ELECTROCHEMICAL SYNTHESIS OF 2,1-BENZISOXAZOLES BY CONTROLLED POTENTIAL CATHODIC ELECTROLYSIS

Byeong Hyo Kim,* Young Moo Jun, Yong Rack Choi, Doo Byung Lee, and Woonphil Baik‡

Department of Chemistry, Kwangwoon University, Seoul, 139-701, Korea.
‡Department of Chemistry and RRC, Myong Ji University, Kyung Ki Do, Korea.

Abstract - Using a divided cell, reductive cyclization of nitroarene compounds into 2,1-benzisoxazoles in mild conditions was successfully accomplished by the controlled potential cathodic electrolysis reactions. Optimum reaction potential of each reaction was determined based on cyclic voltametric behavior in methanol solution at Pb or Pt cathode, and Pt anode.

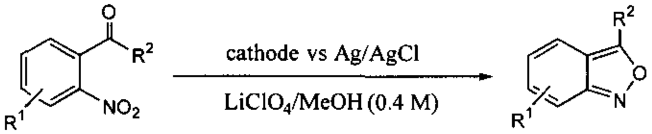
The utilized methods of preparation of 2,1-benzisoxazoles (anthranils) which have patented usages[1a] include some of the earliest recorded examples of nitro and acyl group side chain interaction in *o*-nitroacylbenzene derivatives,[1-8] *i.e.* catalytic hydrogenation,[1] reductive transformations by zinc/acetic acid,[2] triethyl phosphite,[3] and thionyl chloride.[4] Besides those kinds of chemical methods, electrochemical approach could be a powerful methodology for the reductive cyclizations of nitroarenes. Electroreductive cyclization of 2'-nitroacetophenone or 2-nitrobenzaldehyde in acetate buffer[9a,9b] and nitrobenzaldehyde in H_2SO_4 solution[9c,9d] was performed by other groups. However, it was not much successful and/or was not extended for synthetic utilities for halo or alkoxy substituted 2,1-benzisoxazoles probably because they used improper harsh electrolysis condition.

Previously, in the course of our study of reductive cyclization reaction on 2-nitroarenes, we have found an efficient synthetic method for 2,1-benzisoxazoles by using 2-bromo-2-nitropropane/Zn in neutral condition.[10] Based on the result, we decided to try electrochemical reaction of 2-nitroarenes toward 2,1-benzisoxazoles in a neutral condition[11] which usually has some merits over the chemical reactions or acidic electrochemical reactions. Herein we wish to report unique electrochemical reductive cyclizations of 2-nitrobenzaldehyde derivatives or 2'-nitroacetophenone to 2,1-benzisoxazoles under the mild electrolysis condition.

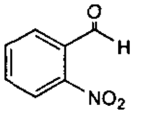
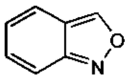
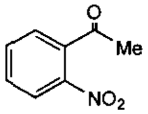
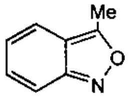
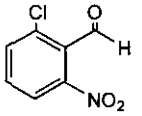
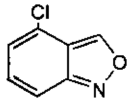
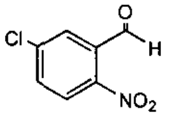
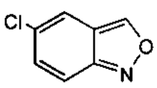
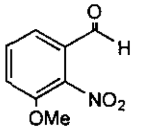
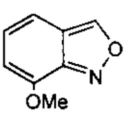
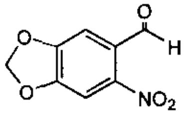
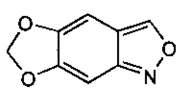
The reductive electrolysis reaction of 2-nitrobenzaldehyde (**1**) was carried out on the basis of cyclic voltametric behavior. Thus, a 0.05 M solution of **1** in methanol (0.2 M $LiClO_4$ electrolyte) was electrolyzed at -0.65 V (vs Ag/AgCl) in a divided cell between Pt cathode and Pt anode at room temperature until 4.6 F/mol was consumed. According to the GC yield analysis, the electrolysis product contribution consisted of 50% of 2,1-benzisoxazole (**2**), ~20% of acetal of 2-nitrobenzaldehyde, and 7% of recovered **1**. However, with increased concentration of supporting electrolyte (0.4 M $LiClO_4$), it produced **2** in 86% yield after the consumption of 5.2 F/mol. Interestingly enough, acetal of 2-nitrobenzaldehyde formation was not observed.

The effect of the cathode on the reaction was examined by replacing Pb instead of Pt. Similar result was

Table. The electrochemical reactions of substituted 2-nitrobenzaldehydes and 2'-nitroacetophenone.



R^1 = H, Cl, OMe, OCH_2O R^2 = H, Me

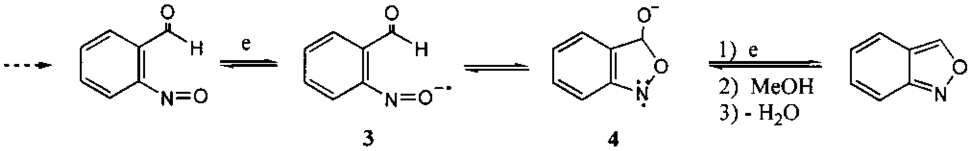
entry	substrate	cathode	charge passed F mol^{-1}	controlled potential (V)	product	yield (%)[a]
1		Pt	5.2	-0.65		86
2		Pb	2.4	-0.55		82
3		Pt	5.2	-1.05		78
4		Pb	4.6	-0.90		52
5		Pt	4.8	-0.85		83
6		Pb	2.1	-0.55		74
7		Pt	4.1	-0.90		54
8		Pb	4.5	-0.75		58
9		Pt	4.3	-0.90		90
10		Pb	4.7	-0.87		100
11		Pt	4.2	-0.92		71
12		Pb	4.9	-0.92		52

[a]GC yield with an internal standard.

obtained under the reductive electrolysis condition of **1** (0.4 M $LiClO_4$/methanol) at -0.55 V using Pb cathode which produced **2** in 82% yield consuming 2.4 F/mol.[12] Apparently, both Pt and Pb are considered to be useful metal cathodes for the reductive electrolysis reaction of 2-nitrobenzaldehyde derivatives. One minor problem associated with Pb cathode was the precipitate formation because of sacrificial Pb cathode.

In order to test the synthetic utility of the electrochemical reaction, we examined the electroreductive cyclization of substituted 2-nitrobenzaldehydes and 2'-nitroacetophenone under the optimized condition. Results are summarized in Table. In most cases, cyclization was successful with fair to excellent yields independent of the position and the electronic effect of the substituents. While 6-chloro-substituted *o*-nitrobenzaldehydes gave the corresponding chloro-substituted 2,1-benzisoxazole products in good yield similar to other substrates (Table, entries 5, 6), 5-chloro-substituted *o*-nitrobenzaldehydes gave relatively lower yields than the other substrates (Table, entries 7, 8). However, the formation of dechlorinated products was not observed under the employed reduction conditions in contrast to the cases in which dechlorination took place at relatively higher reduction potentials.[13] Moreover, for nitroarenes substituted with acid labile alkoxy functional group, our mild electrochemical reaction provided an efficient and selective method for the synthesis of 2,1-benzisoxazole derivatives (Table, entries 9, 10, 11, 12). In the case of 2,4-dinitrobenzaldehyde, only the tarry product was obtained instead of the reductive cyclized product when the reaction was completed.

The mechanism of the above-mentioned electrochemical reductive cyclization reaction of ortho-nitro substituted acylbenzenes is not clear yet. However, cyclization seems to proceed with nitrosoacylbenzene radical anion (**3**) which could be transformed to cyclized radical anion (**4**). After the subsequent electron transfer, proton transfers, and the loss of H_2O, **4** may bring to 2,1-benzisoxazole formation.



In conclusion, we have now established mild reaction route for 2,1-benzisoxazole derivatives by using an electrochemical reaction.

EXPERIMENTAL

1. General consideration

Chemical reagents were purchased from Aldrich and used without further purification in most cases. Solvents were purchased and dried by a standard method.

Analytical gas chromatography (GC) was performed on a Donam 6200 gas chromatograph equipped with a DB-1 column and Hitachi D-2500 integrator. ^{1}H NMR spectra were recorded on 300 or 500 MHz Bruker instrument and ^{13}C NMR spectra were recorded on 75 MHz Bruker instrument. Chemical shifts are in ppm from tetramethylsilane (TMS). High-resolution MS were recorded on a Jeol JMS-DX 303 mass spectrometer. IR spectra were recorded on a Nicolet 205 FT-IR. Analytical data were obtained with an EA-1110, CHNS-O CEinstruments. Melting point were determined on an Electrothermal apparatus and are uncorrected.

Most products were isolated by flash column chromatography on silica gel (70 - 230 mesh ATSM, purchased from Merck) with eluents of mixed solvents (hexane and ethyl acetate). GC yields were determined by using an internal standard (toluene) and were corrected with predetermined response factors.

For 2,1-benzisoxazole,[9b] 3-methyl-2,1-benzisoxazole,[14] and 5-chloro-2,1-benzisoxazole,[2] ^{1}H NMR spectra and the observed mp (5-chloro-2,1-benzisoxazole) were consistent with literature values.

2. General procedure for the electrolysis reactions

An H type glass cell fitted with a glass frit disk diaphragm was used for the electrolysis. The catholyte, MeOH (20 mL) containing 1 mmol of substrate and a supporting electrolyte, $LiClO_4$ (0.4 M). Pt or Pb plate as a cathode and Pt plate as an anode were used respectively, and Ag/AgCl was used as a reference electrode. Controlled potential electrolysis was carried at rt in an atmosphere of nitrogen until the starting substrate was consumed completely (monitored by TLC and coulometer). After the evaporation of MeOH, the reaction mixture was quenched with 10% NaCl and extracted with CH_2Cl_2 (40 mL x 3). The combined CH_2Cl_2 extract was dried over $MgSO_4$ and the solvent was evaporated. The GC yield was determined an internal standard and, if necessary, the products were isolated by flash column chromatography with ethyl acetate-hexane co-solvent.

2,1-Benzisoxazole Liquid, Yield; 86% (Pt cathode), 82% (Pb cathode). TLC (30% ethyl acetate/hexane) R_f 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.64-7.56 (m, 2H), 7.36-7.27 (m, 1H), 7.04-6.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 154.4, 130.8, 124.4, 119.6, 118.1, 115.0; IR (nujol) 3131, 3065, 3000, 1637, 1519, 1427, 1381, 1269 cm^{-1}; GC-MS m/z (rel. intensity) 119 (81, M^+), 92 (100), 64 (47), HRMS(EI) calcd for C_7H_5NO 119.0371, found 119.0372.

3-Methyl-2,1-benzisoxazole Liquid, Yield; 78% (Pt cathode), 52% (Pb cathode). TLC (30% ethyl acetate/ hexane) R_f 0.38; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 8.8 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.28-7.24 (m, 1H), 6.91 (dd, 1H, J = 6.4, 8.8 Hz), 2.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 157.0, 130.7, 122.7, 119.8, 115.6, 114.8, 11.9; IR (nujol) 3065, 2980, 1650, 1532, 1460, 1422 cm^{-1}; HRMS(EI) calcd for C_8H_7NO 133.0528, found 133.0536.

4-Chloro-2,1-benzisoxazole White solid, mp 51 - 53 °C, Yield; 54% (Pt cathode), 58% (Pb cathode). TLC (30% ethyl acetate/hexane) R_f 0.73; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, 1H, J = 0.9 Hz), 7.54 (dd, 1H, J = 0.9, 9.0 Hz), 7.22 (dd, 1H, J = 6.9, 9.0 Hz), 7.00 (d, 1H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 154.8, 131.1, 125.3, 123.2, 119.4, 113.8; IR (KBr) 3127, 3062, 1641, 1511 cm^{-1}; HRMS(EI) calcd for C_7H_4NOCl 152.9981, found 153.003. *Anal.* Calcd for C_7H_4NOCl: C, 54.75; H, 2.62; N, 9.12. Found: C, 54.72; H, 2.64; N, 9.09.

5-Chloro-2,1-benzisoxazole Pale yellowish white solid, mp 80 - 82 °C (lit.[2] mp 78 °C), Yield; 83% (Pt cathode), 74% (Pb cathode). TLC (30% ethyl acetate/ hexane) R_f 0.63; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.61-7.56 (m, 2H), 7.28-7.21 (m, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 154.0, 132.7, 130.2, 118.4, 117.8, 116.7; IR (KBr) 3105, 3069, 1648, 1554, 1518 cm^{-1}; HRMS(EI) calcd for C_7H_4NOCl 152.9981, found 152.9971. *Anal.* Calcd for C_7H_4NOCl: C, 54.75; H, 2.62; N, 9.12. Found: C, 54.82; H, 2.60; N, 9.10.

7-Methoxy-2,1-benzisoxazole Liquid, Yield; 90% (Pt cathode), 100% (Pb cathode). TLC (30% ethyl acetate/hexane) R_f 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.11 (d, 1H, J = 8.7 Hz), 6.93 (dd, 1H, J = 7.2, 8.7 Hz), 6.48 (d, 1H, J = 7.2 Hz), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 151.7, 148.1, 125.3, 119.9, 111.1, 105.3, 55.7; IR (nujol) 3138, 3065, 2987, 2842, 1723, 1637, 1552 cm^{-1}; HRMS(EI) calcd for $C_8H_7NO_2$ 149.0477, found 149.0473. *Anal.* Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.19; H, 4.88; N, 10.08.

2,5,7-Trioxa-1-aza-*s*-indacene White solid, mp 115 - 117 °C, Yield; 71% (Pt cathode), 52% (Pb cathode). TLC (30% ethyl acetate/hexane) R_f 0.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, 1H, J = 0.7 Hz), 6.80 (d, 1H, J = 0.7 Hz), 6.68 (s, 1H), 5.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.9, 152.0, 147.6, 115.2, 101.7, 92.0, 89.5; IR (KBr) 3098, 2940, 1612, 1475, 1367 cm^{-1}; HRMS(EI) calcd for $C_8H_5NO_3$ 163.0269, found 163.0275. *Anal.* Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.82; H, 3.15; N, 8.57.

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We are also indebted to Dr. B. M. Lee, KRICT for elemental analyses.

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11. As the reaction was proceeded, cathodic solution was turned into the basic condition gradually.
12. Electrolysis at -0.55 V (vs Ag/AgCl, 0.2 M $LiClO_4$/Pb cathode-Pt anode/methanol) was completed to give **2** (42%) along with ~13% of acetal of 2-nitrobenzaldehyde and a trace amount of **1** after the consumption of 2.4 F/mol.
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