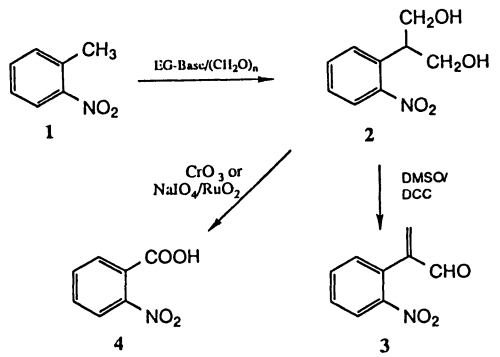
Homologation of the Side Chain of 2-Nitrotoluene. Synthesis of a Tryptophan Precursor

Hideo TANAKA, Yasuo MURAKAMI, and Sigeru TORII*
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700
(Received July 3, 1989)

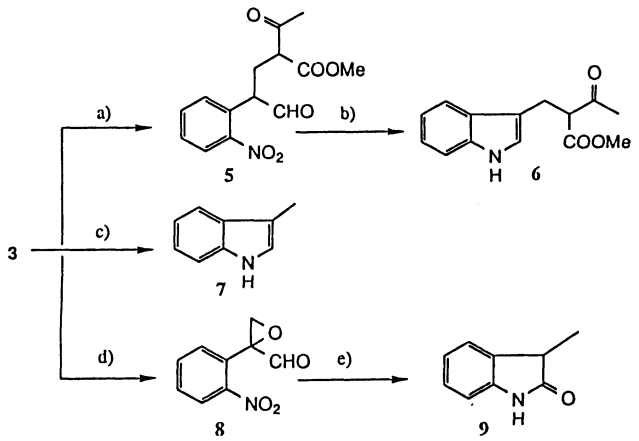
Synopsis. 2-(2-Nitrophenyl)-1,3-propanediol (**2**) was selectively converted to 2-(2-nitrophenyl)propenal (**3**) by the use of a mixture of dicyclohexylcarbodiimide (DCC) and dimethyl sulfoxide in benzene, while 2-nitrobenzoic acid was obtained by the oxidation of the diol **2** with sodium periodate in the presence of a catalytic amount of ruthenium dioxide or with chromic acid. The enal **3** was subjected to further transformation to afford a potent tryptophan precursor and some useful indole derivatives.

A continuing interest in the tryptophan synthesis has led to the development of novel synthetic methodologies.[1] Among them, a straightforward route to tryptophan has been achieved by the homologation of the side chain of 2-nitrotoluene (**1**) followed by the reductive cyclization.[2] The transformation involves a two carbon homologation of the side chain of **1** by a successive treatment with *N,N*-dimethylformamide dimethyl acetal[3] and formaldehyde, leading to 2-(2-nitrophenyl)propenal (**3**) (atropaldehyde). In the previous paper, we reported a facile double hydroxymethylation of 2-nitrotoluene (**1**) with formaldehyde promoted by an electrochemically generated base (EG-base), affording 2-(2-nitrophenyl)-1,3-propanediol (**2**).[4] This finding prompted us to investigate an alternative access to the key intermediate **3** by the oxidative dehydration of **2**. Herein, we describe a selective oxidation of 2-(2-nitrophenyl)-1,3-propanediol (**2**) leading to either the aldehyde **3** or 2-nitrobenzoic acid (**4**) by choosing oxidizing agents.

In the transformation of the diol **2** into the desired enal **3**, one hydroxyl group may serve for the aldehyde group and the other for the olefinic one. After examination of various oxidizing agents, a combination of dicyclohexylcarbodiimide (DCC) and dimethyl sulfoxide (DMSO)[5] was found to be suitable for the present purpose; thus, the oxidative dehydration of **2** to afford **3** took place smoothly (97% yield) by the action of DCC and DMSO in benzene containing pyridine and trifluoroacetic acid at room temperature.



Scheme 1.



(a): $CH_3COCH_2CO_2Me$, NaOMe (0.1 eqiv), MeOH, (b): H_2, Pd/C, MeOH, (c): H_2, PtO_2, MeOH, (d): H_2O_2, aq. NaOH, MeOH, (e): H_2, PtO_2, Ac_2O.

Scheme 2.

Notably, upon oxidation of **2** with chromic acid in acetone (Method A), a completely different reaction occurred to afford 2-nitrobenzoic acid (**4**) in 96% yield. A similar result was obtained by the oxidation of **2** with sodium periodate and a catalytic amount of ruthenium dioxide (Method B). The EG-base-promoted double hydroxymethylation followed by the oxidation (Methods A and B) may offer an access to 2-nitrobenzoic acid (**4**) which has not been prepared by the direct oxidation of **1** efficiently.[6]

2-(Nitrophenyl)propenal (**3**) is an intriguing starting candidate for the indole synthesis. The Michael addition of methyl acetoacetate to the enal **3** in methanol containing a catalytic amount of sodium methoxide afforded adduct **5** (90%). Subsequently, the hydrogenative cyclization of **5** over palladium on charcoal in methanol furnished methyl 2-acetyl-3-(3-indolyl)propionate (**6**, 95%), a potent tryptophan precursor.[7] Under similar hydrogenation conditions, the enal **3** provided 3-methylindole (**7**) which would arise from the hydrogenation of both the olefin and nitro groups. On the other hand, the epoxidation of **3**, leading to **8**, followed by the hydrogenation in acetic anhydride afforded lactam **9**. Although the reaction mechanism is still unclear, the lactam **9** might arise from some mutual interaction between the formyl and the nitro groups.

Experimental

IR spectra were recorded on a JASCO IRA-1 grating spectrometer. ^{1}H NMR spectra were measured at 60 MHz with a Hitachi R-24 spectrometer. Chemical shifts are expressed in parts per million downfield from Me_4Si used as

an internal reference. Melting and boiling points are uncorrected. Column chromatography was carried out with Merck Kieselgel 60 (silica gel) using hexane-EtOAc as an eluent. Elementary analyses were performed in our laboratory. 2-(2-Nitrophenyl)-1,3-propanediol (**2b**) was prepared by the electrolysis of 2-nitrotoluene (**1**) in a $(CH_2O)_n$-DMF-Et_4NOTs (Pt electrode) system.[4]

2-(2-Nitrophenyl)propenal (3). To a mixture of **2** (592 mg, 3.0 mmol), benzene (10 ml), and DMSO (10 ml) were successively added pyridine (0.24 ml, 3 mmol), trifluoroacetic acid (0.12 ml, 1.5 mmol), and DCC (1.5 g, 7.3 mmol) at room temperature. After stirring at room temperature for 2 h, benzene (20 ml) was added and the precipitates (dicyclohexylurea) were removed by filtration and washed with benzene. The filtrates and washings were combined, washed three times with 20 ml portions of water, dried (Na_2SO_4), and concentrated. The residue was chromatographed to give **3** (516 mg, 97%): mp 53—54 °C (lit,[2] mp 54.5—56 °C).

2-Nitrobenzoic Acid (4). Method A. To a solution of **2** (98.5 mg, 0.5 mmol) in acetone (4 ml), was added dropwise the Jones reagent (0.7 ml, 2.2 mmol) at 0 °C over a period of 30 min. After stirring at room temperature for 6 h, most of the solvent was evaporated and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous $NaHCO_3$. The aqueous layers were acidified with aqueous 10% HCl, extracted with EtOAc, washed with brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed to afford **4** (83.6 mg, 96%): mp 143—146° (lit,[8] mp 146—148 °C), whose IR and ^1H NMR spectra data were fully identical with those reported.[9]

Method B. To a mixture of **2** (105 mg, 0.53 mmol), EtOAc (2.5 ml), water (4 ml), and RuO_2 (4 mg, 0.02 mmol) was added portionwise $NaIO_4$ (706.7 mg, 3.57 mmol) at room temperature over a period of 10 h. After being stirred for additional 10 h, the reaction mixture was worked up in a similar manner as described above to afford **4** (83.6 mg, 90%).

Methyl 2-Acetyl-4-formyl-4-(2-nitrophenyl)butyrate (5). A mixture of 2-(2-nitrophenyl)propenal **3** (101.3 mg, 0.57 mmol) and methyl acetoacetate (79.2 mg, 0.68 mmol) in MeOH (2 ml) containing NaOMe (3 mg, 0.06 mmol) was stirred for 1 h at −5 °C and for 2 h at room temperature. After being neutralized with aqueous 5% HCl, the mixture was concentrated under reduced pressure, extracted with EtOAc, washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed to afford **5** (151 mg, 90%): IR (neat) 3400, 2940, 1740, 1720, 1528, 1435, 1350, 1240, 1000, 990, 782, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18—2.27 (m, 3H, $COCH_3$), 3.16—3.23 (m, 3H, CO_2CH_3), 2.5—4.8 (m, 4H, $CHCH_2CH$), 7.2—8.1 (m, 4H, ArH), 9.67 (s, 1H, CHO); Found: C, 57.20; H, 5.21; N, 5.18%. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 5.05%.

Methyl 2-Acetyl-3-(3-indolyl)propionate (6). A mixture of **5** (150 mg, 0.51 mmol) and 5% Pd/C (5 mg) in MeOH (5 ml) was stirred at room temperature under H_2 (1 atm) for 5 h. After the catalysts were removed by filtration, the solvent was evaporated under reduced pressure, the residue was chromatographed to afford **6** (119mg, 95%):[7] IR (neat) 3375, 2943, 1735, 1710, 1458, 1435, 1360, 1218, 1150, 1098, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.07 (s, 3H, $COCH_3$), 3.23—3.98 (m, 3H, $CHCH_2$), 3.59 (s, 3H, CO_2CH_3), 6.8—8.3 (m, 6H, C=CH, NH, ArH).

3-Methylindole (7). A mixture of **3** (32.0 mg, 0.18 mmol) and PtO_2 (3.0 mg) in MeOH (2 ml) was stirred at room temperature under H_2 (1 atm) for 3 h. After the catalysts were removed by filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed to afford 3-methylindole (**7**) (9.6 mg, 40%): mp 92—94 °C (lit,[10] mp 95 °C).

2,3-Epoxy-2-(2-nitrophenyl)propionaldehyde (8). To a mixture of **3** (94.4 mg, 0.53 mmol) and aqueous 31% H_2O_2 (120 mg, 1.1 mmol) in MeOH (2.0 ml) was added dropwise aqueous 24% NaOH (0.03 ml, 0.18 mmol) at −5—0 °C over a period of 30 min. The reaction mixture was stirred for additional 1 h at 10 °C. The usual workup followed by chromatography gave 2,3-epoxy-2-(2-nitrophenyl)propionaldehyde (**8**) (95.7 mg, 93%): mp 64—66 °C; IR ($CHCl_3$) 3050, 2900, 1735, 1530, 1340, 910, 860, 720, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.36 (d, J=5.0 Hz, 1H, CH), 3.64 (d, J=5.0 Hz, 1H, CH), 7.5—8.3 (m, 4H, ArH), 8.98 (s, 1H, CHO); Found: C, 55.88; H, 3.58; N, 7.33%. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25%.

3-Methyl-2-oxoindoline (9). A mixture of **8** (51.0 mg, 0.26 mmol) and Pd/C (10 mg) in acetic anhydride (2 ml) was stirred at room temperature under H_2 (1 atm). After the catalysts were removed by filtration, the mixture was concentrated under the reduced pressure. The residue was taken up with EtOAc, washed with aqueous 5% HCl, brine, and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography afforded 3-methyl-2-oxoindoline **9** (20.6 mg, 53%): mp 117—120 °C (lit,[11] mp 122.5—123.5 °C).

References

1) For example, see: J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Wiley, New York (1961), Vol. 3, pp. 2316—2347; "Aminosan Kogyo, Gosei to Riyo," ed by T. Kaneko, Y. Izumi, I. Chibata, and T. Itoh, Kodansha Scientific, Tokyo (1973), p. 214.

2) U. Hengartner, A. D. Batcho, J. F. Blount, W. Leimgruber, M. E. Larscheid, and J. W. Scott, *J. Org. Chem.*, **44**, 3748 (1979).

3) A. D. Batcho and W. Leimgruber, *Org. Synth.*, **63**, 214 (1985); R. D. Clark and D. B. Repke, *Heterocycles*, **22**, 195 (1984).

4) S. Torii, Y. Murakami, H. Tanaka, and K. Okamoto, *J. Org. Chem.*, **51**, 3143 (1986).

5) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1953); K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965); J. G. Moffatt, *Org. Synth.*, Coll. Vol. 5, 242 (1973).

6) C. Hakanson and M. Nilsson, *Acta Chem. Scand.*, **21**, 1978 (1967); R. Hasegawa and Y. Kamiya, *Bull. Chem. Soc. Jpn.*, **51**, 1490 (1978).

7) D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, **1953**, 280; D. O. Holland, Brit. Patent 723986 (1955); *Chem. Abstr.*, **50**, P8741d (1956).

8) "1988—1989 Aldrich Catalog Handbook of Fine Chemicals," Aldrich Chemical Co., Inc., Milwaukee (1988), p. 1108.

9) "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., Milwaukee (1970), p. 713E; "The Aldrich Library of NMR Spectra," Aldrich Chemical Co., Inc., Milwaukee (1974), Vol. VI, p. 145B.

10) F. E. King and P. Lecuyer, *J. Chem. Soc.*, **1934**, 1903; "Aldrich Library of NMR Spectra," Aldrich Chemical Co., Inc., Milwaukee (1974), Vol. VIII, p. 51C.

11) A. S. Endler and E. I. Becker, *Org. Synth.*, Coll. Vol. 4, 657 (1963).