

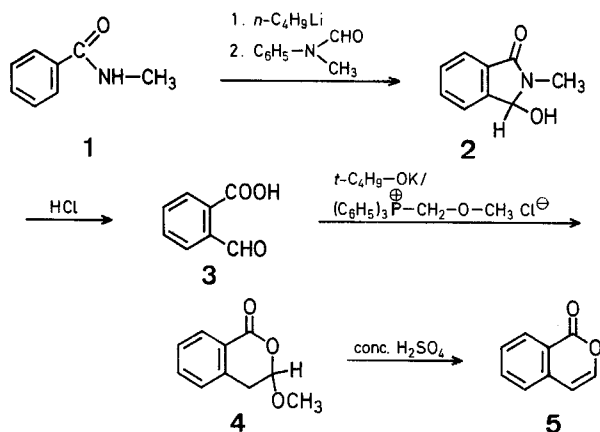
Synthetic Application of Lithiation Reactions; IX¹. A Simplified Synthesis of Isocoumarin

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Recently, we described² a new synthesis of the isocoumarin (1-oxo-1*H*-2-benzopyran, 5) ring system via the 3,4-dihydroisocoumarin which was transformed to the isocoumarin by successive treatment with *N*-bromosuccinimide and triethylamine.

We report here a modification of our earlier synthesis in which a 3,4-dihydroisocoumarin is converted into isocoumarin by simple acid treatment.



Lithiation of *N*-Methylbenzamide and Condensation with *N*-Methylformanilide; 1-Hydroxy-2-methyl-3-oxo-1,3-dihydroisindole (2): A solution of *N*-methylbenzamide (1; 3.375 g, 0.025 mol) in tetrahydrofuran (40 ml, freshly distilled from lithium aluminium hydride) is treated with butyllithium in ether (0.1 mol, prepared from 2.024 g lithium and 12.64 ml 1-bromobutane). The metalation mix-

ture, which turns red, is then refluxed for 45 min and cooled in an ice bath. A solution of *N*-methylformanilide (13.5 ml, 0.1 mol) in ether (30 ml) is added in 20 min, the mixture refluxed for 2 h, then stirred at room temperature for 1 h, and hydrolysed with water (80 ml). The aqueous layer is acidified (hydrochloric acid) and extracted with ether. On evaporation, the ether extract gives a white solid, which is recrystallized from benzene/petroleum ether; yield of 1-hydroxy-2-methyl-3-oxo-1,3-dihydroisindole (2): 2.2 g (53%); m.p. 134°.

C₉H₉NO₂ calc. C 66.24 H 5.56
(163.2) found 66.41 5.72

I.R. (Nujol): ν_{\max} = 3265, 1650 cm⁻¹.

U.V. (methanol): λ_{\max} = 246 (log ϵ = 3.80), 279 nm (3.15).

¹H-N.M.R. (60 MHz, CDCl₃): δ = 2.84 (s, 3H, N-CH₃), 5.30 (d, 1H, -CH-OH, J = 10 Hz), 5.55 (d, 1H, -CH-OH, J = 10 Hz), 7.30–7.56 ppm (m, 4H_{arom}).

¹H-N.M.R. (90 MHz, CDCl₃): δ = 2.84 (s, 3H, N-CH₃), 4.31 (s, 1H, exchangeable with D₂O, -CH-OH), 5.55 (s, 1H, -CH-OH), 7.22–7.6 ppm (m, 4H_{arom}).

Hydrolysis of the Lactam 2 to 2-Formylbenzoic Acid (3):

The lactam 2 (0.5 g) in benzene (50 ml) is refluxed with hydrochloric acid (30%, 20 ml) for 3 h. The organic layer is separated and extracted with sodium hydrogen carbonate solution. The aqueous layer is acidified and extracted with ether to give 3, which is recrystallized from hot water; yield: 0.242 g (52%); m.p. 96–97° (Ref.³, m.p. 96–96.5°).

3-Methoxy-3,4-dihydroisocoumarin (4):

To an ice-cold solution of methoxymethylenetriphenylphosphorane (prepared from 18.3 g of methoxymethyltriphenylphosphonium chloride in 185 ml ether and 4.98 g potassium *t*-butoxide in 50 ml absolute *t*-butanol), a solution of 2-formylbenzoic acid (3; 2.0 g) in ether (25 ml) is added at an even rate (5 min) with stirring. The reaction mixture is stirred for 4 h, allowed to stand overnight, and decomposed with water. The aqueous alkaline layer is acidified with dilute hydrochloric acid and extracted with ether. The extract is dried and evaporated to give a yellowish oil (4.2 g). The oil is chromatographed over silica gel in benzene and the resultant liquid product is distilled in vacuo; yield: 1.2 g (50%); b.p. 135°/1.8 torr.

C₁₀H₁₀O calc. C 67.40 H 5.66
(146.2) found 67.30 5.55

I.R. (film): ν_{\max} = 1740 cm⁻¹.

¹H-N.M.R. (CCl₄): δ = 3.1 (m, 2H, C-4, H's), 3.45 (s, 3H, OCH₃), 5.33 (t, 1H, C-3, H), 8.0 (dd, 1H, C-8, H, J_o = 7 Hz, J_m (WH) = 2 Hz), 7.1–7.5 ppm (m, 3H_{arom}).

Isocoumarin (1-Oxo-1*H*-2-benzopyran, 5):

3-Methoxy-3,4-dihydroisocoumarin (4; 1.2 g) is mixed with conc. sulfuric acid (5 ml), stirred well, then allowed to stand overnight, and poured onto crushed ice. Extraction with ether gives an oily product, which solidifies on cooling. The product is recrystallized from benzene/petroleum ether; yield: 0.780 g (79%); m.p. 48° (Ref.⁴, m.p. 46–47°).

C₉H₆O₂ calc. C 73.96 H 4.14
(146.1) found 74.18 4.37

I.R. (Nujol): ν_{\max} = 1750, 1730, 1700 cm⁻¹.

U.V. (methanol): λ_{\max} = 238.5 (log ϵ = 4.23), 251.5 (3.88), 260 (3.90), 268.5 (3.73), 315 nm (3.62) (Ref.⁵, λ_{\max} = 228, 238, 252, 263, 313 nm).

¹H-N.M.R. (CCl₄): δ = 6.4 (d, 1H, C-4, H, J = 5.5 Hz), 7.47 (d, 1H, C-3, H, J = 5.5 Hz), 8.1 (dd, 1H, C-8, H, J_o = 8 Hz, J_m (WH) = 2 Hz), 7.2–7.7 ppm (m, 3H_{arom}).

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