

(-CO₂-), 153.05, 152.68, 148.12, 146.72, 135.81, 133.16, 133.14, 133.05, 132.81, 132.71, 132.59, 132.47, 131.80, 130.73, 130.36, 130.30, 130.22, 129.66, 129.46, 129.35, 129.30, 129.25, 128.89, 128.68, 128.64, 128.47, 128.41, 128.14, 127.32, 126.32, 125.34, 125.26, 125.18, and 119.18 (Ar), 77.34 (-OCH₂Ar), 38.01, 37.80, 31.70, and 31.11 (ArCH₂Ar). IR (KBr) 3392 cm⁻¹ (OH), 1731 and 1714 cm⁻¹ (-CO₂-).

25,26-Bisbenzoyloxy-27,28-dihydroxycalix[4]arene 4. A mixture of 1.0 g (1.38 mmol) of 3 and 0.05 g of Pd/C in THF/ethanol (7:3) was shaken for 7 hrs under H₂ atmosphere at 50 psi. After filtered off the catalyst, the solvents were removed and the residue was triturated with methanol. Recrystallization from chloroform-methanol produced 0.73 g (72%) of colorless crystals 4. mp 239-241 °C. ¹H NMR (CDCl₃) δ 7.42 (t, 2H, ArH), 7.16-7.00 (m, 14H, ArH and OH), 6.84 (d, 2H, ArH, *J*=7.52 Hz), 6.72 (d, 2H, ArH, *J*=7.52 Hz), 6.59 (t, 2H, ArH, *J*=7.52 Hz), 6.45 (t, 2H, ArH, *J*=7.52 Hz), 3.88, 3.85, 3.84, and 3.81 (four s, 8H, ArCH₂Ar). ¹³C NMR (CDCl₃) δ 163.54 (-CO₂-), 151.01, 146.73, 133.18, 133.05, 132.40, 130.06, 129.57, 129.50, 128.96, 128.59, 128.06, 127.94, 127.22, 126.44, and 121.04 (Ar), 37.80, 34.55, and 31.38 (ArCH₂Ar). IR (KBr) 3432 and 3376 cm⁻¹ (OH), 1730 and 1706 cm⁻¹ (-CO₂-).

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Rhodium Catalyzed Reactions of Cyclic 2-Diazo-1,3-dicarbonyl Compounds with Nitriles

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Various benzoxazole derivatives are found as the sub-unit of the several natural products,¹ drugs² and industrial chemicals³ and of interest for useful intermediates in the area of organic synthesis.⁴ In the continuation of our research work on the use of α-diazocarbonyl compounds for the synthesis of heterocycles such as β-furoic acid,⁵ γ-pyrone,⁶ oxazole,⁷ and thiazole,⁸ we have investigated efficient method for the preparation of the 4-oxo-4,5,6,7-tetrahydrobenzoxazole. While the rhodium-catalyzed dipolar cycloaddition of cyclic 2-diazo-1,3-dicarbonyl compounds such as 2-diazo-1,3-cy-

clohexanedione (1a), 2-diazo-5-methyl-1,3-cyclohexanedione (1b), and diazodimedone (1c) to aromatic heterocycles,⁹ acetylenes,¹⁰ vinyl ethers,^{9b} vinyl acetates,¹¹ are developed, the utility of these reagents for the synthesis of 4-oxo-4,5,6,7-tetrahydrobenzoxazole has not been exploited. Consequently, we examined the reactions of cyclic 2-diazo-1,3-dicarbonyl compounds with nitriles. We describe herein our results on the synthesis of oxotetrahydrobenzoxazoles via 1,3-dipolar cycloadditions of cyclic rhodium carbenoids with nitriles.

Experimental

General. Melting points were determined using a Thomas-Hoover capillary melting point apparatus, and are uncorrected. IR spectra were measured on a Matton GL-6030E spectrophotometer using KBr pellets or thin film on NaCl. ^1H and ^{13}C NMR spectra were obtained on either a Bruker AM-300 or a Varian Unity Plus-300 instruments as solution in CDCl_3 . Chemical shifts are reported in δ units downfield from the internal tetramethylsilane. Mass spectra were recorded on a Shimadzu QP-1000 spectrometer with electron energy of 20 or 70 eV with direct sample introduction. Analytical TLC were carried out on Merck silica gel 60F₂₅₄ plates, visualizing with a 254-nm UV lamp. For routine column chromatography, Merck silica gel (70-230 mesh) was used as the adsorbent. All reactions were carried out under an atmosphere of nitrogen. Solvent were dried and purified according to the known method.¹² Organic chemicals and rhodium(II) acetate were purchased from Aldrich Chemical Co. 2-Diazo-1,3-cyclohexanedione (**1a**), 2-diazo-5-methyl-1,3-cyclohexanedione (**1b**), diazodimedone (**1c**) were prepared by known procedures.^{13,14}

Preparation of 2-Substituted-4-oxo-4,5,6,7-tetrahydrobenzoxazole. To a stirred solution of $\text{Rh}_2(\text{OAc})_4$ (10 mg, 0.02 mmol) in nitrile (10 mmol) was added a solution of **1a** (138 mg, 1.0 mmol) in nitrile (40 mmol) with syringe pump over 10 h period at 80 °C. After the reaction was completed, the solution was cooled and concentrated. The residue was purified by flash column chromatography on silica gel (ethyl acetate:hexane 1:4) to give product. The solid product was recrystallized from diethyl ether.

2a: Yield 48%, white solid; mp 173.5-174.5 °C; TLC R_f 0.39 (ethyl acetate:hexane 2:1), 0.29 (diethyl ether); IR (KBr) 2953, 1685 (C=O), 1483, 1398, 1018 cm^{-1} ; ^1H NMR δ 8.26 (d, 2H, $J=7.5$ Hz, *o* of Ph), 7.64-7.47 (m, 3H, *m*, *p* of Ph), 2.96 (t, 2H, $J=7.0$ Hz, H-7), 2.82 (t, 2H, $J=5.7$ Hz, H-5), 2.17-2.05 (m, 2H, H-6); MS (m/z) 213 (M^+ , 74), 185 (46), 157 (38), 115 (17), 105 (base).

2b: Yield 65%, yellow oil; TLC R_f 0.16 (ethyl acetate:hexane 2:1), 0.14 (diethyl ether); IR (neat) 2916, 1669 (C=O), 1604, 1394, 1209 cm^{-1} ; ^1H NMR δ 2.94 (t, 2H, $J=6.2$ Hz, H-7), 2.56 (t, 2H, $J=6.5$ Hz, H-5), 2.49 (s, 3H, 2- CH_3), 2.27-2.21 (m, 2H, H-6); ^{13}C NMR δ 191.4 (C=O), 164.4 (C-7), 134.2 (C-4), 37.6 (C-5), 22.3 (C-7), 22.1 (C-6), 13.8 (CH_3); MS (m/z) 151 (M^+ , 35), 123 (63), 95 (39), 43 (base).

2c: Yield 65%, yellow oil; TLC R_f 0.20 (ethyl acetate:hexane 1:1); IR (neat) 2961, 1690 (C=O), 1615, 1399, 1204, 1055, 1040 cm^{-1} ; ^1H NMR δ 3.08 (dd, 1H, $J=16.6$, 4.5 Hz, H-7), 2.73-2.62 (m, 3H, H-5,6,7), 2.57 (s, 3H, 2- CH_3), 2.40 (dd, 1H, $J=15.7$, 11.3 Hz, H-5), 1.28 (d, 3H, $J=6.3$ Hz, 6- CH_3); MS (m/z) 165 (M^+ , 42), 123 (100), 95 (24), 81 (5).

2d: Yield 68%, white solid, mp 75-75.5 °C; TLC R_f 0.34 (ethyl acetate:hexane 2:1), 0.29 (diethyl ether); IR (KBr) 2963, 2932, 1691 (C=O), 1395, 1048 cm^{-1} ; ^1H NMR δ 2.79 (s, 2H, H-7), 2.50 (s, 3H, 2- CH_3), 2.44 (s, 2H, H-5), 1.17 (s, 6H, 6,6'- CH_3); MS (m/z) 179 (M^+ , 46), 164 (20), 123 (base).

2e: Yield 56%, white solid, mp 60-60.5 °C; TLC R_f 0.30 (ethyl acetate:hexane 2:1), 0.29 (diethyl ether); IR (KBr) 2962, 1680 (C=O), 1396 cm^{-1} ; ^1H NMR δ 4.62 (s, 2H, 2- CH_2Cl), 3.07 (t, 2H, $J=6.3$ Hz, H-7), 2.59 (t, 2H, $J=6.5$ Hz,

H-5), 2.27 (m, 2H, H-6); MS (m/z) 185 (M^+ , 34), 157 (base), 129 (30).

2f: Yield 45%, white solid, mp 46-48 °C; TLC R_f 0.30 (ethyl acetate:hexane 1:1); IR (KBr) 2969, 1676 (C=O), 1399, 1051, 804, 723 cm^{-1} ; ^1H NMR δ 4.60 (s, 2H, 2- CH_2Cl), 2.83 (s, 2H, H-7), 2.45 (s, 2H, H-5), 1.16 (s, 6H, 6,6'- CH_3); MS (m/z) 213 (M^+ , 100), 198 (76), 178 (46), 157 (8), 69 (8).

2g: Yield 38%, white solid, mp 61.5-62 °C; TLC R_f 0.30 (ethyl acetate:hexane 2:1), 0.26 (diethyl ether); IR (KBr) 2941, 1689 (C=O), 1579, 1336, 1014 cm^{-1} ; ^1H NMR δ 7.37-7.23 (m, 5H, C_6H_5), 4.12 (s, 2H, $-\text{CH}_2\text{C}_6\text{H}_5$), 2.89 (t, 2H, $J=6.2$ Hz, H-7), 2.54 (t, 2H, $J=6.5$ Hz, H-5), 2.19 (m, 2H, H-6); MS (m/z) 227 (M^+ , 35), 171 (8), 91 (base).

2h: Yield 42%, yellow oil; TLC R_f 0.30 (ethyl acetate:hexane 1:2); IR (neat) 2961, 1694 (C=O), 1582, 1399, 1179, 1049, 729 cm^{-1} ; ^1H NMR δ 7.29 (m, 5H, C_6H_5), 4.12 (s, 2H, $-\text{CH}_2\text{C}_6\text{H}_5$), 2.75 (s, 2H, H-7), 2.42 (s, 2H, H-5), 1.46 (s, 6H, 6,6'- CH_3); MS (m/z) 255 (M^+ , 100), 240 (14), 199 (69), 123 (9), 105 (18), 91 (87).

2i: Yield 45%, white solid, mp 105-107 °C; TLC R_f 0.30 (ethyl acetate:hexane 1:1); IR (KBr) 2949, 1678 (C=O), 1614, 1583, 1404, 1379, 1194, 1171, 1082, 1057, 1020 cm^{-1} ; ^1H NMR δ 2.90 (t, 2H, $J=6.3$ Hz, H-7), 2.54 (t, 2H, $J=6.0$ Hz, H-5), 2.20 (m, 2H, H-6), 2.04 (m, 1H), 1.14 (m, 2H), 1.07 (m, 2H).

2j: Yield 42%, yellow oil; TLC R_f 0.30 (ethyl acetate:hexane 1:2); IR (neat) 2961, 1690 (C=O), 1616, 1589, 1508, 1468, 1402, 1372, 1217, 1182, 1047, 974 cm^{-1} ; ^1H NMR δ 2.75 (s, 2H, H-7), 2.41 (s, 2H, H-5), 2.02 (m, 1H), 1.14 (s, 6H, 6,6'- CH_3), 1.01-1.13 (m, 4H); MS (m/z) 205 (M^+ , 100), 190 (10), 178 (6), 159 (12), 149 (40), 121 (26), 83 (10), 69 (38).

2k: Yield 26%, yellow oil; TLC R_f 0.26 (ethyl acetate:hexane 2:1), 0.13 (diethyl ether); IR (neat) 2941, 1736 (ester C=O), 1686 (C=O), 1607, 1392, 1183, 1013 cm^{-1} ; ^1H NMR δ 4.22 (q, 2H, $J=7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.88 (s, 2H, CH_2CO_2), 2.97 (t, 2H, $J=6.3$ Hz, H-7), 2.58 (t, 2H, $J=6.3$ Hz, H-5), 2.29-2.20 (m, 2H, H-6), 1.28 (t, 3H, $J=7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); MS (m/z) 223 (M^+ , 30), 194 (6), 166 (10), 151 (base).

2l: Yield 6%; mp 111 °C; TLC R_f 0.50 (ethyl acetate:hexane 2:1), 0.39 (diethyl ether); IR (KBr) 2958, 1690 (C=O), 1480, 1389, 1301, 1156, 1090, 1006 cm^{-1} ; ^1H NMR δ 7.81 (d, 2H, $J=8.3$ Hz, *o* of Ar), 7.31 (d, 2H, $J=8.2$ Hz, *m* of Ar), 3.05 (t, 2H, $J=6.3$ Hz, H-7), 2.63 (t, 2H, $J=6.5$ Hz, H-5), 2.29 (m, 2H, H-6); MS (m/z) 247 (M^+ , 54), 219 (29), 191 (32), 139 (base).

2m: Yield 4%; mp 122.5-123 °C; TLC R_f 0.60 (ethyl acetate:hexane 2:1), 0.45 (diethyl ether); IR (KBr) 2962, 2927, 1677 (C=O), 1394, 1302, 1161, 1012, 726 cm^{-1} ; ^1H NMR δ 8.01 (d, 1H, $J=7.8$ Hz, 6' of Ar), 7.36 (d, 1H, $J=7.5$ Hz, 3' of Ar), 7.32-7.26 (m, 2H, 4',5' of Ar), 3.05 (t, 2H, $J=6.3$ Hz, H-7), 2.71 (s, 3H, Ar CH_3), 2.64 (t, 2H, $J=6.7$ Hz, H-5), 2.33-2.69 (m, 2H, H-6); MS (m/z) 227 (M^+ , base), 226 (13), 198 (11), 171 (37), 155 (14), 143 (18), 130 (10), 91 (76).

2n: Yield 8%; mp 115-116 °C; TLC R_f 0.57 (ethyl acetate:hexane 2:1), 0.39 (diethyl ether); IR (KBr) 2934, 1678 (C=O), 1303, 1219, 1159, 1099, 903, 723 cm^{-1} ; ^1H NMR δ 7.97 (s, 1H, 2' of Ar), 7.89 (d, 1H, $J=7.8$ Hz, 6' of Ar), 7.37 (d, 1H, $J=7.5$ Hz, 4' of Ar), 7.33-7.30 (m, 1H, 5' of

Ar), 3.05 (t, 2H, $J=6.2$ Hz, H-7), 2.64 (t, 2H, $J=6.5$ Hz, H-5), 2.41 (s, 3H, ArCH₃), 2.31-2.66 (m, 2H, H-6); MS (m/z) 227 (M⁺, 33), 171 (44), 167 (42), 155(32), 149 (base), 91 (92).

2o: Yield 9%; mp 112-113 °C; TLC R_f 0.54 (ethyl acetate:hexane 2:1), 0.37 (diethyl ether); IR (KBr) 2936, 1688 (C=O), 1395, 1306, 1159, 901, 816 cm⁻¹; ¹H NMR δ 7.99 (d, 2H, $J=8.2$ Hz, *o* of Ar), 7.80 (d, 2H, $J=8.4$ Hz, *m* of Ar), 3.03 (t, 2H, $J=6.2$ Hz, H-7), 2.62 (t, 2H, $J=6.5$ Hz, H-5), 2.41 (s, 3H, ArCH₃), 2.31-2.25 (m, 2H, H-6); MS (m/z) 227 (M⁺, 36), 171 (84), 155 (70), 91 (base).

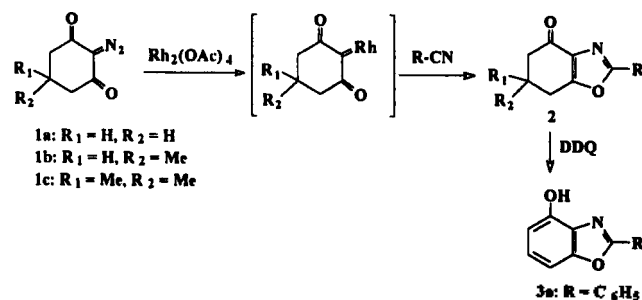
4: mp 193.5 °C (CH₂Cl₂/hexane); TLC R_f 0.43 (methanol), 0.50 (acetone); IR (KBr) 3148, 2982, 1578 (C=O), 1335 cm⁻¹; ¹H NMR (CDCl₃+DMSO-*d*₆) δ 2.56 (t, 8H, $J=6.4$ Hz, H-4,6), 1.99 (quin, 4H, $J=6.4$ Hz, H-5); MS (m/z) 148 (12, M⁺), 118 (base).

2-Phenyl-4-hydroxybenzoxazole (3a). To a stirred solution of **2a** (55.0 mg, 0.26 mmol) in dioxane (7 mL) was added DDQ (108 mg, 0.47 mmol), and then refluxed for 48 h. The mixture was extracted with ethyl acetate (25 mL), the organic extract was dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on silica-gel (ethyl acetate:hexane 2:1) to give **3a** (33.3 mg, 61%) as a white solid. mp 137-138 °C (CH₂Cl₂/hexane); TLC R_f 0.58 (ethyl acetate:hexane 1:1), 0.70 (diethyl ether); IR (KBr) 3260, 3199 (OH), 3057, 1619, 1499, 1483, 1445, 1263, 1247, 1046 cm⁻¹; ¹H NMR δ 8.62 (s, 1H, 4-OH), 8.18 (d, 2H, $J=8.0$ Hz, *o* of Ph), 7.52-7.42 (m, 3H, *m, p* of Ph), 7.26 (dd, 1H, $J=8.0, 8.3$ Hz, H-6), 7.15 (d, 1H, $J=8.0$ Hz, H-7), 6.93 (d, 1H, $J=8.3$ Hz, H-5); MS (m/z) 211 (M⁺, base), 154 (11), 105 (96).

Results and Discussion

Cyclic diazo ketones used in this study include 2-diazo-1,3-cyclohexanedione (**1a**), 2-diazo-5-methyl-1,3-cyclohexanedione (**1b**) and diazodimedone (**1c**) and they are readily prepared as handleable solids. Initial studies on the reactions of cyclic 2-diazo-1,3-dicarbonyl compounds with nitriles were carried out with rhodium(II) acetate. Several attempts to optimize the reaction conditions as model reaction were carried out between **1a** and benzonitrile.

Reaction of **1a** occurs with a catalytic quantity of rhodium(II) acetate in benzonitrile (50 equiv, 80 °C, 24 h) to give dipolar cycloadduct 2-phenyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2a**) in 48% yield. Similar treatment of **1a** with benzonitrile (50 equiv, 80 °C, 24 h) using copper(II) sulfate, palladium acetate, and copper acetoacetate as ca-



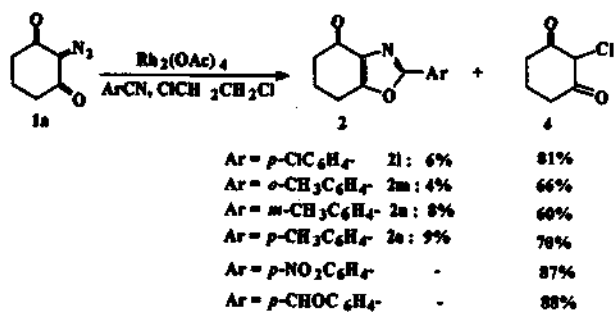
Scheme 1.

talyst gave **2a** in 9, 17, and 10% yields, respectively. The structure of **2a** is established from its MS, IR, and NMR spectra, and its conversion to **3a** by dehydrogenation with DDQ in dioxane.

Study has been made of reactions of **1a** with varied aliphatic nitriles in 1:50 molar ratio with rhodium(II) acetate at 80 °C. Decomposition of **1a** by rhodium(II) acetate in acetonitrile, chloroacetonitrile, benzyl cyanide, cyclopropyl cyanide, and ethyl cyanoacetate, respectively, yields the following 2-substituted-4-oxo-4,5,6,7-tetrahydrobenzoxazoles: 2-methyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2b**, 65%), 2-chloromethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2e**, 56%), 2-benzyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2g**, 42%), 2-cyclopropyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2i**, 45%) and 2-carbomethoxymethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2k**, 26%). Similar treatment of 2-diazo-5-methyl-1,3-cyclohexanedione (**1b**) with acetonitrile gave 2,6-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2c**) in 65% yield. Reaction of diazodimedone (**1c**) under similar conditions with acetonitrile, chloroacetonitrile, benzyl cyanide, and cyclopropyl cyanide, gave 2,6,6'-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2d**, 68%), 2-chloromethyl-6,6'-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2f**, 45%), 2-benzyl-6,6'-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2h**, 42%), 2-

Table 1. Synthesis of 2-Substituted-4-oxo-4,5,6,7-tetrahydrobenzoxazole

Entry	2-Diazo-1,3-dicarbonyl	R-CN	Product	Yield (%)
1		C ₆ H ₅ -CN		48
2		CH ₃ -CN		65
3		CH ₃ -CN		65
4		CH ₃ -CN		68
5		Cl-CH ₂ -CN		56
6		Cl-CH ₂ -CN		45
7				42
8				42
9				45
10				55
11		NC-CH ₂ -CO ₂ Et		26



Scheme 2.

cyclopropyl-6,6'-dimethyl-4-oxo-4,5,6,7-tetrahydrobenzoxazole (2j, 55%), respectively. (Table 1). This result suggests that **1** under the rhodium(II) acetate condition generate initially rhodium carbenoid which yields 4-oxo-4,5,6,7-tetrahydrobenzoxazole by 1,3 dipolar cycloaddition.

We then investigated rhodium(II) acetate catalyzed reactions of **1a** with various substituted benzonitriles in 1:8 molar ratio in 1,2-dichloroethane. Reactions of 4-chlorobenzonitrile, 2,3,4-tolunitrile with **1a** under similar conditions afford the corresponding 4-oxo-4,5,6,7-tetrahydrobenzoxazole (**2**) in very low yields (4-9%) along with 2-chloro-1,3-cyclohexanedione (**4**, 60-81%) which is formed by reaction with 1,2-dichloroethane.^{9a} Electron withdrawing group such as nitro and aldehyde group at *para*-position of benzonitrile retards the dipolar cycloaddition reaction and yields only 2-chloro-1,3-cyclohexanedione as a product (Scheme 2).

Transformation of 4-oxo-tetrahydrobenzoxazole **2** into benzoxazole **3** was achieved by DDQ oxidation. Dehydrogenation of **2a** with DDQ in dioxane for 48 h provides **3a** in 61% yield.

Thus the present procedure provides a convenient synthetic approach to the 2-substituted-4-oxo-4,5,6,7-tetrahydrobenzoxazoles, and further application of this reaction will be reported in the future.

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