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The Chemistry of Indoles. XII.[1] A Facile Route to 5-Nitroisocoumarins and Methyl Indole-4-carboxylate

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A convenient synthesis of 5-substituted isocoumarin derivatives, such as 5-nitroisocoumarin (**2**), 5-aminoisocoumarin (**8**), 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), and 5-amino-3,4-dihydro-3-methoxyisocoumarin (**10**), from 2-methyl-3-nitrobenzoic acid (**1**) is reported. Several synthetic routes to methyl indole-4-carboxylate (**9**) from methyl 2-methyl-3-nitrobenzoate (**4**) directly or *via* these isocoumarins (**8** and **10**) are also presented.

Keywords——5-nitroisocoumarin; 5-aminoisocoumarin; 3,4-dihydro-3-methoxy-5-nitroisocoumarin; 5-amino-3,4-dihydro-3-methoxyisocoumarin; methyl indole-4-carboxylate; 2-methyl-3-nitrobenzoic acid; titanium (III) chloride; ring transformation

Formylation of activated methyl groups on aromatics and heteroaromatics with dimethylformamide acetal is well established[2] and the reaction was successfully applied in the synthesis of substituted indoles.[3] Examination of the reaction of dimethylformamide dimethylacetal (DMFDMA) with 2-methyl-3-nitrobenzoic acid (**1**) has led us to find a novel route to 5-nitroisocoumarin (**2**) and 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), which are not readily available[4] as yet, but are suitable synthetic equivalents[5] for 4-substituted indoles. In this paper, we describe a facile synthesis of **2** and **3**, together with their conversion into methyl indole-4-carboxylate (**9**).

Refluxing of 2-methyl-3-nitrobenzoic acid (**1**) in abs. dimethylformamide (DMF) in the presence of DMFDMA resulted in the formation of 5-nitroisocoumarin (**2**), 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**), and methyl 2-methyl-3-nitrobenzoate (**4**) in yields of 30.2%, 20.8%, and 1.6%, respectively (Chart 1). The structure of **2** was assigned from the nuclear magnetic resonance (NMR) spectrum, which showed characteristic protons on C-3 and C-4 of isocoumarin as two sets of doublets at δ 7.23 and 7.38 ($J=6$ Hz), and the infrared spectrum, which indicated the presence of both lactone carbonyl (1730 cm^{-1}) and nitro groups (1518 and 1350 cm^{-1}). The final confirmation of the structure (**2**) was provided by the following

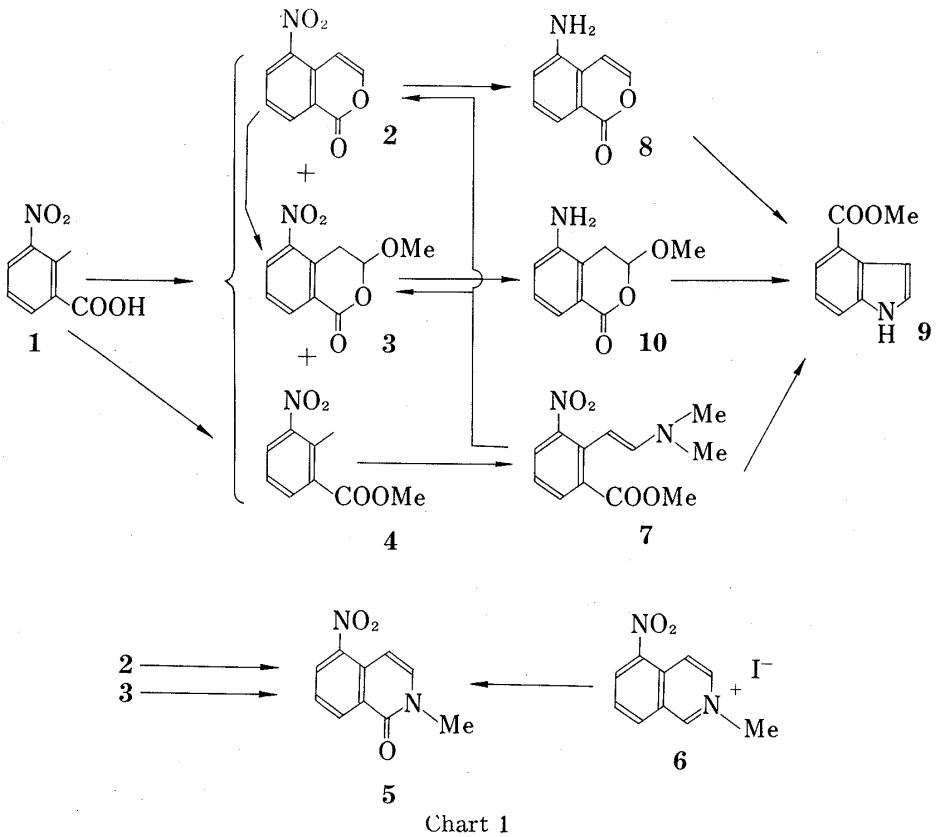

Chart 1

experiments. Thus, the reaction of **2** with methylamine in methanol afforded 2-methyl-5-nitroisocarbostyril[6] (**5**) in 79.1% yield; this product was identical with a sample prepared from 2-methyl-5-nitroisoquinolinium iodide (**6**).

The structure of **3** was assigned from its NMR spectrum, in which the methylene and methine protons on the 4 and 3 positions of the dihydroisocoumarin ring appeared at δ 3.51 (2H, d, J=3.2 Hz), and 5.42 (1H, t, J=3.2 Hz), and by its conversion to **5** in 86.3% yield upon reaction with methylamine. Definitive evidence of the structure (**3**) was obtained by the reaction of **2** with methanolic hydrochloric acid to afford **3** in 41.3% yield, together with 21.4% recovery of the starting material.

Alternatively, **2** and **3** were prepared by the following reaction sequences. Thus, the ester[3b,e] (**4**) obtained by usual methylation of **1** was heated under reflux in abs. DMF in the presence of DMFDMA. Subsequent column chromatography on silica gel converted the resulting enamine[3b,e] (**7**) into **2** and **3** in yields of 45.9% and 15.2%, respectively.

Reduction of 5-nitroisocoumarin (**2**) to 5-aminoisocoumarin (**8**) with aqueous titanium (III) chloride was achieved in 86.6% yield by the application of our modified procedure.[7] Subsequent treatment of **8** with sodium methoxide in abs. methanol produced methyl indole-4-carboxylate[3e,5,8] (**9**) in 97.6% yield. Similarly, 3,4-dihydro-3-methoxy-5-nitroisocoumarin (**3**) was reduced to 5-amino-3,4-dihydro-3-methoxyisocoumarin (**10**) in 88.0% yield by the action of aqueous titanium (III) chloride, and this compound, on treatment with sodium methoxide, gave **9** in 80.3% yield. Since both compounds, (**2**) and (**3**) ,are led to **9** by the same reaction sequences, it is not necessary to separate **2** and **3** for an experiment aimed at the preparation of **9**. It was also found that the reduction of the enamine (**7**) with 7 mol equiv. of titanium (III) chloride in methanol afforded methyl indole-4-carboxylate (**9**) in 73.6% overall yield[9] from the ester (**4**).

Although an all-encompassing mechanism is beyond the scope of the present study, possible mechanisms for the formation of **2**, **3** (routes **a**, **b**, and **c**), and **9** *via* **15** (route **d**) are shown in chart 2. Carboxylic acids were often reported to give the corresponding esters[2c]

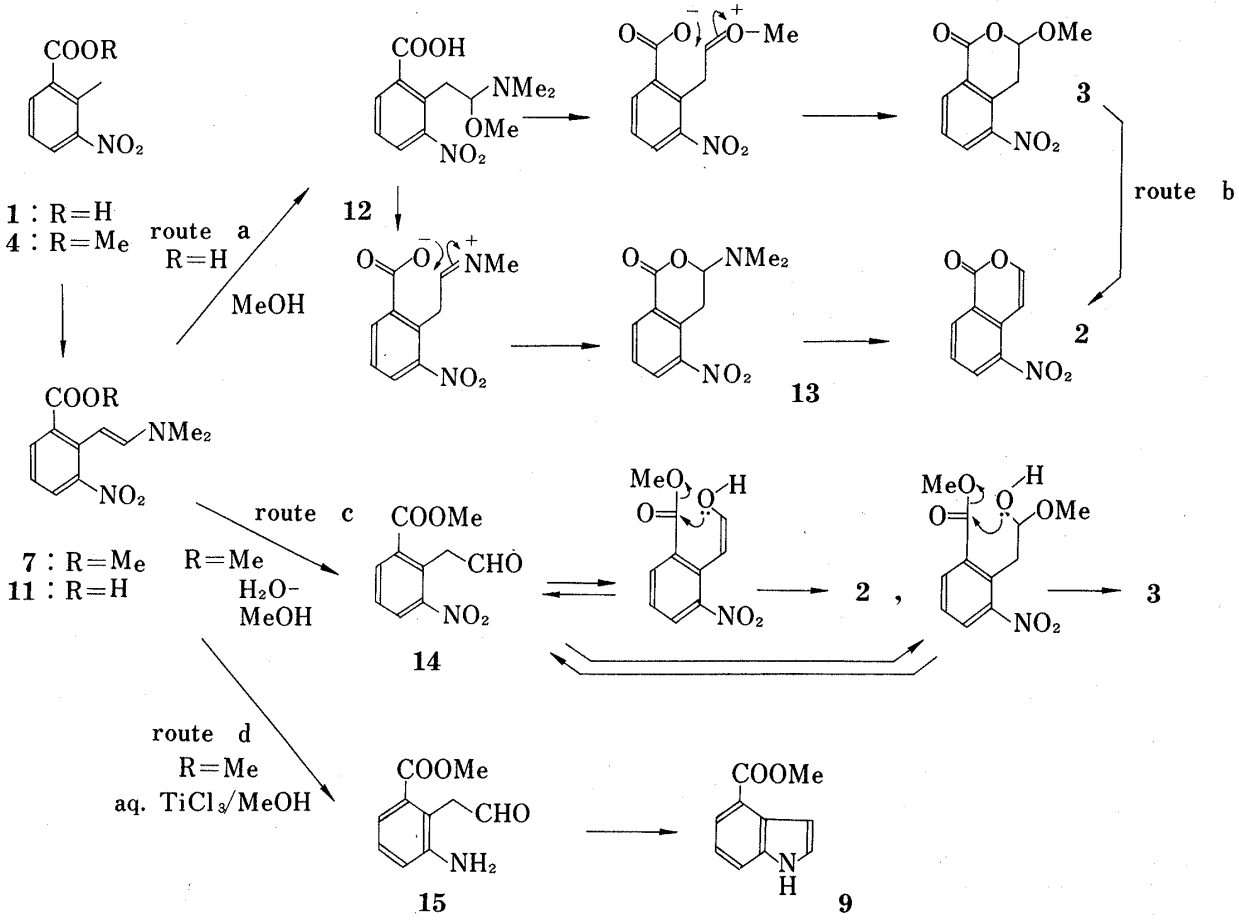

Chart 2

upon treatment with DMFDMA, but in our case (**1**→**2**+**3**+**4**) the ester (**4**) was formed in only 1.6% yield and the formation of the enamine (**7**) was not detected. Considering that once the ester (**4**) is formed, **4** is converted into **7** in almost quantitative yield under the reaction conditions, route **a** (R=H) seems to be reasonable: thus, initial formation of the enamine (**11**, R=H), with subsequent addition of methanol (generated from DMFDMA) to **11** affords **12**, then cyclization occurs to give either **3** or **13**, and final elimination of dimethylamine from the latter provides **2**. The operation of route **b** was established by refluxing **3** in abs. DMF for 12 hr to afford **2** and **3** in yields of 18.1% and 61.2%, respectively. Routes c and d (R=Me) involve initial hydrolysis of **7** to aldehyde, (**14**) or (**15**), and subsequent intra-molecular cyclization either between enol (or hemiacetal) and ester groups (route c) or between amino and aldehyde groups (route d).

The present study provides a ready access to 5-substituted isocoumarins. Since various nucleophiles are known to be introduced into the 1-position of isocoumarins,[4] the present route might be widely applicable for the synthesis of 4-substituted indoles.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Silica gel (Kanto Chemical Co., Inc., 100—200 mesh) was used for column chromatography. Dimethylformamide dimethylacetal (DMFDMA, Aldrich Chemical Co., Inc.) was used without further purification. NMR spectra were determined with a JEOL JNM-C60H spectrometer (with tetramethylsilane as an internal standard), mass spectra with a JEOL-JNM-01SG spectrometer, and IR spectra with a Shimadzu IR-420 spectrophotometer.

5-Nitroisocoumarin (**2**), **3,4-Dihydro-3-methoxy-5-nitroisocoumarin** (**3**), **and Methyl 2-Methyl-3-nitro-**

benzoate (4) from 2-Methyl-3-nitrobenzoic Acid (1)——A solution of **1** (5.083 g) in abs. dimethylformamide (DMF, 40 ml) and DMFDMA (10.011 g, 3 mol equiv.) was refluxed for 22 hr with stirring. After removal of the solvent, the residue was column chromatographed on silica gel with CH_2Cl_2–hexane (2: 1, v/v) as an eluent. From the early part of the fraction, **4** (89.6 mg, y. 1.6%, mp 64—65°) was obtained. From the middle part, **2** (1.621 g, y. 30.2%) was obtained. **2**: mp 173—174° (colorless prisms from MeOH). NMR ($CDCl_3$) δ: 7.23 (1H, d, J=6 Hz), 7.38 (1H, d, J=6 Hz), 7.55 (1H, t, J=8 Hz), 8.35 (1H, d.d, J=8 and 1.6 Hz), 8.50 (1H, d.d, J=8 and 1.6 Hz). MS *m/e*: 191 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1730, 1630, 1518, 1350. *Anal.* Calcd for $C_9H_5NO_4$: C, 56.55; H, 2.64; N, 7.33. Found: C, 56.48; H, 2.50; N, 7.07. From the later part of the fraction, **3** (1.306 g, y. 20.8%) was obtained. **3**: mp 111.5—112.5° (colorless prisms from MeOH). NMR ($CDCl_3$) δ: 3.50 (3H, s), 3.51 (2H, d, J=3.2 Hz), 5.42 (1H, t, J=3.2 Hz), 7.45 (1H, t, J=8.0 Hz), 8.15 (1H, d.d, J=8 and 1.6 Hz), 8.32 (1H d.d, J=8 and 1.6 Hz). MS *m/e*: 223 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1728, 1611, 1522, 1348. *Anal.* Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.79; H, 3.93; N, 6.18.

5-Nitroisocoumarin (2) and 3,4-Dihydro-3-methoxy-5-nitroisocoumarin (3) from Methyl 2-Methyl-3-nitrobenzoate (4)——A solution of **4** (1.003 g) in abs. DMF (5 ml) and DMFDMA (1.856 g, 3 mol equiv.) was refluxed for 10 hr with stirring. The residue obtained after removal of the solvent was found to be pure methyl *trans*-2-(2-dimethylaminovinyl)-3-nitrobenzoate [**7**, NMR (CCl_4) δ: 2.78 (6H, s), 3.75 (3H, s), 5.50 (1H, d, J=14 Hz), 6.20 (1H, d, J=14 Hz), 6.95 (1H, d.d, J=8 and 7.5 Hz), 7.60 (1H, d.d, J=7.5 and 2 Hz), 7.61 (1H, d.d, J=8 and 2 Hz)]. Water was added to the residue and the whole was extracted with ether. The extract was washed with sat. NaCl solution, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to column chromatography on silica gel with CH_2Cl_2–hexane (1: 1, v/v) as an eluent. From the early part of the fraction, **2** (450.7 mg, y. 45.9%) was obtained. From the later part of the fraction, **3** (174.0 mg, y. 15.2%) was obtained.

3,4-Dihydro-3-methoxy-5-nitroisocoumarin (3) from 5-Nitroisocoumarin (2)——A mixture of a solution of **2** (28.0 mg) in MeOH (2 ml) and concd. hydrochloric acid (1 ml) was refluxed for 6.5 hr. After removal of the solvent, the whole was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline solid, which was column chromatographed on silica gel with CH_2Cl_2–hexane (8: 5, v/v) as an eluent. From the early part of the fraction, **2** (6.0 mg, y. 21.4%) was obtained. From the later part, **3** (13.5 mg, y. 41.3%) was obtained.

2-Methyl-5-nitroisocarbostyril (5)——i) From 3,4-Dihydro-3-methoxy-5-nitroisocoumarin (**3**): A solution of **3** (73.6 mg) in MeOH (4 ml) and methylamine (40%, 1 ml) was refluxed for 1 hr. After removal of the solvent, the residue was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness to give **5** (58.1 mg, y. 86.3%), mp 114.5—115.5° (yellow prisms from MeOH). Lit.[6] mp 115—116°. The product was identical with an authentic sample prepared from 2-methyl-5-nitroisoquinolinium iodide (**6**).

ii) From 5-Nitroisocoumarin (**2**): A solution of **2** (74.9 mg) in MeOH (4 ml) and methylamine (40%, 1 ml) was refluxed for 1 hr. After removal of the solvent, the residue was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness to give **5** (63.3 mg, y. 79.1%).

5-Aminoisocoumarin (8) from 5-Nitroisocoumarin (2)——A solution of **2** (51.5 mg) in AcOH–H_2O (5: 1, v/v, 6 ml) was treated with aqueous $TiCl_3$ (16%, d=1.5, 1.2 ml, 7 mol equiv.), added as a single portion. After stirring for 7 min, water (20 ml) and CH_2Cl_2–MeOH (9: 1, v/v, 20 ml) were added. The whole was carefully basified with sat. aqueous $NaHCO_3$ solution, salted out by adding NaCl, and the organic layer was separated. The water layer was further extracted with the same solvent described above and the combined extract was washed with sat. NaCl solution, dried over Na_2SO_4, and concentrated to afford **8** (37.6 mg, y. 86.6%). mp 194—195° (lit.[5] mp 189.5—191°). NMR (CD_3OD: $CDCl_3$, 1: 1, v/v) δ: 6.63 (1H, d, J=5.6 Hz), 6.93 (1H, d.d, J=7.2 and 1.6 Hz), 7.16 (1H, d, J=5.6 Hz), 7.18 (1H, t, J=7.2 Hz), 7.50 (1H, d.d, J=7.2 and 1.6 Hz). IR ν_{max}^{KBr} cm^{-1}: 3380, 3310, 1702, 1625. MS *m/e*: 161 (M^+).

5-Amino-3,4-dihydro-3-methoxyisocoumarin (10) from 3,4-Dihydro-3-methoxy-5-nitroisocoumarin (3)——A solution of **3** (65.0 mg) in MeOH (4 ml) was treated with aqueous $TiCl_3$ (16%, d=1.5, 1.3 ml, 7 mol equiv.), added as a single portion. After stirring for 7 min at room temperature, water (7 ml) and CH_2Cl_2 (40 ml) were added. The whole was carefully basified with sat. aqueous $NaHCO_3$ solution, and the organic layer was separated. The water layer was further extracted with CH_2Cl_2 and the combined extract was washed with water, dried over Na_2SO_4, and concentrated to afford **10** (49.5 mg, y. 88.0%). mp 155—156° (colorless prisms from MeOH). NMR ($CDCl_3$) δ: 2.73 (1H, d.d, J=15 and 4 Hz), 3.05 (1H, d.d, J=15 and 4 Hz), 3.53 (3H, s), 3.70 (2H, br.s, NH_2), 5.36 (1H, t, J=4 Hz), 6.80 (1H, d.d, J=8 and 2 Hz), 7.10 (1H, t, J=8 Hz), 7.48 (1H, d.d, J=8 and 2 Hz). IR ν_{max}^{KBr} cm^{-1}: 3440, 3350, 3240, 1708. MS *m/e*: 193 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.66; N, 7.13.

Methyl Indole-4-carboxylate (9)——i) From 5-Aminoisocoumarin (**8**): A mixture of a solution of sodium (87.0 mg) in abs. MeOH (10 ml) and **8** (61.2 mg) was heated under reflux for 15 min. After removal of the solvent, water was added and the whole was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness to leave colorless prisms, **9** (64.9 mg, y. 97.6%). mp 66—67° (from ether–hexane). Lit.[3e,5,8] mp 64—65°. Spectral data were identical with those of an authentic sample.

ii) From 5-Amino-3,4-dihydro-3-methoxyisocoumarin (**10**): A mixture of a solution of sodium (62.0 mg) in abs. MeOH (5 ml) and **10** (29.5 mg) was heated under reflux for 20 min. After removal of the solvent, water was added and the whole was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness to leave colorless prisms, **9** (18.6 mg, y. 80.3%).

iii) From Methyl 2-Methyl-3-nitrobenzoate (**4**): A solution of **4** (2.017 g) in abs. DMF (10 ml) and DMFDMA (3.812 g, 3.1 mol equiv.) was refluxed for 10 hr. After removal of the solvent, the residue (**7**) was dissolved in MeOH (50 ml). Aqueous $TiCl_3$ solution (16%, d=1.5, 46.5 ml, 7 mol equiv.) was added to the resulting solution as a single portion. After stirring for 7 min at room temperature, CH_2Cl_2 (450 ml) was added and organic layer was separated. The water layer was further extracted with CH_2Cl_2 and the combined CH_2Cl_2 layer was washed with sat. aqueous $NaHCO_3$ solution, then with sat. aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness to leave crude **9**, which was purified by column chromatography on silica gel with CH_2Cl_2–hexane (2: 1, v/v) as an eluent to afford **9** (1.830 g, y. 73.6%).

5-Nitroisocoumarin (2) from 3,4-Dihydro-3-methoxy-5-nitroisocoumarin (3)——A solution of **3** (33.5 mg) in abs. DMF (2 ml) was heated under reflux for 12 hr. After removal of the solvent, the residue was extracted with CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness to leave a crystalline solid, which was column chromatographed on silica gel with CH_2Cl_2–hexane (2: 1, v/v) as an eluent. From the early part of the fraction, **2** (5.2 mg, y. 18.1%) was obtained. From the later part of the fraction, unchanged **3** (20.5 mg, y. 61.2%) was obtained.

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