A Facile Approach for New Dibenzo [*b,f*][1,5] Diazocinones

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Abstract: The synthesis of new eight-membered cycle dibenzo[*b,f*][1,5]-diazocine-6-(5*H*)-one derivatives **11**, **12** was developed. The key step in this synthesis was the intramolecular cyclization of the amino aldehyde precursors **9**,**10** obtained by a selective reduction of the nitro benzamides **7**, **8**.

Keywords: Dibenzodiazocinones, Tröger's base, nitroaldehydes

INTRODUCTION

Troger's base,[1–3] 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo [*b,f*] [1,5]-diazocine **I** is a chiral rigid molecule that has attracted much attention mainly because of its interesting biological activities, such as host in recognition phenomena,[4] DNA intercalation,[5] enzyme inhibition, and as a ligand for asymmetric catalysis.[6] In this field the dibenzodiazocinic skeleton[7–9] has gained considerable interest as a challenging target and pharmacologically interesting compound. Recently Hassner et al.[10]

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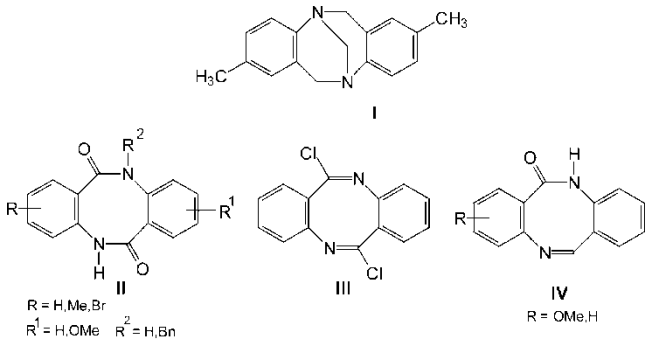
reported the synthesis of dibenzodiazocinedione **II**, the first substituted asymmetrical dilactam by reaction of a sulfinamide lactone of anthranilic acid with different *N*-alkyl anthranilic acids. On the other hand, reactivity studies reported by Wakankar and Hosangadi[11] on dibenzodiazocine **III** demonstrated the flexibility and the applications of the dibenzodiazocine framework. However, as far as we know, the synthesis of dibenzodiazocinones of type **IV** has not been reported yet.

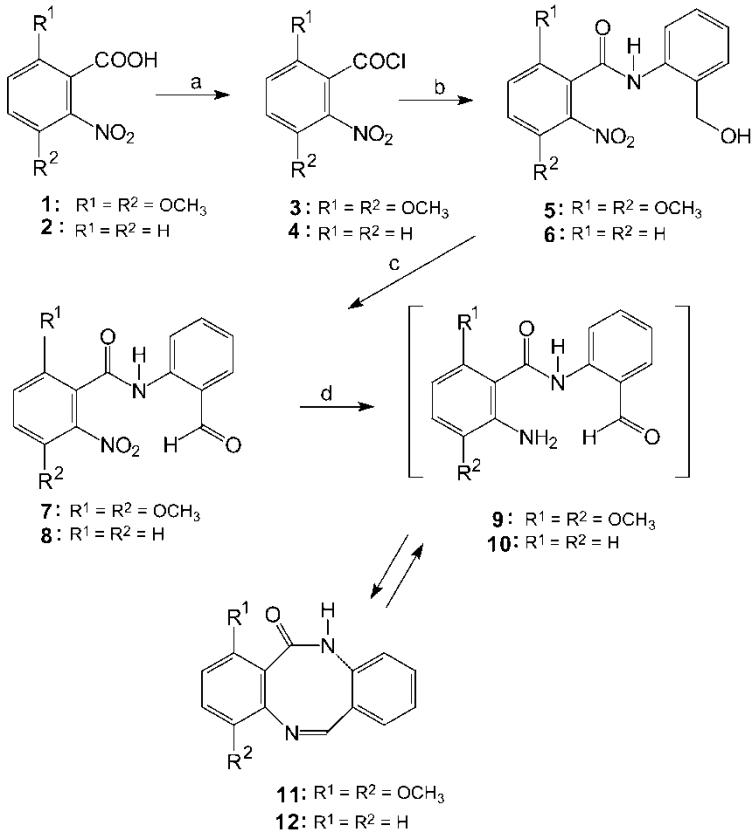


In a previous work by our group, a versatile approach for obtaining Troger's base precursors from easily available 2-nitrobenzaldehyde and 2-aminobenzyl alcohol was described.[12] Based on these results and given our interest in the azaheterocyclic chemistry, we decided to explore the synthesis of the diazocinone **IV**.

In this article, we report a convenient synthetic method for the preparation of novel dibenzo [*b,f*][1,5] diazocinones **11** and **12**, following a four-step reaction sequence.

RESULTS AND DISCUSSION

The general strategy is depicted in Scheme 1. Benzoyl halides **3, 4** were prepared in quantitative yield from the corresponding carboxylic acids **1** and **2** by refluxing in thionyl chloride at 50°C for 3 h. The resulting oils were characterized by IR (1795 and 1797 cm^{-1}) and, without further purification, immediately reacted with 2-aminobenzylic alcohol under an inert atmosphere at 0°C to give the expected benzamide alcohols **5** (83%) and **6** (87%), respectively. Subsequent oxidation of alcohol derivatives **5** and **6** with pyridinium chlorochromate in dichloromethane at room temperature provided the corresponding nitroaldehydes **7** and **8** in high yield. The aldehydes were easily purified by silica-gel column chromatography, showing in the ^{1}H-NMR spectra the characteristic singlet signals at low field: (**7** $\delta_{CHO} = 10.1$ ppm and **8** $\delta_{CHO} = 9.93$ ppm), supporting the presence of these functions. The key and final step of this synthesis consisted of a

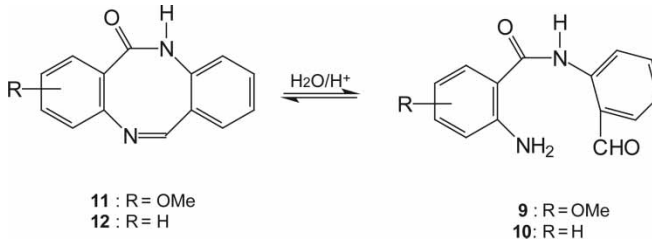


Scheme 1. Reagents: a) $SOCl_2$, 50 °C (3 h); b) 2-aminobenzyl alcohol, anhydrous THF, dry pyridine, N_2 atmosphere; c) pyridinium chlorochromate/CH_2Cl_2 25 °C; d) Fe°/H_2O, EtOH, HOAc (1:1:1 v/v), 20 °C.

chemoselective nitroreduction of nitro aldehydes **7**, **8**, which was carried out under diluted conditions with iron powder, in ethanolic, aqueous, acetic acid medium.[13] The reaction afforded a mixture of amine aldehyde intermediates **9, 10** along with the desired cyclized products **11, 12** (Scheme 1) as was detected by the ^{1}H-NMR spectral analysis of the crude mixtures.

The presence of the aminoaldehydes **9** and **10**, together with the cyclized products **11**, **12** in the crude reduction mixture, is not dependent on the reduction time, as we confirmed by utilizing longer reduction times, but probably results from the acidic, aqueous medium of the reaction, which might promote imine hydrolysis and ring opening as is illustrated in Scheme 2.

Compounds **9, 11**, and **12** were purified by chromatography, followed by recrystallization, except for the amine aldehyde intermediate **10**, which could not be isolated from the crude product mixture.



Scheme 2.

In summary, the present study provides a simple and short method for the preparation of new benzofused eight-membered diazaheterocycles from easily available reagents.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a FT Bruker spectrophotometer for KBr. ^{1}H-NMR and ^{13}C-NMR spectra were obtained with a Bruker DRX-300 spectrophotometer. The chemical shifts are expressed in ppm (δ scale) downfield from TMS, J values are given in Hertz for solutions in $CDCl_3$ unless otherwise indicated. Microanalysis were determined on a Fisons EA 1108 analyzer. Silica gel Merck 60 (70–230 mesh) and DC-alufolien 60 F_{254} were normally used for column and TLC chromatography respectively.

General Procedure for Preparation of *N*-[2-(hydroxymethyl) aryl] nitrobenzamide Derivatives (5, 6) using Compound (5) as a Model

***N*-[2-(Hydroxymethyl) phenyl]-3,6-dimethoxy-2-nitrobenzamide (5).** Benzoylchloride **3** (1.02 g, 4.39 mmol) in dry THF (30 mL) was slowly added to a stirred solution at 0 °C of 2-aminobenzyl alcohol (541 mg, 4.39 mmol), pyridine (348 mg, 4.39 mmol), and dry THF (80 mL) in a nitrogen atmosphere. The mixture was maintained with stirring for 8 h at room temperature and then diluted with water (100 mL). The solution was extracted with ethyl acetate (3 × 50 mL) and the organic layers dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by silica-gel column chromatography ($AcOEt/CH_2Cl_2$, 1:1) to give dimethoxy nitrobenzamide **5** (1.21 g, 83%) as a yellow pale solid. Mp 108–109 °C (EtOH/hexane 3:1). Anal. calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.81; N, 8.43. Found: C, 57.68; H, 4.99; N, 8.62%. IR ν_{max}: 3433 (O—H), 3300 (N—H), 1646 (NHC=O), 1540 (NO_2), 1369 (NO_2). ^{1}H-NMR (DMSO-d_6) δ: 3.89 (s, 3H, OCH_3), 3.95

(s, 3H, OCH_3), 4.61 (s, 2H, -CH_2-OH), 5.35 (br s 1H, OH), 7.13 (t,1H, $J = 7.3$ Hz, Ar 4′-H), 7.24–7.38 (m, 4 H, Ar-3H, Ar-4-H, Ar-3′-H, Ar-5′-H), 7.84 (d, 1H, $J = 7.9$ Hz, Ar 6′-H), 10.12 (s, 1H, NHCO).^{13}C-NMR (75 MHz, DMSO-d_6) δ: 61.8, 62.0, 66.6, 120.1, 121.0, 124.4, 128.1, 129.7, 132.4, 133.0, 138.2, 140.8, 145.1, 149.7, 154.7, 165.1.

***N*-[(2-Hydroxymethyl) phenyl]-6-nitrobenzamide (6).** Compound (**6**) (630 mg, 91%), white crystals, was prepared from benzoyl chloride (**4**) (472 mg, 2.54 mmol) and 2-aminobenzyl alcohol (313 mg, 2.54 mmol); mp 169–170 °C (EtOH/hexane 3 : 1). Anal. calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.43; H, 4.51; N, 10.12%. IR ν_{max}: 3421 (O—H), 3240 (N—H), 1650 (NHC═O), 1530 (NO_2), 1352 (NO_2). ^{1}H-NMR (DMSO-d_6) δ: 4.59 (d, 2H, $J = 5.5$ Hz, CH_2-OH), 5.29 (t,1H, $J = 5.5$ Hz, OH), 7.22–7.33 (m, 2H, Ar 4′-H and 5′-H), 7.51 (m,2H, Ar-6′-H and Ar-3′-H), 7.69–7.91 (m, 3H, Ar 4-H, Ar-5-H, and Ar-6-H), 8.14 (d, 1H, $J = 8.0$ Hz, Ar 3-H), 10.11 (s, 1H, NHCO). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 60.0, 124.8, 125.4, 126.2, 127.4, 127.5, 129.6, 131.5, 133.1, 134.5, 134.6, 136.9, 147.2, 164.8.

General Procedure for Preparation of *N*-(2-Formylaryl) Nitrobenzamide Derivatives (7, 8) using Compound (7) as a Model

***N*-(2-Formylphenyl)-3,6-dimethoxy-2-nitrobenzamide (7).** To a well-stirred solution of alcohol benzamide **5** (300 mg, 0.90 mmol) in CH_2Cl_2 (50 mL) at rt is added a solution of pyridinium chlorochromate (300 mg, 1.39 mmol) in CH_2Cl_2 (20 mL). After complete conversion as indicated by TLC, the reaction mixture was concentrated and chromatographed on silica-gel column ($CHCl_3$), and yielded nitroaldehyde **7** (200 mg, 67.1%). Mp 195–196 °C (EtOH). Anal. calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.95; H, 4.34; N, 8.63%. IR ν_{max}: 3242 (N—H), 1686 (Ar-CHO), 1668 (NHC═O), 1540 (NO_2), 1368 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.11 (d, 1H, $J = 9.3$ Hz, Ar 3-H or Ar 4-H), 7.16 (d, 1H, $J = 9.3$ Hz, Ar 4-H or Ar 3-H), 7.29 (t, 1H, $J = 7.5$ Hz, Ar 4′-H), 7.62 (td, 1H, $Jo = 7.3$ Hz, $Jm = 1.4$ Hz, Ar 5′-H), 7.70 (dd, 1H, $Jo = 7.6$ Hz, $Jm = 1.54$ Hz, Ar 6′-H), 8.85 (d, 1H, $J = 8.5$ Hz, Ar 3′-H), 9.93 (s, 1H, Ar CHO), 11.94 (s, 1H, N*H*CO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.7, 57.3, 114.3, 116.5, 118.9, 120.8, 122.4, 123.6, 136.1, 136.2, 139.9, 141.3, 145.4, 150.2, 161.4, 194.9.

***N*-(2-formylphenyl)-2-nitrobenzamide (8).** Compound (**8**) (253 mg, 86%); white pale solid was prepared from alcohol benzamide (**6**) (296 mg, 1.08 mmol) and pyridinium chlorochromate (360 mg, 1.67 mmol). Purified by column chromatography (CH_2Cl_2/AcOEt 1:1); mp 148–149 °C (EtOH). Anal. calcd. for $C_{14}H_{10}N_2O_4$: C, 62.21; H, 3.73; N, 10.37. Found: C, 62.09; H, 3.67; N, 10.32%. IR ν_{max}: 3240 (N—H), 1686 (Ar-CHO), 1666 (NHC═O), 1530 (NO_2), 1350 (NO_2). ^{1}H-NMR (DMSO-d_6) δ: 7.44 (t,1H,

$J = 7.3$ Hz, Ar 4′-H), 7.75–7.85 (m, 2H, Ar 4-H, and 5′-H), 7.92–7.95 (m, 3H, Ar 5-H, 3′-H, and 6′-H), 8.03 (d, 1H, $J = 7.8$ Hz, Ar 6-H), 8.2 (d, 1H, $J = 7.9$ Hz, Ar 3-H), 10.1 (s, 1H, Ar-CHO), 11.3 (s, 1H, Ar-N*H*CO). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 123.3, 12.5.1, 125.8, 126.8, 129.5, 132.0, 132.1, 132.3, 134.8, 135.7, 139.5, 147.2, 165.4, 193.5.

General Procedure for Reduction of *N*-(2-Formylaryl)-2-nitrobenzamides (7,8) and Reduction of *N*-(2-Formylphenyl)-3,6-dimethoxy-2-nitrobenzamide (7)

To a solution of nitrobenzamide (**7**) (173 mg, 0.52 mmol) in acetic acid–ethanol–water (100 mL, 1:1:1 v/v) was added powder iron (234 mg, 4.19 mmol). After stirring for 3 h at rt, 50 mL of water was added. The reaction mixture was neutralized with solid sodium hydrogencarbonate and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness in vacuo to give a crude mixture, which was purified by column chromatography ($CHCl_3$) to afford two main fractions. The first fraction provided pure aminoaldehyde (**9**) (88 mg, 56%). Mp 113–114°C (AcOEt/hexane 3:1). Anal. calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.74; H, 5.34; N, 9.29%. IR ν_{max}: 3476 and 3370 (Ar-NH_2), 3250 (Ar-N*H*CO), 1683 (Ar-CHO), 1651 (Ar-NHC=*O*). ^{1}H-NMR ($CDCl_3$) δ: 3.77 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.1 (d, 1H, $J = 8.7$ Hz, Ar 5-H), 6.22 (br s, 2H, Ar-NH_2), 6.70 (d, 1H, $J = 8.7$ Hz, Ar 4-H), 7.15 (t, 1H, $J = 7.5$ Hz, Ar 4′-H), 7.55 (td, 1H, $Jo = 8.7$ Hz, $J\ m = 1.7$ Hz, Ar 5′-H), 7.61 (dd, 1H, $Jo = 7.6$ Hz, $Jm = 1.6$ Hz, Ar-3′-H), 8.87 (d, 1H, $J = 8.6$ Hz, Ar-6′-H), 9.9 (s, 1H, Ar-CHO), 12.2 (s, 1H, Ar-NHCO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 55.5, 56.1, 95.9, 105.3, 112.2, 121.1, 122.5, 123.0, 135.5, 136.1, 140.6, 141.9, 142.5, 152.6, 167.8, 194.1.

The second fraction isolated from the column provided diazocinone **11**:

7,10-Dimethoxy-dibenzo[*b*,*f*] [1,5]-diazocine-6-(5*H*)-one (11). (37 mg, 32%), white powder. Mp 78–80 °C (AcOEt/hexane 3 : 1). Anal. calcd. for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 67.74; H, 5.14; N, 9.89%. IR ν_{max}: 3252 (Ar CO*NH*-Ar), 1636 (Ar-*CO*NH-Ar), 1610 (Ar-C=N-Ar). ^{1}H-NMR ($CDCl_3$) δ: 3.59 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.66 (d, 1H, $J = 8.9$ Hz, Ar 8-H or 9-H), 6.81 (d, 1H, $J = 8.9$ Hz, Ar-9-H or 8-H), 7.06 (t, 1H, $J = 7.4$ Hz, Ar 2-H), 7.30 (dd, 1H, $Jo = 7.7$ Hz, $Jm = 1.4$ Hz, Ar 1-H), 7.39 (td, 1H, $Jo = 7.87$ Hz, $Jm = 1.4$ Hz, Ar 3-H), 8.30 (s, 1H, Ar 12-H), 8.78 (d, 1H, $J = 8.33$, Ar-4-H), 12.34 (s, 1H, Ar-N*H*CO). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.6 (2 × C), 107.8, 113.4, 119.9, 120.6, 120.8, 123.1,132.8, 134.7, 138.7, 139.7, 144.5, 151.6, 164.2, 167.3.

Reduction of *N*-(2-formylphenyl)-2-nitrobenzamide (8). The reduction of *N*-(2-formylphenyl)-2-nitrobenzamide **8** afforded a complex mixture of products, where it was only possible to isolate diazocinone **12.**

Dibenzo [*b,f*] [1,5]-diazocine-6-(5*H*)-one (12). Compound (**12**) (37.8 mg, 36%), obtained from nitrobenzamide (**8**) (128 mg, 0.47 mmol) and powder iron (210 mg, 3.76 mmol), white powder, mp 265 °C (decomp). (CH_2Cl_2/hexane 3 : 1). Anal. calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.74; H, 4.37; N, 12.58%. IR ν_{max}: 3258 (Ar-CONH-Ar), 1639 (Ar-CONH-Ar), 1615 (Ar-C=N-Ar). ^{1}H-NMR (DMSO-d_6) δ: 6.56 (s,1H, Ar 12-H), 6.85 (t, 1H, $J = 7.4$ Hz, Ar-2-H), 6.96 (d, 1H, $J = 6.8$ Hz, Ar 10-H or Ar-4-H), 6.97 (d, 1H, $J = 7.2$ Hz, Ar 4-H, or Ar- 10-H), 7.21–7.24 (m, 2H, Ar 3-H, and Ar-8-H), 7.38 (td, 1H, *Jo* = 7.7 Hz, *Jm* = 1.5 Hz, Ar 9-H), 7.52 (s, 1H, Ar-NHCO), 7.71 (d, 2H, $J = 6.73$ Hz, Ar- 1-H, and Ar-7-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 116.0, 116.6, 119.0, 127.3, 127.9, 128.7, 129.9, 130.1, 133.5,133.9, 139.8, 150.0, 163.2, 166.7.

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