ANODIC RING-OPENING REACTION OF 4-PHENYL-*2H*-PHTHALAZIN-1-ONE INTO METHYL *o*-(α-METHOXY AND α-CYANO) BENZYL-SUBSTITUTED BENZOATES

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Abstract: Heteroaromatic compound, 4-phenyl-*2H*-phthalazin-1-one that is easily prepared by condensation reaction of equimolar amount of methyl *o*-benzoyl benzoate and hydrazine hydrate was subjected to electrooxidation to undergo ring-opening reaction in MeOH containing NaOMe or NaCN as the supporting electrolyte. Some of the methoxylated and cyanated products obtained in this electrooxidation are novel compounds.

Keywords: anodic oxidation, ring-opening reaction, heteroaromatic compound, acetal, nitrile.

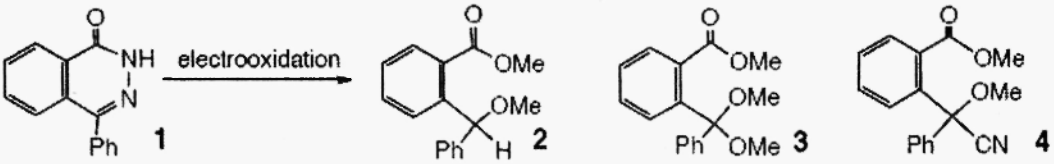
Introduction

Despite the widespread use of hydrazones as mediators in organic synthesis, the frequent use of Ag_2O (1, 2) or HgO (3,4) as oxidants in the oxidation of hydrazones remains expensive and/or produces environmentally harmful wastes. An inexpensive and environmentally-friendly alternative involves the electrochemical oxidation of nitrogenous organic compounds such as hydrazones (5-8). Herein, we describe the electrooxidative ring-opening reaction of 4-phenyl-*2H*-phthalazin-1-one **1** in MeOH to afford the corresponding methoxy compounds **2**, **3** and cyano compound **4**, as shown in Table 1. Although various reports on the chemistry of heterocyclic compound **1** have been described (9-11), the electrooxidation of **1** into the corresponding oxidized products has yet to be reported, to the best of our knowledge.

Results and Discussion

The relationship between the supporting electrolytes and the yields of the products is shown in Table 1. The use of three equivalents of NaOMe (relative to the substrate) afforded methyl ether **2** (12) with a favorable yield of 50% (Run 2). In the case of NaCN, cyano methoxy compound **4** was formed in 35% yield (Run 4). Interestingly, although the addition of 20 mmol of AcOH was somewhat favorable for the formation of **4** (Run 5), an excess amount of AcOH (30 mmol) resulted in the exclusive formation of dimethylacetal **3** (Run 6, 51 %). As a note, the electrooxidation could be carried out without any ventilation, because HCN formed due to the reaction of AcOH and NaCN sufficiently dissolve in the MeOH solution. Moreover, a separate electrooxidation of isolated **2** in MeOH in the presence of NaOMe or NaCN did not give **3** and **4**, respectively, and therefore, for this reaction system, the formation of **2**, **3** and **4** should proceed in parallel. In all cases, at the beginning of the reaction, the substrate was not completely dissolved in the MeOH solution, and required agitation of the anolyte during the course of the electrooxidation process. With the exception of Run 8, in which most of the substrate remained unreacted, the substrate gradually dissolved upon passage of the electric current to result in a brownish pellucid liquid at the end point of the electrolysis. Although details of the electrooxidation process remain unclear, a reasonable reaction pathway for the formation of the ring-opening compounds **2**, **3** and **4** can be described as follow (as shown in Scheme 1): first, substrate **1** would lose one electron from the lone electron pair on the nitrogen atom adjacent to carbonyl group to the anode, followed by deprotonation to form radical **A**. The radical A would immediately undergo further one-electron oxidation and methoxylation to give methoxy azo ketone **B** as an intermediate. Subsequently the intermediate **B** would undergo nucleophilic attack by methoxide ion involving elimination of nitrogen to form corresponding anion **C**. Methyl ether obtained **2** is considered as protonated product of the anion **C**. On the other hand, further two-electron oxidation of **C** would produce cation

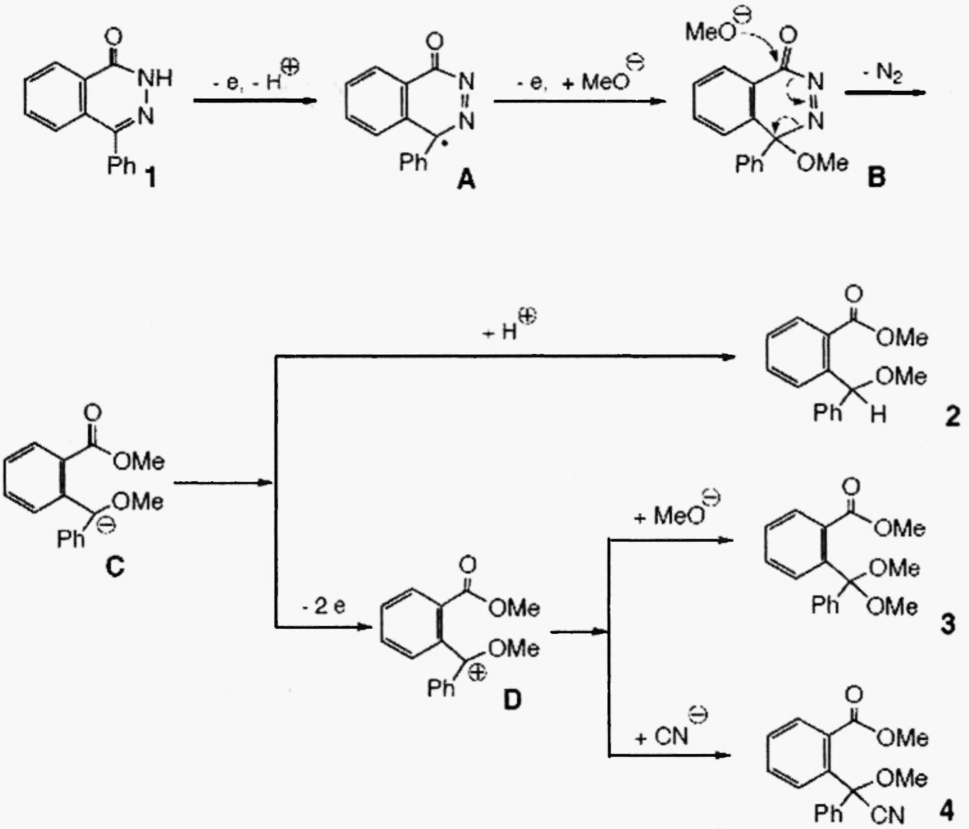
Table 1 Effects of supporting electrolytes on the anodic ring-opening reaction of 4-phenyl-*2H*-phthalazin-1-one [a]



Run	Supporting electrolyte (mmol)	Yield of product (%)[b]		
		2	3	4
1	NaOMe (10)	43	21	-
2	NaOMe (30)	50	21	-
3	NaOMe (40)	31	42	-
4	NaCN (40)	15	20	35
5	NaCN (40), AcOH (20)	3	32	37
6	NaCN (40), AcOH (30)	3	51	2
7	NaOAc (10)	13	39	-
8	NaOMe (10), KI[c] (5)	4	7	-

[a] Substrate 1, 10 mmol; MeOH, 40 mL; Constant current, 0.3 A; Current passed, 5.2 F mol^{-1}; Reaction temperature,*ca.*15°C. b) Determined by GC analysis. c) Iodide ion often plays as an useful electron carrier (7).

D that can react with methoxide or cyan ion to produce **3** or **4**, respectively, as the final products. Essentially, substrate **1** loses four electrons during the course of the reaction for the formation of **3** or **4**. In conclusion, our electrochemical technique was utilized for the oxidative ring-opening reaction of **1** to afford **2** along with novel compounds **3** and **4**. This electrooxidative ring-opening reaction can be carried out at room temperature, and in the absence of any oxidants and/or special reagents. Further investigations on the reaction conditions are currently underway to improve the selectivity of the reaction and the yield of the products.



Scheme 1 Proposed reaction pathway for the oxidative ring-opening reaction of 4-phenyl-*2H*-phthalazin-1-one

Experimental

IR spectra were recorded using a Shimadzu FT-IR 8200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Jeol JNM-EX 90A spectrometer, with TMS as the internal standard, and in $CDCl_3$ as the solvent. EI- and CI-MS spectra were obtained on a Jeol JMS-SX 102A spectrometer. GC analysis were carried out on a Shimadzu GC-8A gas chromatograph using a 2.0 m glass column packed with 10% FFAP on Uniport B. N_2 served as the carrier gas.

General procedures : 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 and a nickel coil cathode (diameter: 0.8 mm, length: 300 mm), and a cylindrical platinum net anode (diameter: 32 mm, height: 35 mm, 55 mesh). A solution of the substrate (**1**, 2.22 g, 10 mmol) in MeOH (40 mL) containing NaOMe or NaCN-AcOH (see Table 1) was electrooxidized under a constant current (0.3 A). During the course of the electrooxidation, the anolyte was magnetically stirred at *ca.* 15 °C. Upon passage of the electrolytic current (5.2 F mol-1, *ca.* 280 min), the reaction mixture was concentrated *in vacuo* (*ca.* 10 mL) at approximately 50°C. The resulting oily residue was treated with water (*ca.* 20 mL) , then extracted with ether (3×30 mL) , and dried over magnesium sulfate. After removal of the solvent *in vacuo* the desired compounds were isolated by silica gel column chromatography (diameter: 30 mm, lenght: 600 mm) using ether/*n*-hexane (1 : 2) as the elution solvent.

Methyl 2-(α,α-dimethoxy)benzyl benzoate 3

Colorless viscous oily liquid. Silica gel TLC (ether : *n*-hexane = 1 : 2) Rf = 0.51. IR (neat): 2944, 1732, 1108, 1058, 772, 702 cm^{-1}. ^1H NMR ($CDCl_3$): δ =3.08(s, 6H, 2×OCH_3), 3.78(s, 3H, $COOCH_3$), 7.2-7.7(m, 9H, Arom). ^{13}C NMR ($CDCl_3$): δ = 49.48(CH_3), 51.88(CH_3), 102.94(C), 127.13(CH), 127.25(CH), 127.46(CH), 127.66(CH), 127.78(CH), 128.84(CH), 129.25(CH), 133.20(C), 139.10(C), 141.46(C), 171.35(CO). MS(EI) m/z (%): 255(100) [M^+-OMe], 209(30), 163(21), 151(29), 105(31), 77(35). MS(CI) m/z: 287(M^++1). HRMS: m/z calcd for C16H15O3: 255.1021; found: 255.0992 [M^+-OMe].

Methyl 2-(α-cyano-α-methoxy)benzyl benzoate 4

Colorless viscous oily liquid. Silica gel TLC (ether : *n*-hexane = 1 : 2) Rf = 0.34. IR (neat): 2950, 2229, 1728, 1266, 760, 701 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.35(s, 3H, OCH_3), 3.69(s, 3H, $COOCH_3$), 7.2-7.7(m, 9H, Arom). ^{13}C NMR ($CDCl_3$): δ = 51.96(CH_3), 53.83(CH_3), 81.48(C), 117.19(CN), 127.54(CH), 128.23 (CH), 128.51(CH), 129.17(CH), 129.33(CH), 129.78(CH), 130.63(CH), 132.06(C), 137.07(C), 137.55(C), 168.79(CO). MS(EI) m/z (%): 281(76) [M^+], 250(100), 219(46), 190(54), 146(64), 105(22). HRMS: m/z calcd for $C_{17}H_{15}NO_3$: 281.1052; found: 281.1054 [M^+]

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