, there is no doubt that the iodide ion plays an important role in the electron transfer during the electrooxidation.[5] As illustrated in Scheme 4, first, the nitrogen atom adjacent to the phenyl group of the hydrazone is attacked by an iodonium ion, (I^+) which is produced through a two-electron oxidation of an iodide ion (I^-) on the anode, to form iodide intermediates (**1b'**) and (**1d'**). Following the loss of the iodide ion, the azomethine carbon is attacked by either 1) a methoxide ion to form methoxylated compounds **3b**, **3c** (n=2) or 2) the intramolecular oxygen atom of the hydroxy group to form tetrahydrofuran derivative **2d** (n=3). In the cases of Runs 1~3, the electron transfer is carried out exclusively by the iodide ions, whereas, in the absence of iodide ions (Runs 4~8), the electron transfer occurs directly between the substrate and the anode, albeit with low efficiencies. Overall, the oxidation process involves two deprotonations and the loss of two electrons.

In conclusion, our electrochemical technique was successfully applied towards the oxidative formation of a tetrahydrofuran derivative **2d** and methoxylated novel compounds **3b** and **3c**. This electrooxidative

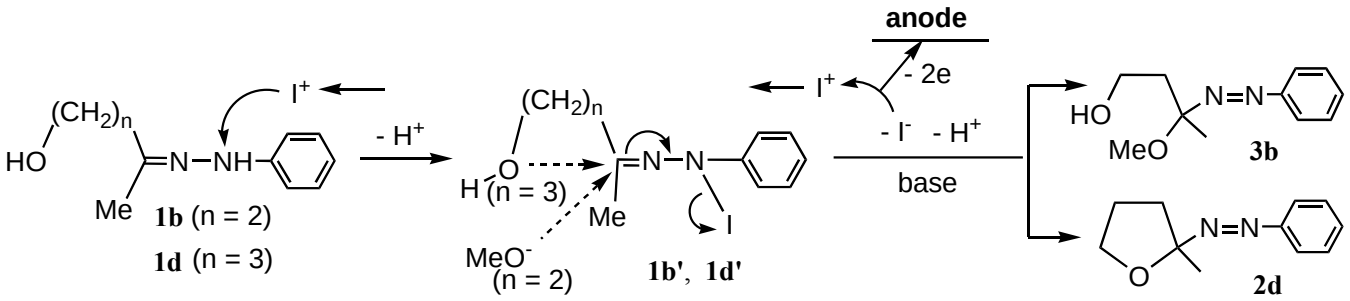
Table 1 Tetrahydrofuran ring formation via electrooxidation of hydroxyketone phenylhydrazone **1d**[a]



1d **2d**

Run	Supporting Electrolytes	(mmol)	Yield of **2d** (%)[b]
1	NaOMe (2)	KI (5)	84
2	NaOMe (5)	KI (10)	82
3	None	KI (5)	59
4	NaOMe (2)	None	33
5	NaOMe (2)	KBr (5)	42
6	NaOMe (2)	KCl (5)	20
7	*p*-TsON(Et)$_4$ (10)	None	13
8	$LiClO_4$ (10)	None	14

[a]Substrate **1d** (10 mmol), MeOH (40 mL), Constant current (0.3 A), Current passed (2.5 $Fmol^{-1}$).
[b]Yields were determined using GC (SE-30, 1.5 m) analysis.



Scheme 4 Proposed reaction pathway of the electrooxidation

ring-formation can be carried out at room temperature, and in the absence of any harsh oxidants and/or special reagents. Further investigations using a similar class of substrates are currently underway to expand our synthetic methodology to afford six-, seven-, and eight-membered cyclic ether phenylazo compounds.[6]

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6. EXPERIMENTAL: Hydroxyketone phenylhydrazone **1** were prepared via typical condensation reaction by refluxing the hydroxyketone with slightly excess molar amounts (1.1-1.2 molar equivalent to hydroxyketone used) of phenylhydrazine in EtOH.[7] Preparative-scale electrooxidations were carried out in a tall 50-mL beaker equipped with a fine frit cup (as the cathode compartment) and a nickel coil (as the cathode), and a cylindrical platinum net (55 mesh) (as the anode). Electrooxidations of the substrates were carried out as follow: a solution of the substrate (**1a**-**1d**, 10 mmol) and KI (0.83 g, 5 mmol) in absolute MeOH (40 mL) containing NaOMe (2 mmol) 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 *ca*. 15 °C. Upon nearly complete consumption of the substrate (*ca*. 2.5 $Fmol^{-1}$, 134 min), the DC power supply was switched off, and the reaction mixture was concentrated *in vacuo* to about 10 mL at approximately 50 °C. The residue was subsequently extracted with Et_2O (3 × 30 mL). The ether extracts were combined, and dried over anhydrous magnesium sulfate. After the removal of the solvent, the residue was purified by silica gel column chromatography using mixture of Et_2O and *n*-hexane (1:1 ~1:2) as the elution solvent.

   2-Methyl-2-phenylazotetrahydrofuran **2d**

   orange, oily liquid. Silica gel TLC (Et_2O : *n*-hexane = 1 : 1) *Rf* = 0.64.

   IR (neat): 2981, 2880, 1454, 1190, 1125, 1028, 765, 691 cm^{-1}. ^1H NMR (CD_3OD): δ =1.51 (s, 3H, CH_3), 1.71-1.88 (m, 1H, 1/2CH_2), 1.94-2.08 (m, 2H, CH_2), 2.29-2.39 (m, H, 1/2CH_2), 4.01-4.10 (m, 2H, CH_2), 7.42-7.52 (m, 3H, Arom), 7.65-7.73 (m, 2H, Arom). ^{13}C NMR (CD_3OD): δ =23.31 (CH_3), 25.60 (CH_2), 36.31(CH_2), 69.80 (CH_2), 106.71 (C), 123.31 (CH), 130.19 (CH), 132.02 (CH), 153.12 (C). MS (EI): m/z (%)= 85 ($[M-PhN_2]^+$, 88), 77 (17), 51 (9), 43 (100), 39 (3). HRMS: m/z calcd

for C_5H_9O: 85.0653; found: 85.0682 $(M\text{-}PhN_2)^+$. MS (CI): m/z= 191 $(M+1)^+$.

3-Methoxy-3-phenylazobutanol **3b**

burgundy red, viscous oily liquid. Silica gel TLC (Et_2O : *n*-hexane = 1 : 1) *Rf* = 0.20.

IR (neat): 3412 (OH), 2939, 1454, 1182, 1116, 1071, 1019, 767, 691 cm^{-1}. ^1H NMR (CD_3CN): δ =1.37 (s, 3H, CH_3), 1.86-2.01 (m, 2H, CH_2), 2.70 (bs, 1H, OH), 3.45 (s, 3H, OCH_3), 3.56-3.71 (m, 2H, CH_2), 7.47-7.56 (m, 3H, Arom), 7.64-7.72 (m, 2H, Arom). ^{13}C NMR (CD_3OD): δ =21.10 (CH_3), 41.35 (CH_2), 51.09 (OCH_3), 58.49 (CH_2), 100.40 (C), 123.28 (CH), 130.26 (CH), 132.21 (CH), 153.21 (C). MS (EI): m/z (%)=103 ($[M\text{-}PhN_2]^+$, 100), 85 (25), 77 (26), 73 (35), 43 (12). HRMS: m/z calcd for $C_5H_{11}O_2$: 103.0759; found: 103.0770 $(M\text{-}PhN_2)^+$. MS (CI): m/z= 209 $(M+1)^+$.

4-Methoxy-4-phenylazo-2-methylpentan-2-ol **3c**

burgundy red, viscous oily liquid. Silica gel TLC (Et_2O : *n*-hexane = 1 : 1) *Rf* = 0.42.

IR (neat): 3517 (OH), 2973, 1455, 1362, 1207, 1148, 1054, 766, 691 cm^{-1}. ^1H NMR (CD_3CN): δ =0.99 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.96-2.10 (m, 2H, CH_2), 3.58 (s, 3H, OCH_3), 4.87 (s, 1H, OH), 7.47-7.57 (m, 3H, Arom), 7.65-7.72 (m, 2H, Arom). ^{13}C NMR (CD_3OD): δ =22.48 (CH_3), 31.15 (CH_3), 31.62 (CH_3), 51.10 (OCH_3), 52.70 (CH_2), 71.80 (C), 102.57 (C), 123.31 (CH), 130.29 (CH), 132.24 (CH), 153.11 (C). MS (EI): m/z (%)=131 ($[M\text{-}PhN_2]^+$, 16), 77 (17), 73 (100), 59 (59), 43 (21). HRMS: m/z calcd for $C_7H_{15}O_2$: 131.1072; found: 131.1091 $(M\text{-}PhN_2)^+$. MS (CI): m/z= 237 $(M+1)^+$.

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