Nitro Olefination of Indoles and Some Substituted Benzenes with 1-Dimethylamino-2-nitroethylene

George Büchi* and Ching-Pong Mak

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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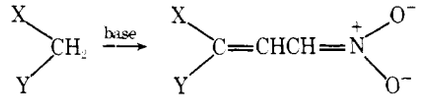
Indoles and certain hydroxy- and alkoxy-substituted benzenes condense with 1-dimethylamino-2-nitroethylene in trifluoroacetic acid to give 3-(2-nitrovinyl)indoles and β-nitrostyrenes, respectively.

Base-catalyzed condensations of 1-dimethylamino-2-nitroethylene (1) with active methylene compounds **2** such as β-diketones, β-keto esters, and cyanoacetic esters were first investigated by Severin and co-workers.[1] The resulting products **3** contain an additional two-carbon unit in which the β-carbon atom is functionalized.

$(CH_3)_2NCH{=}CHNO_2$

1



2 3

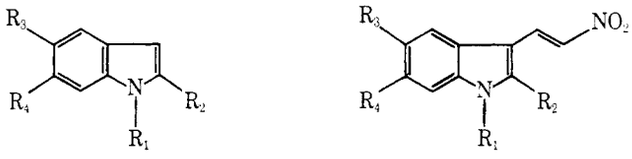
X, Y = RCO, CN, COOR

The possibility of preparing 3-(2-nitrovinyl)indoles in one step from indoles and readily available 1-dimethylamino-2-nitroethylene (1) caught our attention because reduction of the former class of substances is known to give tryptamines.[2] Conventionally, tryptamines can be prepared from indoles in three steps via 3-formylindoles and 3-nitrovinylindoles but yields in the condensation of nitromethane with 3-formylindoles are often low.

Reagent **1** was synthesized from nitromethane and dimethyl sulfate–dimethylformamide complex following a previously described procedure.[3] In the solid state, at room temperature, the compound seems to be stable indefinitely but in solution decomposition is accelerated by acids. A solution of **1** in 1 M aqueous–alcoholic hydrochloric acid at room temperature lost its intense ultraviolet absorption at 354 nm within 3 h. Similarly, prolonged exposure to acetic acid or trifluoroacetic acid led to irreversible changes. Parenthetically, the configuration of **1** remains unknown because a vicinal coupling of 10 Hz between the vinyl protons probably is of no diagnostic value in a compound in which the double bond character is reduced drastically by charge delocalization.

The condensation of indoles with dimethylaminonitroethylene (**1**) has received prior attention. Colonna and Marchetti[4] obtained 3-(2-nitrovinyl)indoles in unspecified yields from the reaction of 2-substituted indoles with **1** in the presence of a catalytic amount of hydrochloric acid in ethanol or without added catalyst in glacial acetic acid. Using this procedure, we obtained approximately 10% of 2-methyl-3-(2-nitrovinyl)indole (**11**) and 15% of 1-methyl-3-(2-nitrovinyl)indole (**12**) from 2-methyl- (**5**) and 1-methylindole (**6**), respectively. No reaction occurred when the condensations were attempted in the presence of ethyldiisopropylamine and low but not useful yields were realized when indole was replaced by its "Grignard reagent".

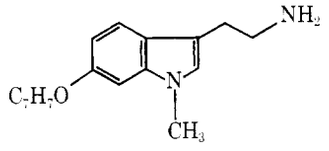
We found that 3-(2-nitrovinyl)indole (**10**) is formed in nearly quantitative yield when indole (**4**) is treated with **1** at 0 °C in trifluoroacetic acid for 10 min. Compounds **12, 13, 14,** and **15** were prepared analogously in 92, 95, 66, and 40% yield, respectively, from the indoles **6, 7, 8,** and **9.** The last example



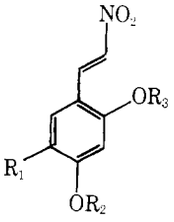
4	$R_1 = R_2 = R_3 = R_4 = H$	**10**
5	$R_1 = R_3 = R_4 = H; R_2 = CH_3$	**11**
6	$R_2 = R_3 = R_4 = H; R_1 = CH_3$	**12**
7	$R_1 = CH_3; R_2 = R_3 = H;$ $R_4 = C_7H_7O$	**13**
8	$R_1 = R_2 = R_4 = H; R_3 = OCH_3$	**14**
9	$R_1 = CH_3; R_2 = R_3 = H;$ $R_4 = C_7H_7SO_3$	**15**

suggests that electron-withdrawing substituents on the indole nucleus lower the rate of substitution, thus allowing self-decomposition of the reagent **1.** All nitrovinylindoles obtained are highly colored, crystalline substances and, unlike other nitro olefins, they showed no tendency to polymerize. Absence of infrared absorption bands typical of nitro compounds, appearance of two new bands between 1250 and 1350 cm^{-1}, intense ultraviolet absorption near 400 nm, and an AB quartet between δ 7.5 and 8.5 for the vinyl protons are characteristic of these substances. Reduction of the nitrovinylindoles to the corresponding tryptamines was accomplished most conveniently with lithium aluminum hydride.[5,6] The utility of this new tryptamine synthesis became apparent when compound **16,** a critical intermediate in the synthesis of vindoline,[7] was prepared from 6-benzyloxyindole in 79% overall yield.

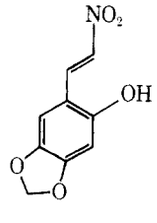
In addition to indoles, certain substituted benzenes carrying electron-donating substituents combine with dimethylaminonitroethylene (**1**). Compounds **17, 18,** and **19** were prepared



16



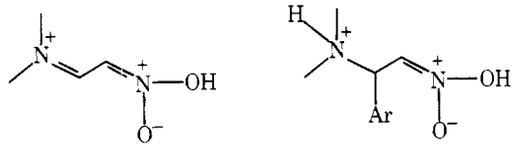
17, $R_1 = H; R_2 = R_3 = CH_3$
18, $R_1 = OCH_3; R_2 = R_3 = CH_3$



19

by heating resorcinol dimethyl ether, 1,2,4-trimethoxybenzene, and sesamol, respectively, with **1** in neat trifluoroacetic acid. Anisole, phenol, veratrole, 3,5-dimethylphenol, and *N,N*-dimethylaniline failed to yield the β-nitrostyrenes. Dimethylaniline is undoubtedly rendered inert by protonation

in trifluoroacetic acid while the other substrates seem to be too weakly nucleophilic to combine with the reagent. Trifluoroacetic acid appears to serve two functions in these condensations. Protonation of 1 on oxygen should produce a species A that is more electrophilic than starting material. Secondly, protonation of the amino group in intermediate B



A B

should facilitate elimination of dimethylamine and make it irreversible. We have no firm data in support of this hypothesis but the hypsochromic shift of 20 nm (to 330 nm) that the ultraviolet spectrum of 1 undergoes in trifluoroacetic acid might be attributed to the formation of A.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were measured in a Varian T-60 instrument and a Perkin-Elmer R-22 spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer. Ultraviolet and visible spectra were recorded on Cary 14 and Perkin-Elmer 202 spectrometers. Infrared (IR) spectra were obtained on Perkin-Elmer 247 or 237B grating spectrometers. Melting points were determined on a Reichert hot stage microscope and are corrected. Progress of most reactions was followed by thin layer chromatography (TLC) using Merck precoated silica gel 60F-204 plates. Ultraviolet (UV) light or sprays such as phosphomolybdic acid were used to visualize spots. Merck silica gel or Woelm silica gel (0.063–0.02 mm) were used for column chromatography. The trifluoroacetic acid used was reagent grade purchased from Aldrich Chemical Co. or from Mallinckrodt Chemical Co. and no further purification was necessary. Microanalyses were performed by the Robertson Laboratory, Florham Park, N.J.

1-Dimethylamino-2-nitroethylene (1). This reagent was prepared according to the method of Severin[3] from nitromethane and dimethyl sulfate–dimethylformamide complex in the presence of sodium ethoxide in ethanol. Recrystallization from hot ethanol yielded 1 as yellow flakes (62%): mp 103–105 °C (lit.[3] mp 104 °C); IR ($CHCl_3$) 2950, 1630, 1495, 1395, 1320, 1305, 1120 cm^{-1}; NMR ($CDCl_3$) δ 2.90 (s, 3), 3.20 (s, 3), 6.60 (d, 1, J = 10 Hz), 8.15 (d, 1, J = 10 Hz); UV (95% EtOH) 241 nm (ϵ 3400), 354 (25 300). The absorption at 354 nm gradually disappeared when 1 M HCl was added.

1-Methylindole (6). This material was prepared according to the procedure of Szmuzkovicz,[8] from indole with sodium hydride in dry dimethylformamide and methyl iodide, at 0 °C. The oily product obtained was purified by bulb-to-bulb distillation to produce 6 in 86% yield: bp 79 °C (1 mm) [lit.[9] bp 133 °C (26 mm)]; IR (neat) 1600, 1500, 1450, 1310, 1260 cm^{-1}; NMR ($CDCl_3$) δ 3.67 (s, 3), 6.47 (d, 1, J = 3 Hz), 6.97 (d, 1, J = 3 Hz), 7.06–7.40 (m, 3), 7.53–7.77 (m, 1).

1-Methyl-6-benzyloxyindole (7).[10] 1-Methyl-6-benzyloxyindole (1.03 g, 85%) was synthesized by methylation of 1.16 g (5.2 mmol) of 6-benzyloxyindole using the procedure developed for the preparation of 6. Removal of solvent in vacuo yielded an oil containing some dimethylformamide. A benzene/ethyl acetate (10:1 v/v) solution of this oil was filtered through a column of silica gel (50 g). After removal of solvent the residual oil crystallized from ether/hexane as small, white plates: mp 88–89 °C; IR (neat) 1625, 1570, 1510, 1245, 1180 cm^{-1}; NMR ($CDCl_3$) δ 3.67 (s, 3), 5.10 (s, 2), 6.40 (d, 1, J = 3 Hz), 6.70–6.93 (m, 3), 7.13–7.67 (m, 6).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.18; H, 6.42; N, 6.16.

3-(2-Nitrovinyl)indole (10). To a stirred solution of 1 in trifluoroacetic acid (15 mL) at ice-bath temperature was added 3.51 g (30 mmol) of indole and the mixture was stirred in a nitrogen atmosphere for 10 min. During this time the color of the solution changed from light yellow to dark. The mixture was then allowed to warm up to room temperature and was poured into ice water (300 mL), from which a yellow semisolid precipitated. The aqueous solution was extracted with ethyl acetate (350 mL) and then twice with the same solvent (100 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (150 mL) and with saturated NaCl solution (100 mL) and dried (Na_2SO_4). Removal of solvent in vacuo afforded 5.40 g (96%) of a yellow solid. Recrystallization from hot methanol gave yellow prisms: mp 172 °C (lit.[11] mp 171 °C); IR (Nujol) 3455, 2980, 1630, 1530, 1500, 1300, 1225 cm^{-1}; NMR (CD_2Cl_2) δ 7.10–7.70 (m, 6), 7.72 (d, 1, J = 14 Hz), 8.25 (d, 1, J = 14 Hz); UV (95% EtOH) 219 nm (ϵ 19 000), 278 (7300), 284 (sh, 6900), 398 (16 400).

1-Methyl-3-(2-nitrovinyl)indole (12). This compound was produced following the procedure described for the preparation of **10.** 1-Methylindole (655 mg, 5.2 mmol) yielded 930 mg (92%) of 12 as yellow needles: mp 167–168 °C (lit.[12] mp 164–165 °C); IR (CH_2Cl_2) 1625, 1532, 1500, 1420, 1315, 1260 cm^{-1}; NMR (CD_2Cl_2) δ 3.76 (s, 3), 7.15–7.66 (m, 4), 7.44 (s, 1), 7.75 (d, 1, J = 15 Hz), 8.25 (d, 1, J = 15 Hz); UV (95% EtOH) 224 nm (ϵ 14 000), 283 (5400), 403 (11 900).

1-Methyl-3-(2-nitrovinyl)-6-benzyloxyindole (13). This compound (4.20 g, 95%) was obtained from the reaction of 3.42 g (14.4 mmol) of 1-methyl-6-benzyloxyindole (7) with 1 (1.67 g, 14.4 mmol) in trifluoroacetic acid (7.20 mL). Recrystallization from methanol/ethyl acetate afforded yellow prisms: mp 194–195 °C; IR ($CHCl_3$) 1610, 1570, 1520, 1480, 1320, 1290 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3), 5.17 (s, 2), 6.93 (m, 1), 7.03 (d of d, 1, J = 2, 10 Hz), 7.41 (s, 5), 7.57 (s, 1), 7.58 (d, 1, J = 10 Hz), 7.72 (d, 1, J = 14 Hz), 8.17 (d, 1, J = 14 Hz); UV (95% EtOH) 232 nm (ϵ 50 500), 265 (sh, 11 800), 295 (12 800), 411 (36 600); mass spectrum (70 eV) m/e (rel intensity) 308 (M^+, 34), 217 (55), 91 (100).

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.16; H, 5.31; N, 9.27.

3-(2-Nitrovinyl)-5-methoxyindole (14). A 15-mL flask equipped with reflux condenser was charged with 580 mg (5 mmol) of 1 and 3 mL of trifluoroacetic acid. To this stirred solution was added 735 mg (5 mmol) of 5-methoxyindole (8). The resulting suspension was heated to 30–45 °C for 10 min and the solution was then allowed to cool. The dark slurry was poured into ice water. Extraction with ethyl acetate was followed by washing of the organic layer with saturated $NaHCO_3$ and saturated NaCl solution. After drying (Na_2SO_4), the solvent was evaporated, yielding 1.1 g of dark green crystals. Purification by column chromatography (100 g, silica gel, CH_2Cl_2) yielded 60 mg (8%) of 5-methoxyindole (8) and 697 mg (64%) of **14.** Recrystallization from acetone/hexane gave yellow needles: mp 162–165 °C (lit.[13] mp 157–158 °C); IR (Nujol) 3200, 1600, 1290, 1250, 1200, 1100 cm^{-1}; NMR (acetone-d_6) δ 3.93 (s, 3), 6.93 (d of d, 1, J = 2, 9 Hz), 7.40 (d, 1, J = 2 Hz), 7.50 (d, 1, J = 9 Hz), 7.87 (d, 1, J = 13 Hz), 8.08 (s, 1), 8.36 (d, 1, J = 13 Hz); UV (95% EtOH) 224 nm (ϵ 19 300), 281 (9000), 291 (sh, 7950), 303 (sh, 6100), 398 (20 150).

1-Methyl-3-(2-nitrovinyl)-6-tosyloxyindole (15). 1-Methyl-6-tosyloxyindole (9) was prepared by the method used for the conversion of indole to 1-methylindole (6). 6-Tosyloxyindole (2.23 g, 7.8 mmol) afforded 2.01 g (86%) of 1-methyl-6-tosyloxyindole as white prisms recrystallized from ether/hexane: mp 122–123 °C; IR (CH_2Cl_2) 1600, 1330, 1050, 960 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3), 3.67 (s, 3), 6.40 (d, 1, J = 3 Hz), 6.54 (d of d, 1, J = 9, 2 Hz), 7.00–7.13 (m, 2), 7.27 (d, 2, J = 9 Hz), 7.40 (d, 1, J = 9 Hz), 7.70 (d, 2, J = 9 Hz).

1-Methyl-6-tosyloxyindole (9, 602 mg, 2 mmol) was added to a stirred mixture of 232 mg (2 mmol) of 1 and trifluoroacetic acid (2 mL). The resulting mixture was heated in a nitrogen atmosphere for 1 h. It was worked up as in the preparation of 14 and the dark oil that was obtained after removal of solvent was purified by column chromatography (silica gel, 100 g). The first fraction eluted with methylene chloride/hexane (1/1 v/v) yielded 385 mg (64%) of 1-methyl-6-tosyloxyindole (9). A second fraction was eluted with methylene chloride and crystallization from CH_2Cl_2/heptane yielded 158 mg (13%) of **15** as a yellow, amorphous solid: mp 206–208 °C; IR ($CHCl_3$) 1650, 1500, 1375, 1300, 1180 cm^{-1}; NMR ($CDCl_3$) δ 2.43 (s, 3), 3.57 (s, 3), 6.67 (d, of d, 1, J = 9, 1.5 Hz), 7.10 (d, 1, J = 1.5 Hz), 7.16 (d, 2, J = 8 Hz), 7.43 (s, 1), 7.53 (d, 1, J = 9 Hz), 7.57 (d, 2, J = 8 Hz), 7.65 (d, 1, J = 14 Hz), 8.10 (d, 1, J = 14 Hz); UV (95% EtOH) 229 nm (ϵ 32 600), 285 (9900), 274 (10 100), 391 (16 000); mass spectrum (70 eV) m/e (rel intensity) 372 (M^+, 10), 217 (55), 91 (100).

Anal. Calcd for $C_{18}H_{16}N_2O_5S$: C, 58.06; H, 4.33; N, 7.52. Found: C, 58.18; H, 4.41; N, 7.38.

1-Methyl-6-benzyloxytryptamine (16).[14] This compound was prepared by reduction of 13 with lithium aluminum hydride in boiling tetrahydrofuran. The reduction was complete after heating for 60 min. Crude 1-methyl-3-(2-nitrovinyl)-6-benzyloxyindole (3.83 g, 12.4 mmol) produced 3.4 g (98%) of 16 as a brown oil: IR ($CHCl_3$) 3500–3000 (br), 2930, 1625, 1560, 1360, 1330 cm^{-1}; NMR ($CDCl_3$) δ 1.83 (br, 2, D_2O exchangable), 2.90 (t, 4, J = 4 Hz), 3.67 (s, 3), 5.11 (s, 2), 6.67–7.00 (m, 3), 7.20–7.60 (m, 6); UV (95% EtOH) 229 nm (ϵ 36 500), 294 (6100); mass spectrum (70 eV) m/e (rel intensity) 280 (M^+, 94), 250 (100), 189 (46), 160 (62). Picrate: red needles (ethanol/water); mp 225 °C; IR (Nujol) 1630, 1620, 1560 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}N_5O_8$ (picrate): C, 56.58; H, 4.55; N, 13.75. Found: C, 57.13; H, 4.60; N, 13.73.

2,4-Dimethoxy-β-nitrostyrene (17). A mixture of 580 mg (5 mmol) of nitroenamine **1**, *m*-dimethoxybenzene (690 mg, 5 mmol), and trifluoroacetic acid (2.5 mL) was heated to 55–65 °C for 30 min. The dark purple mixture was than poured into ice water and extracted with methylene chloride and the organic layer was then washed with saturated $NaHCO_3$ and NaCl solution followed by drying (Na_2SO_4). Removal of solvent in vacuo yielded a semisolid which on trituration with methanol yielded 570 mg of **17** as yellow crystals. The mother liquor, which contained a mixture of compounds, was separated by column chromatography on silica gel (50 g). *m*-Dimethoxybenzene (141 mg, 24%) and 126 mg (18%) of **1** were recovered, together with 135 mg of **17**, affording a total of 705 mg (69%) of the desired product. Recrystallization from hot methanol gave yellow needles: mp 106–108 °C (lit.[15] mp 104 °C); IR ($CHCl_3$) 2950, 1600, 1495, 1325, 1260 cm^{-1}; NMR ($CDCl_3$) δ 3.86 (s, 3), 3.94 (s, 3), 6.50 (d, 1, J = 2 Hz), 6.57 (d of d, 1, J = 2, 8 Hz), 7.40 (d, 1, J = 8 Hz), 7.85 (d, 1, J = 13 Hz), 8.05 (d, 1, J = 13 Hz); UV (95% EtOH) 250 nm (ε 9230), 309 (sh, 6600), 366 (19 000).

2,4,5-Trimethoxy-β-nitrostyrene (18). This was prepared as described for **17**. Starting 1,2,4-trimethoxybenzene (64 mg, 18%) and 46 mg (18%) of nitroenamine **1** were recovered together with 178 mg (36%) of the desired **18** isolated after recrystallization from hot methanol as reddish-orange prisms: mp 132–133 °C (lit.[16] 132 °C); IR ($CDCl_3$) 2940, 2830, 1600, 1320, 1270 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 3), 3.95 (s, 3), 3.97 (s, 3), 6.55 (s, 1), 6.93 (s, 1), 7.81 (d, 1, J = 14 Hz), 8.19 (d, 1, J = 14 Hz); UV (95% EtOH) 245 nm (ε 8350), 265 (9200), 316 (7300), 396 (15 400).

2-Hydroxy-4,5-methylenedioxy-β-nitrostyrene (19). A mixture of 138 mg (1 mmol) of sesamol, 116 mg (1 mmol) of nitroenamine **1**, and trifluoracetic acid (0.5 mL) was heated at 40–55 °C for 15 min. The dark mixture was poured into ice water and extracted with ethyl acetate. The acidic aqueous solution was cooled overnight at 5 °C and 59 mg (mp 194–196 °C) of **19** crystallized as red needles. The organic phase was washed with saturated $NaHCO_3$ and NaCl solution and dried ($MgSO_4$). Removal of solvent yielded 150 mg of **19** as a red, amorphous solid. Recrystallization from ethyl acetate/hexane furnished small, red needles (mp 180–182 °C). Further recrystallization from 1 N HCl/methanol gave red needles (mp 200 °C). A quantitative yield of **19** was thus obtained: IR (Nujol) 3360, 1630, 1615, 1610, 1360, 1270 cm^{-1}; NMR (acetone-d_6) δ 6.03 (s, 2), 6.60 (s, 1), 7.17 (s, 1), 7.93 (d, 1, J = 14 Hz), 8.30 (d, 1, J = 14 Hz); UV (95% EtOH) 248 nm (sh, ε 7400), 270 (9300), 315 (5850), 405 (14 700); (1 M NaOH) 266 nm (ε 8400), 298 (4750), 345 (9100), 530 (21 700); reacidification with 1 M HCl gave the original spectrum; mass spectrum (70 eV) *m/e* (rel intensity) 209 (M^+, 29), 162 (100), 161 (39).

Anal. Calcd for $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C, 51.79; H, 3.50; N, 6.40.

Acknowledgment. This work was supported by the National Institutes of Health (GM 09868).

Registry No.—**1**, 1190-92-7; **6**, 603-76-9; **7**, 61675-16-9; **8**, 1006-94-6; **9**, 61675-17-0; **10**, 3156-51-2; **12**, 2731-00-2; **13**, 61675-18-1; **14**, 61675-19-2; **15**, 61675-20-5; **16**, 61675-21-6; **16** picrate, 61675-22-7; **17**, 1891-10-7; **18**, 24160-51-8; **19**, 61675-23-8; 6-benzyloxyindole, 15903-94-3; indole, 120-72-9; 6-tosyloxyindole, 56596-14-6; *m*-dimethoxybenzene, 151-10-0; 1,2,4-trimethoxybenzene, 135-77-3; sesamol, 533-31-3.

References and Notes

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Synthesis of 4-Aminodiphenylamine and Its Relatives

Christian S. Rondestvedt, Jr.

Research and Development Division Publication No. 546, Jackson Laboratory, Organic Chemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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Formanilide is readily converted to its sodium salt by heating with metallic sodium or sodium hydride. Sodium formanilide condenses rapidly with *p*-nitrochlorobenzene in a high-boiling solvent at 150–165 °C. The condensation is further accelerated by addition of dimethylformamide. The product is 4-nitrodiphenylamine (1) (87–91% yield) which is readily hydrogenated to the title compound. Several other nitrodiphenylamines were prepared by this technique. *p*-Nitrobenzenediazonium bisulfate couples rapidly with diphenylamine in 25–30% sulfuric acid, but not so well in either weaker or stronger acid. The product is almost entirely 4-(4-nitrobenzeneazo)diphenylamine, which is readily hydrogenated to a separable mixture of the title compound and *p*-phenylenediamine.

p-Aminodiphenylamine and derived compounds have long been used as dye intermediates and as polymer stabilizers, for example, as antioxidants or antiozonants for elastomers. The following brief review of the literature shows the scope of the methods tried for their synthesis. The nitro and nitroso products are readily reduced to aminodiphenylamines.

A recent Russian review [1]of industrial processes concluded that the preferred process involves N-nitrosation of diphenylamine and Fischer–Hepp rearrangement to 4-nitrosodiphenylamine. These steps can be combined by nitrosation in *anhydrous* methanolic hydrogen chloride with sodium nitrite or nitrogen oxides. However, 4-nitrosodiphenylamine is unpleasant to handle. A related procedure nitrosates phenol (predominantly para), etherifies, and finally displaces the alkoxyl group with aniline.[2] The overall yield is lower, and etherifying the nitrosophenol before anilinolysis is inconvenient and expensive.

Another important synthesis involves condensation of aniline or an acylanilide with *p*-nitrochlorobenzene to 4-nitrodiphenylamine (or its *N*-acyl derivative). The condensation usually requires some form of copper and a base to neutralize