A General Synthesis of 4-Substituted 1,1-Dioxo-1,2,5-thiadiazolidin-3-ones Derived from α-Amino Acids

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Introduction

In recent years, a large effort has been expended by many investigators on the search for novel sweeteners. The commercial success of aspartame demonstrated the existence of a large market for nonnutritive sweeteners.

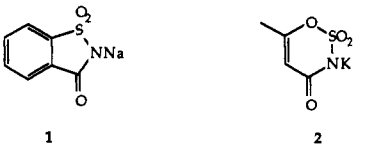
Sodium saccharin (1)[1] and acesulfam-K (2)[2] are attractive sweeteners because of their low cost, high solubility in aqueous solutions, and high hydrolytic stability (Scheme I). The essential pharmacophore in saccharin and acesulfam-K is believed to be the sulfonimide moiety. Both are far from ideal sweeteners because of poor flavor profiles.[3] We became interested in sulfonimide sweeteners because of the attractive cost, solubility, and stability properties. We were especially interested in 4-substituted 1,1-dioxo-1,2,5-thiadiazolidin-3-ones **3** since their hydrolysis products are anticipated to be α-amino acids and ammonium sulfate. We report here a new facile synthetic method for the synthesis of these heterocycles from α-amino acid esters and chlorosulfonyl isocyanate (Scheme II).

Four target compounds were chosen so as to cover a range of heterocyclic hydrophobicity. These compounds, **3a–d**, can be considered to be derived from glycine, D,L-alanine, D,L-phenylalanine, and D,L-methionine, respectively.

No general methods of preparing 4-substituted 1,1-dioxo-1,2,5-thiadiazolidin-3-ones were found in the literature, although other substitutions of the 1,1-dioxo-thiadiazolidinone ring are known.[4] Chlorosulfonyl isocyanate has been found to be a versatile reagent in organic synthesis.[5,6] It has found considerable use in the synthesis of heterocycles. Chlorosulfonyl isocyanate contains the requisite sulfonyl group and one of the nitrogens of the 1,1-dioxo-1,2,5-thiadiazolidin-3-ones. Treatment of chlorosulfonyl isocyanate with benzyl alcohol at 0 °C in methylene chloride followed by in situ treatment with amino acid ester hydrochlorides and triethylamine in methylene chloride gave the desired sulfamides **4** in good yield (70–90%). These compounds were readily purified by recrystallization or silica gel chromatography.

The benzyloxycarbonyl protecting groups of **4** were removed by hydrogenolysis under 60 psi of hydrogen in the presence of 5% Pd/C to yield the unprotected sulfamides **5** in nearly quantitative yields except for the methionine case. Deprotection of **4d** was achieved by iterative treatment with fresh batches of 5% Pd/C catalyst. The observed lethargy in the hydrogenolysis of **4d** was probably due to catalyst poisoning by the divalent sulfur moiety.

Scheme I



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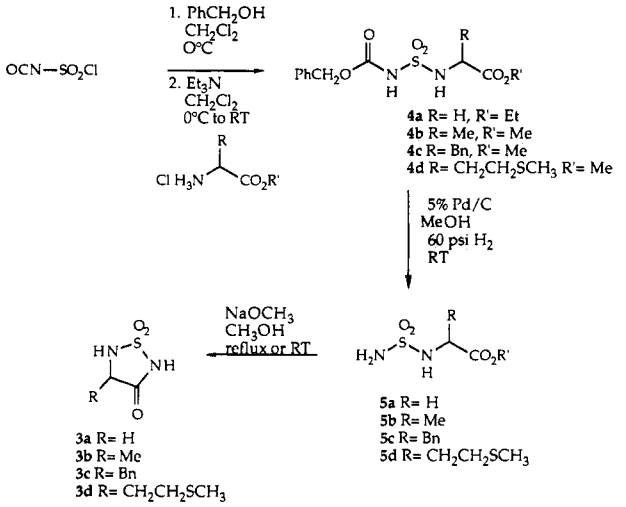
Scheme II



Syntheses of the 1,1-dioxo-1,2,5-thiadiazolidin-3-ones were completed by sodium methoxide promoted cyclization of sulfamides **5**. In all cases the heterocycle was formed in good yield.[7]

Compounds **3a–d** were evaluated for sweet taste at concentrations of 0.01 mg/mL, 0.1 mg/mL, and 1.0 mg/mL in water. Sweet taste intensities equivalent to 2% sucrose would be indicative of sweetness potencies of 2000, 200, and 20 times sucrose, respectively. None of **3a–d** were found to be sweet even at 1.0 mg/mL. These results are quite surprising in view of the general sweet taste activity among sulfonimide sweeteners.

In summary, a simple, facile, general four-step synthesis of 4-substituted 1,1-dioxo-1,2,5-thiadiazolidin-3-ones from α-amino acids and chlorosulfonyl isocyanate has been developed. These cyclic sulfonimides, although analogous to sodium saccharin and acesulfam-K, are not sweet or have sweetness potencies of less than 10 times sucrose.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. IR spectra were taken as KBr pellets on a Perkin-Elmer Model 283 or 681 instrument. NMR spectra were obtained on either a Varian FG-80 or General Electric QE-300 spectrometer. Microanalyses were performed by the Searle Laboratories Microanalytical Department. Chromatography was performed according to the method of Still.[8] Hydrogenolyses were done on a Parr shaker type hydrogenation apparatus No. 3911 with 5% Pd/C catalyst purchased from Aldrich.

***N*-(Carbethoxymethyl)-*N'*-carbobenzyloxysulfamide (4a).** To a stirred solution of 7.36 mL of chlorosulfonyl isocyanate (12.00 g, 84.8 mmol) in 180 mL of dichloromethane at 0 °C was added 8.82 mL of benzyl alcohol (9.17 g, 84.8 mmol) at such a rate that the reaction solution temperature did not rise above 5 °C. After being stirred for 1.5 h, a solution (trace amounts of solid was present) of glycine ethyl ester hydrochloride (13.02 g, 93.27 mmol)

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and 35.3 mL of triethylamine (25.6 g, 253 mmol) in 540 mL of dichloromethane was added at a rate so that the reaction temperature did not rise above 5 °C. When the addition was complete, the reaction solution was allowed to warm to room temperature, while being stirred overnight. The reaction mixture was poured into 600 mL of 10% HCl saturated with NaCl. The organic layer was separated and the aqueous layer extracted with ether (2 × 250 mL, 1 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield 26.75 g (99%) of crude product. Recrystallization from $CHCl_3$/hexane (70 mL/125 mL) afforded 22.5 g (76%) of analytically pure **4a** as a white powder: ^1H NMR ($CDCl_3$) δ 7.90 (br s, 1 H), 7.30 (s, 5 H), 5.90 (t, 1 H, J = 5.8 Hz), 5.15 (s, 2 H), 4.15 (q, 2 H, J = 7.0 Hz), 3.92 (d, 2 H, J = 5.8 Hz), 1.23 (t, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.54; H, 5.10; N, 8.86. Found: C, 45.47; H, 5.08; N, 8.91.

***N*-(Carbethoxymethyl)sulfamide (5a).** A solution of compound **4a** (19.08 g, 60.3 mmol) in 200 mL of methanol was treated with 1.9 g of 5% Pd/C under a 60-psi atmosphere of hydrogen at room temperature in a Parr shaker for 2 h. The reaction mixture was then filtered through Celite and concentrated to afford 13.15 g (quantitative yield) of the desired product **5a** as a white solid: mp 46–47 °C; IR (KBr) cm^{-1} 3295, 2990, 2970, 1790, 1560; ^1H NMR ($CDCl_3$) δ 5.67 (t, 1 H, J = 5.8 Hz), 5.59 (br s, 2 H), 4.20 (q, 2 H, J = 7.0 Hz), 3.90 (d, 2 H, J = 5.8 Hz), 1.29 (t, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 26.37; H, 5.53; N, 15.38. Found: C, 26.58; H, 5.45; N, 15.43.

1,1-Dioxo-1,2,5-thiadiazolidin-3-one (3a). To a stirred solution of NaOMe (91 mmol) in 250 mL of dry methanol was added ester **5a** (11.67 g, 64.05 mmol). The resulting solution was heated to reflux for 20 h. After cooling to room temperature, the base was neutralized by treatment with Bio-Rad AG 50W-X12 H^+ ion-exchange resin (36 g, 93–105 mmol). The reaction mixture was then filtered and concentrated in vacuo to yield 6.68 g (77%) of the crude product. Microanalysis revealed the presence of sodium. Thus, the crude product was redissolved in MeOH and then treated with Bio-Rad AG 50W-X12 H^+ ion-exchange resin. After filtration, the solution was decolorized with Norit A and concentrated to a wax. Recrystallization from iPrOH/hexane (40 mL/90 mL) afforded 2.70 g (33%) of the desired product as a waxlike solid: mp 132–139.5 °C; ^1H NMR (DMSO-d_6) δ 8.50 (br s, 2H), 3.92 (s, 2H); HRMS calcd for $C_{12}H_{16}N_2O_6S$ 134.9864, found 134.9861. Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 17.65; H, 2.96; N, 20.58, S, 23.55. Found: C, 18.11; H, 3.19, N, 20.27; S, 23.46.

***N*-(1-Carbomethoxyethyl)-*N'*-carbobenzyloxysulfamide (4b).** Compound **4b** was prepared analogously to **4a**, except D,L-alanine methyl ester hydrochloride was used in place of glycine ethyl ester hydrochloride. The crude product was recrystallized from $CHCl_3$/hexane (60 mL/45 mL), affording after drying in vacuo 25.81 g (83%) of analytically pure **4b** as a white powder: mp 91.5–92.5 °C; IR (KBr) cm^{-1} 3420, 3280, 3205, 1750, 1720, 1470; ^1H NMR ($CDCl_3$) δ 7.98 (br s, 1 H, CONHS), 7.33 (s, 5 H, Ph), 6.00 (d, 1 H, J = 8 Hz, NH), 5.16 (s, 2 H, CH_2Ph), 4.26 (dq, 1 H, CH, J = 8 Hz, J = 7.2 Hz), 3.67 (s, 3 H, CO_2CH_3), 1.41 (d, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.7 (CO_2Me), 151.5, 134.7, 128.6, 128.4, 68.4, 52.8, 52.4, 19.0. Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.56; H, 5.10; N, 8.86; S, 10.14. Found: C, 45.48; H, 5.08; N, 8.79; S, 10.13.

***N*-(1-Carbomethoxyethyl)sulfamide (5b).** Compound **5b** was prepared, analogously to **5a**, from **4b**, yielding 14.3 g (98%) of sulfamide **5b** as a solid: mp 67.5–68.5 °C; TLC (1/9 MeOH/CH_2Cl_2, I_2 stain) R_f = 0.46; IR (KBr) cm^{-1} 3330 (vs), 3270 (vs), 3250 (vs), 1730 (vs), 1565 (w), 1455 (m), 1435 (s), 1345 (s), 1320 (s), 1305 (s); ^1H NMR (DMSO-d_6) δ 7.05 (d, 1 H, J = 8.8 Hz), 6.54 (s, 2 H, NH_2), 3.93 (dt, 1 H, J = 8.8 Hz, J = 7.2 Hz), 3.64 (s, 3 H, CO_2CH_3), 1.28 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 173.3 (CO), 51.8 (OCH_3), 50.9 (CH), 18.2. Anal. Calcd for $C_9H_{10}N_2O_3S$: C, 26.37; H, 5.53; N, 15.38; S, 17.60. Found: C, 26.42; H, 5.46; N, 15.31; S, 17.93.

4-Methyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one (3b). Compound **3b** was prepared, analogously to **3a**, from **5b**, except the crude product, a white powder, needed no purification to afford 8.87 g (98%) of **3b**: mp 85–87 °C; ^1H NMR (CD_3OD) δ 4.29 (q, 1 H, J = 7.2 Hz), 1.45 (d, 3 H, J = 72 Hz); ^{13}C NMR (CD_3OD) δ 174.5 (CO), 58.6 (CH), 17.2 (CH_3). Anal. Calcd for $C_3H_6N_2O_3S$: C, 24.00; H, 4.03; N, 18.66; S, 21.35. Found: C, 24.18; H, 4.08; N, 18.55; S, 21.67.

***N*-(1-Carbomethoxy-2-phenylethyl)-*N'*-carbobenzyloxysulfamide (4c).** Compound **4c** was prepared analogously to **4a**, except D,L-phenylalanine methyl ester hydrochloride was substituted for glycine ethyl ester hydrochloride. Recrystallization of the crude product from hexane/$CHCl_3$ yielded 19.05 g (70%) of pure **4c** as a white solid. An additional 5.98 g (22%) of **4c** was isolated from the mother liquor: mp 101.5–102.5 °C; IR (KBr) cm^{-1} 3470 (NH), 3280, 3040, 2960, 1740, 1720; ^1H NMR ($CDCl_3$) δ 7.64 (s, 1 H), 7.32 (s, 5 H, Ph), 7.18 (m, 5 H, Ph), 5.73 (d, J = 8 Hz, 1 H, NH), 5.13 (d, J = 12 Hz, 2 H, CH_2Ph), 5.06 (d, J = 12 Hz, 2 H, OCH_2Ph), 4.50 (dd, J = 6 Hz, 2 H), 3.62 (s, 3 H, CO_2CH_3), 3.07 (d, J = 7 Hz, 2 H, CH_2Ph); ^{13}C NMR ($CDCl_3$) δ 171.4, 135.1, 134.7, 129.4, 128.6, 128.3, 127.2, 68.4, 57.7, 52.6, 38.8. Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 54.84; H, 5.12; N, 7.19.

***N*-(1-Carbomethoxy-2-phenylethyl)sulfamide (5c).** Compound **5c** was prepared, analogously to **5a**, from **4c** to afford 12.05 g (99%) of **5c** as a solid: mp 114.5–115.5 °C; TLC (0.5/9.5 CH_3OH/CH_2Cl_2, I_2 stain) R_f = 0.30; IR (KBr) cm^{-1} 3480 (vs), 3030 (w), 2960 (w), 1735 (vs), 1550 (m), 1500 (m), 1460 (s), 1435 (s), 1350 (vs), 1325 (s); ^1H NMR (CD_3OD) δ 7.2 (s, 5 H, Ph), 4.2 (dt, 2 H, J = 7 Hz, CH), 3.65 (s, 3 H, CO_2CH_3), 3.0 (dd, 2 H, J = 7 Hz, CH_2Ph); ^{13}C NMR (CD_3OD) δ 173.9 (CO), 137.5, 130.3, 129.2, 127.7, 58.6, 52.5, 39.7. Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50, H, 5.46; N, 10.85. Found: C, 46.33; H, 5.39; N, 10.68.

4-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one (3c). Compound **3c** was prepared, analogously to **3b**, from **5c** to afford 9.12 g (91%) of **3c** as a white solid: mp 163–164 °C; IR (KBr) cm^{-1} 3420, 3300, 3240, 1745, 1720, 1350, 1325, 1300, 1290, 1170, 1160; ^1H NMR (DMSO-d_6) δ 9.5–795 (br m, 2 H, 2 NH), 7.26 (s, 5 H, Ph), 4.41 (dd, 1 H, J = 4 Hz, J = 10 Hz), 3.14 (dd, 1 H, J = 14 Hz, J = 4 Hz), 2.76 (dd, 1 H, J = 10 Hz, J = 4 HZ); ^{13}C NMR (DMSO-d_6) δ 1713, 136.7, 129.3, 128.2, 126.6, 62.3, 36.6. Anal. Calcd for $C_9H_{10}N_2O_3S$: C, 47.38; H, 4.45; N, 12.38; S, 14.17. Found: C, 47.68; H, 4.44; N, 12.38; S, 14.22.

***N*-[1-Carbomethoxy-3-(methylthio)propyl]-*N'*-carbobenzyloxysulfamide (4d).** Sulfamide **4d** was prepared analogously to **4a**, except D,L-methionine methyl ester hydrochloride was substituted for glycine ethyl ester hydrochloride. The crude product was purified by chromatography on a Waters LC 500A (silica gel, 2 columns, 7.5/92.5 EtOAc/hexane) to yield 22.15 g (67%) of the **4d** as a white powder: mp 79–82 °C; ^1H NMR ($CDCl_3$) δ 7.85 (s, 1 H, NHCO), 7.32 (s, 5 H, Ph), 6.25 (d, 1 H, J = 8 Hz), 5.15 (s, 2 H, CH_2Ph), 4.35 (m, 1 H, CH), 3.18 (s, 3 H, CO_2CH_3), 2.55 (t, 2 H, J = 8 Hz), 2.10 (m, 2 H), 2.07 (s, 3 H). Anal. Calcd for $C_{14}H_{20}N_2O_6S_2$: C, 44.67; H, 5.36; N, 7.44; S, 17.04. Found: C, 44.64; H, 5.33; N, 7.45; S, 17.22.

***N*-[1-Carbomethoxy-3-(methylthio)propyl]sulfamide (5d).** A solution of **4d** (19.18 g, 50.95 mmol) in 190 mL of methanol was treated with 43.16 g of 5% Pd/C (added in 3 portions) under 60 psi atmosphere of hydrogen in a Parr hydrogenator at room temperature. The reaction mixture was then filtered though Celite and concentrated to afford 9.83 g (80%) of the crude product as an oil. Crystallization from hexane/iPrOH (40 mL/80 mL) afforded 6.16 g (50%) of **5d**: mp 64–67 °C; ^1H NMR (CD_3OD) δ 4.19 (dd, 1 H, J = 5.5 Hz, J = 8.0 Hz), 3.75 (s, 3 H), 2.61 (m, 2 H), 2.08 (s, 3 H, SCH_3), 2.0 (m, 2 H); ^{13}C NMR (CD_3OD) δ 174.5, 56.1, 52.9, 33.1, 30.7, 15.1. Anal. Calcd for $C_6H_{14}N_2O_4S_2$: C, 29.74; H, 5.8; N, 11.56; S, 26.46. Found: C, 29.89; H, 5.85; N, 11.63; S, 26.30.

4-[2-(Methylthio)ethyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (3d). Compound **3d** was prepared analogously to **3a**, except the reaction was run at room temperature for 3 h. The crude product was isolated as an oil, which was crystallized by dissolving in iPrOH, concentrating in vacuo, and adding CH_2Cl_2. The product was isolated by filtration. The white solid was dried in vacuo at 50 °C to afford 2.85 g (55%) of **3d**: mp 80–82.5 °C; IR (KBr) cm^{-1} 3300, 3240, 3160, 1740, 1700, 1440, 1430, 1415, 1350, 1320; ^1H NMR (CD_3OD) δ 4.30 (dd, 2 H, J = 5.0 Hz, J = 8.0 Hz), 2.75–2.45 (m, 2 H), 2.08 (s, 3 H); ^{13}C NMR (CD_3OD) δ 173.7, 61.5, 32.0, 30.8, 15.0. Anal. Calcd for $C_5H_{10}N_2O_3S$: C, 28.56; H, 4.79; N, 13.32; S, 30.49. Found: C, 28.69; H, 4.76; N, 13.52; S, 30.48.

Registry No. **3a**, 121142-96-9; **3b**, 121142-97-0; **3c**, 121142-98-1; **3d**, 121142-99-2; **4a**, 121142-89-0; **4b**, 121157-68-4; **4c**, 121142-90-3;

4d, 121142-91-4; **5a**, 121142-92-5; **5b**, 121142-93-6; **5c**, 121142-94-7; **5d**, 121142-95-8; $OCNSO_2Cl$, 1189-71-5; H-Gly-OEt·HCl, 623-33-6; H-DL-Ala-OMe·HCl, 13515-97-4; H-DL-Phe-OMe·HCl, 5619-07-8; H-DL-Met-OMe·HCl, 16118-36-8.

Disproportionation of 4-Nitroacetophenone to 4-Aminoacetophenone and 4-Nitrobenzoic Acid

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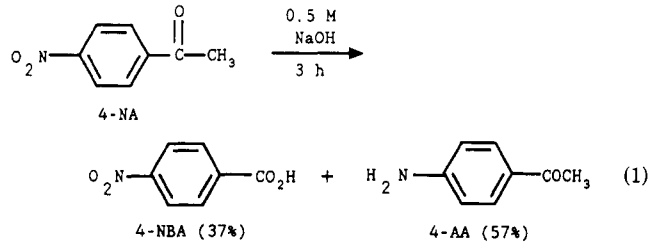
The base-catalyzed aldol condensation of an aldehyde or ketone containing an α-hydrogen involves initial ionization of the α-proton to form an enolate ion, followed by addition to the carbonyl of another molecule of substrate.[1] The Cannizzaro reaction is a disproportionation of an aldehyde lacking an α-hydrogen, to give an equimolar mixture of the corresponding alcohol and acid, usually under strongly basic conditions, the mechanism of which is believed to involve transfer of a hydride ion.[2,3] Aldehydes containing an α-hydrogen may also react via the Cannizzaro pathway when the aldol reaction is slow, although this is rare.[2] We now report an unusual disproportionation reaction of 4-nitroacetophenone (4-NA) in aqueous NaOH, to give 4-aminoacetophenone (4-AA) and 4-nitrobenzoic acid (4-NBA) in high yield. The reaction is interesting for three reasons: (i) 4-NA does not undergo the expected aldol reaction; (ii) the disproportionation reaction is the equivalent of a "Cannizzaro" reaction for 4-NA; and (iii) the mechanism probably involves electron transfer from the initially generated enolate ion of 4-NA.

In a typical run, 4-NA was dissolved in CH_3CN and added to an argon-purged solution of 0.5 M NaOH. After 3 h at room temperature, the products were isolated by extraction. The isolated yields of 4-AA and 4-NBA were 57% and 37%, respectively (eq 1), with a recovery yield of ≈70–85%. The structures of the products were confirmed by comparison with the authentic materials, by ^1H NMR, IR, and MS. The reaction was found to be strongly base catalyzed, as shown in Figure 1. Below pH 11, the substrate was recovered unchanged. Above approximately



(1)

pH 13, the conversion of substrate to products was complete within the time of the experiment. Therefore, the appearance of the curves shown in Figure 1 will depend somewhat on the time allowed for reaction. No trace of the expected aldol condensation product(s) was observed in the pH range studied. When air was allowed into the system, the rate of the reaction was retarded, and when

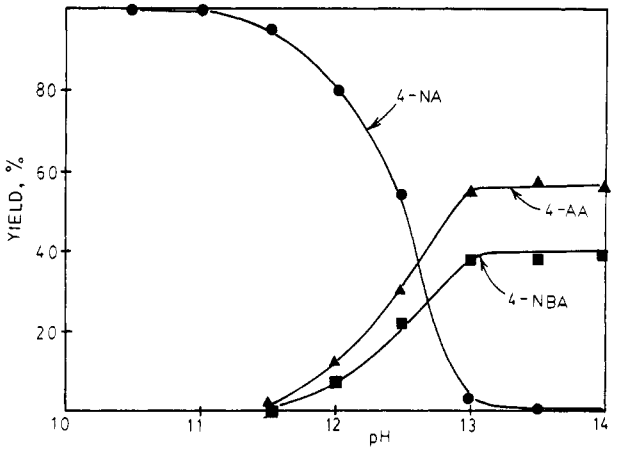
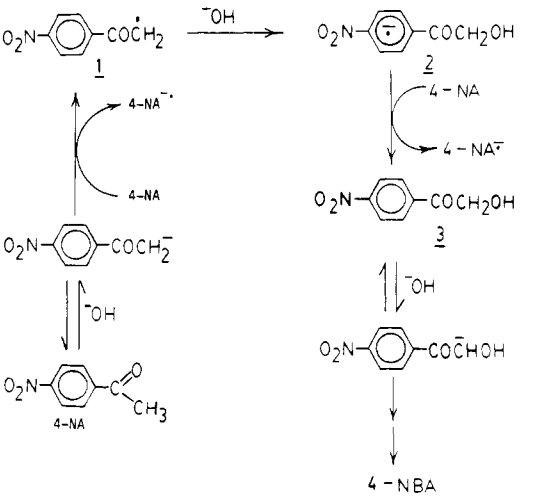


Figure 1. Plot of yield of 4-AA and 4-NBA as a function of pH of the aqueous (NaOH) portion of the solution (≈30% CH_3CN) after 3-h reaction at 22 ± 2 °C.

Scheme I



pure oxygen was used, the only product observed was 4-NBA. When a freshly prepared solution of 4-NA in aqueous NaOH was transferred to a quartz flat cell and placed in the cavity of a Bruker E200TT ESR spectrometer, strong signals assignable to the radical anion of 4-NA were observed, by comparison with the known spectrum for this species.[4] In lower base strength, the signal was weaker or not observed at all.

Neither 4-nitrobenzophenone nor 4-nitrobenzaldehyde underwent the above reaction when dissolved in aqueous NaOH, showing that the process requires the presence of ionizable α-protons. In addition, acetophenone itself failed to undergo the disproportionation, indicating the requirement of the nitro group. However, 3-nitroacetophenone did react to give 3-aminoacetophenone and 3-nitrobenzoic acid, although the rate of reaction was substantially slower than for 4-NA.

Addition of 1,4-dinitrobenzene or 4-nitrobenzonitrile, both excellent electron acceptors, to the reaction mixture resulted in a decrease in the yield of 4-AA (from 58% to 30%) but the yield of 4-NBA was unchanged. When 4-nitrobenzonitrile was used, a new product, 4-aminobenzonitrile, was observed (yield 30%) in the product mixture.

Our studies of the chemistry of photogenerated nitrobenzyl carbanions[4-6] have shown that, when photogener-

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