An Unusual Intramolecular Aromatic Nucleophilic Addition to an Activated Diazonium Salt

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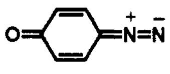
Introduction

The diazonium function has been reported as the strongest activating group for nucleophilic aromatic substitution.[2-4] The first observations of this reaction were published almost 100 years ago and described the displacement of halogen atoms from the *para* positions of diazonium salts with halide[5] and thiocyanate[6] ions as the nucleophiles. Since then, nitro, alkoxy, and halogens *ortho* or *para* to the diazonium group were sometimes replaced by the hydroxyl function from water or halide ions.[7] The former affords quinone diazides 1, while the latter yield a new diazonium salt. The effect is especially pronounced when an electron-withdrawing group is located *ortho* to the leaving group *in addition to* the *p*-diazonium function.[8] The *ortho* position was the preferred site of substitution when identical leaving groups were present at both *ortho* and *para* positions in a diazonium salt.[9]



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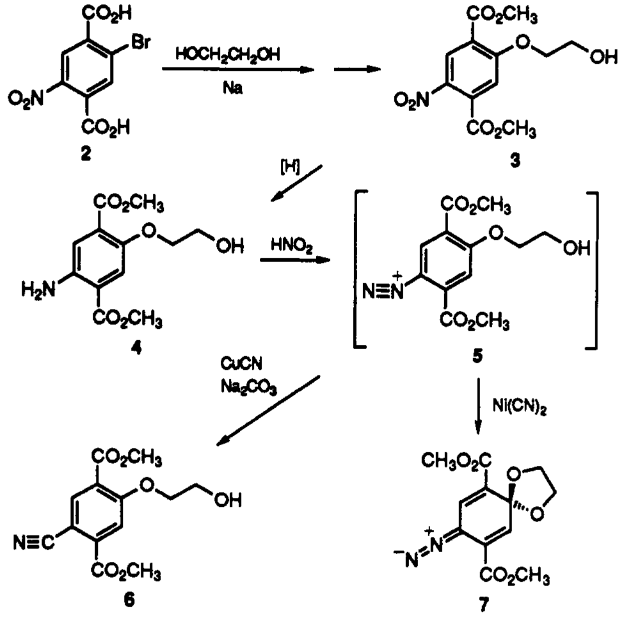
In the present work, an unusual *intramolecular nucleophilic addition* to, rather than substitution of, a dicarbomethoxy-substituted diazonium salt is reported which produced a stable ketal-protected quinone diazide. The authors are not aware of any analogous additions to diazonium salts under similar conditions.

Results and Discussion



Our laboratory has been working on the syntheses of a series of electron acceptors that include some of the steps shown in the accompanying scheme. 2-Bromo-5-nitroterephthalic acid (2) is a known compound that can be prepared from 2-bromoterephthalic acid by a mixed-acid nitration.[10] The starting material was then treated in successive steps to a Williamson reaction and an esterification to afford the nitro alcohol, 3, followed by catalytic reduction to dimethyl 2-(2′-hydroxyethoxy)-5-aminoterephthalate (4). Attempts were then made to replace the amine with a cyano function via a Sandmeyer-type reaction. Copper(I) cyanide produced the expected product, 6, in low yield (12%). When the alcohol function of 4 was protected as an acetate ester, the yield of the cuprous cyanide reaction was no better (~10%). However, when nickel cyanide (from nickel(II) nitrate hexahydrate, KCN, and NaOH) was used in an effort to improve the yield of 6, a new product was isolated whose elemental analysis indicated two nitrogen atoms per molecule instead of the anticipated one. The infrared spectrum showed the usual absorptions for the ester functions, but the expected nitrile stretching frequency (2235 cm^{-1}) was absent and a strong, sharp peak was observed at 2089 cm^{-1} (diazo group stretching) instead. The mass spectrum confirmed a molecular weight of 280 which agreed with the molecular formula of $C_{12}H_{12}N_2O_6$ obtained from elemental analysis. The ultraviolet spectrum showed two absorptions at shorter wavelengths than those of the aminoterephthalate starting material, 4. Finally, X-ray crystallography provided conclusive evidence that the product was a ketal of a dicarbomethoxyquinone diazide, 7: the reaction yield was 73%. These results imply an uncommon intramolecular attack by the alcohol oxygen atom on the carbon atom activated by the *para*-diazonium function. Apparently, the somewhat more basic medium of the nickel cyanide reaction sufficiently increases the nucleophilicity of the alcohol enough to initiate the cyclization reaction.

Experimental Section[11]

5-Nitro-2-bromoterephthalic Acid (2). A mixture of 24 g (0.097 mol) of 2-bromoterephthalic acid and 120 mL of concd sulfuric acid was stirred in an ice–water bath. Twenty mL of a mixture of sulfuric acid and nitric acid (1:1) was added dropwise. The mixture was warmed on a steam bath with occasional shaking for 2 h and then stored at rt for 8 h. The reaction mixture was poured into 1 L of ice–water, and the resulting white solid was collected, washed with water, and dried in an oven for 8 h. A crude product (22.5 g) was obtained which was recrystallized from 100% formic acid to afford 19 g (68%) of 2: mp 261–264 °C (lit.[10] mp 260–262 °C); IR (KBr) 3400 (OH), 3067 (CH), 1707 (C=O), 1534 (NO_2), 1341 (NO_2), 1270 (CO) cm^{-1}; ^{1}H-NMR (DMSO) δ 8.34 (1H, s), 8.18 (1H, s).

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[11] For a summary of some of the experimental protocols see: Torres, E.; Panetta, C. A.; Heimer, N. E.; Clark, B. J.; Hussey, C. L. *J. Org. Chem.* **1991**, *56*, 3737.

5-Nitro-2-(2′-hydroxyethoxy)terephthalic Acid. Sodium metal (1.5 g, 0.065 g mol) and 30 mL of ethylene glycol were stirred at 50–60 °C under nitrogen. After a solution was formed, it was stirred for an extra 30 min at 60 °C. 5-Nitro-3-bromoterephthalic acid (**2**, 4 g, 0.0138 mol) was added and a red solution formed after about 30 min, which was stirred at 110 °C for 10 h. After the mixture was cooled to rt, 10 mL of cold water was added and the solution was poured into ice–water. The result was acidified with 1.2 N HCl and extracted with EtOAc. The organic layer was washed with water and dried with anhyd $MgSO_4$. The solvent was removed by distillation under reduced pressure, and the crude product was recrystallized from EtOAc to yield 2.5 g (67%) of product: mp 171–173 °C; IR (KBr) 3519 (OH), 3412 (OH), 2950 (CH), 1723 ($C{=}O$), 1703 ($C{=}O$), 1525 (NO_2), 1349 (NO_2), 1253 (CO) cm^{-1}; ^1H-NMR (CD_3COCD_3) δ 8.49 (1H, s), 7.56 (1H, s), 4.49 (2H, t, J = 4.7 Hz, CH_2), 3.97 (2H, t, J = 4.7 Hz, CH_2). Anal. Calcd for $C_{10}H_9NO_8$: C, 44.28; H, 3.32; N, 5.17. Found: C, 44.30; H, 3.43; N, 4.98.

Dimethyl 5-Nitro-2-(2′-hydroxyethoxy)terephthalate (3). 5-Nitro-2-(2′-hydroxyethoxy)terephthalic acid (23.0 g, 0.011 mol) and 20 mL of thionyl chloride were heated at reflux for 30 min. A solution was formed, and the excess of thionyl chloride was removed by distillation under reduced pressure. The residue was dissolved in 20 mL of dry $CHCl_3$, and this was cooled in an ice bath while 20 mL of a 1:1 mixture of $CHCl_3$ and methanol was added dropwise. The solution was stirred at rt for 18 h, and the solvents were then removed to afford 4.2 g of a residue that was purified by column chromatography (EtOAc:hexane = 7:3) affording 3 g (90%) of a homogeneous oil (**3**): IR (neat) 3462 (OH), 2957 (CH), 1740 ($C{=}O$), 1527 (NO_2), 1438 (CH_3), 1346 (NO_2), 1256 (CO) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 8.58 (1H, s), 7.18 (1H, s), 4.31 (2H, t, J = 4.5 Hz), 4.00 (2H, t, J = 4.5 Hz), 3.96 (3H, s), 3.95 (3H, s).

Dimethyl 5-Amino-2-(2′-hydroxyethoxy)terephthalate (4). Dimethyl 5-nitro-2-(2′-hydroxyethoxy)terephthalate (500 mg, 1.67 mmol, **3**) was dissolved in 30 mL of 95% ethanol, and the solution was added to 50 mg of 10% Pd–C in a 500-mL pressure bottle. The bottle was shaken for 1 h under 50 psi of H_2. The color of the reaction mixture changed from light yellow to green. The mixture was filtered, and the solvent was removed by distillation. The residual solid was recrystallized from benzene to obtain 460 mg (90%) of **4**: mp 82–83 °C; IR (KBr) 3446 (OH), 3341 (NH), 2945 (CH), 1710 ($C{=}O$), 1698 ($C{=}O$), 1440 (CH_3), 1209 (CO) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.52 (1H, s), 7.13 (1H, s), 4.17 (2H, t, J = 4.4 Hz), 3.90 (6H, s) 3.86 (2H, t, J = 4.4 Hz); UV (EtOH) 231 nm (ϵ 20 000) 385 nm (ϵ 3500). Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.58; N, 5.20. Found: C, 53.40; H, 5.60; N, 5.16.

Dimethyl 5-Cyano-2-(2′-hydroxyethoxy)terephthalate (6). One g (0.0037 mol) of dimethyl 5-amino-2-(2′-hydroxyethoxy)-terephthalate (**4**), 3 mL of water, and 0.5 mL of concd HCl were warmed on a steam bath. A clear solution was formed and was cooled in an ice bath. $NaNO_2$ (0.3 g, 0.0043 mol) in 2 mL of water was added to the cooled solution. The resulting solution was stored at 0–5 °C. In another flask were placed 1.0 g (0.011 mol) of CuCN and 30 mL of water, and this mixture was stirred at 60–70 °C. The diazonium salt solution was treated with solid Na_2CO_3 until it was neutral to litmus, and the resulting solution was added to the CuCN solution. The reaction solution was stirred at 60 °C for 1 h and was then extracted with $CHCl_3$ (50 mL). The $CHCl_3$ layer was washed with water twice and was dried with anhyd $MgSO_4$. The solvent was removed by distillation under reduced pressure leaving 1.0 g of a residue which by TLC was a multicomponent mixture. A homogeneous product was isolated by centrifugally-accelerated radial thick-layer (2 mm) chromatography (Chromatotron, Harrison Research, Palo Alto, CA, EtOAc:hexane = 1:1) and was recrystallized from benzene to afford 0.12 g (12%) of **6**: mp 95–96 °C; IR (KBr) 3448 (OH), 3377 (OH), 2955 (CH), 2235 ($C{\equiv}N$), 1745 ($C{=}O$), 1724 ($C{=}O$), 1437 (CH_3), 1263 (CO) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 8.24 (1H, s), 7.72 (1H, s), 4.33 (2H, t, J = 4.5 Hz), 4.03 (3H, s), 3.10 (2H, t, J = 4.5 Hz), 3.95 (3H, s). Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.66; N, 5.02. Found: C, 55.72; H, 4.76; N, 4.92.

Ketal of 2,5-Dicarbomethoxyquinone Diazide (7).[12] One g (0.0037 mol) of dimethyl 5-amino-2-(2′-hydroxyethoxy)terephthalate (**4**) was dissolved in 1 mL of water and 0.75 mL of concd HCl on a steam bath. The solution was cooled in an ice bath, and a solution of 0.3 g (0.0043 mol) of $NaNO_2$ in 0.5 mL of water was added dropwise. The resulting solution was stored in an ice bath. In another flask, 1.5 g (0.0052 mol) of $Ni(NO_3)_2$ hexahydrate, 0.9 g (0.014 mol) of KCN, 0.3 g (0.0075 mol) of NaOH, and 4 mL of water were mixed at rt to form a green solution. This solution was then cooled in an ice bath. The diazonium salt solution was added to the nickel cyanide solution, and the resulting reaction mixture was stirred for 30 min. It was extracted with 30 mL of $CHCl_3$, and the organic layer was dried with anhyd $MgSO_4$. The solution was concentrated under reduced pressure, and the crude residue was recrystallized from EtOAc to yield 0.76 g (73%) of **7**: mp 152–153 °C; IR (KBr) 2944 (CH), 2089 ($C{=}N{=}N$), 1728 ($C{=}O$), 1689 ($C{=}O$), 1417 (CH_3), 1255 (CO), 1206 (C-O) cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.71 (1H, s), 6.35 (1H, s), 4.35–4.31 (2H, m), 4.18–4.14 (2H, m), 3.86 (3H, s), 3.78 (3H, s); MS m/z (relative intensity) 280 (M^+, 13.0), 252 (4.7), 221 (43.1), 193 (22.2), 164 (100), 78 (20.9) 62 (35.3) 45 (43.2); UV (EtOH) 214 nm (ϵ 16 000), 321 nm (ϵ 10 000). Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.29; N, 10.00. Found: C, 51.56; H, 4.30; N, 9.97.

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Supplementary Material Available: X-ray diffraction data for the ketal quinone diazide **7** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] The author has deposited atomic coordinates for **7** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.