A Convenient Synthesis of N-Methyl-1(2H)-isoquinolones

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The isoquinoline (1-oxo-1,2-dihydroisoquinoline) ring system is of interest not only because of its presence in several alkaloids,1,2 but also as a useful intermediate in the synthesis of indenoisoquinolines3, protoberberins4,5, and dibenzoquinolizine derivatives6. Isoquinolones are also of interest in medicinal chemistry7.

Several methods have been reported for the synthesis of isoquinolones8. Most of these methods involve the use of either a preformed isoquinoline or homophthalic acid, which is in turn obtained by a several-step sequence. Isoquinolines are converted into isoquinolones by a further two-step sequence either through isoquinolinium salts and their oxidation with different reagents, or by the photolysis of isoquinoline N-oxides6. Homophthalic acids are transformed into isoquinolones via isocoumarins or isoquinolone-4-carboxylic acid9, or via homophthalimide3.

None of the above-mentioned methods is of sufficiently general applicability. We report here a general one-step synthesis of 2-methyl-1-oxo-1,2-dihydroisoquinolines (2, isoquinolones) from N,2-dimethylbenzamide (1) via lithiation and reaction of the dilithiated derivative with N,N-dimethylcarboxamides. The yields of 2 are 58-77%. The reaction of the dilithio derivative of 1 with dimethylformamide affords 3-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (3) together with the desired product 2a. However, compound 3 is readily dehydrated to give 2a in quantitative yield by treatment with acid. Compound 3 even was dehydrated by acidic impurities during 1H-N.M.R. measurements in deuteriochloroform.

2-Methyl-1-oxo-1,2-dihydroisoquinoline (2a) and 3-Hydroxy-2-methyl-1-oxotetrahydroisoquinoline (3):
A solution of N,N-dimethylbenzamide (1; 2.5 g, 0.017 mol) in tetrahydrofuran (40 ml, freshly distilled from lithium aluminium hydride) is treated with butyllithium in ether (0.05 mol, prepared from 1.012 g lithium and 6.32 ml 1-bromobutane). The metallation mixture, which refluxes spontaneously and turns red, is then refluxed for 45 min and cooled to room temperature. A solution of dimethylformamide (5.5 ml, 0.05 mol) in ether (30 ml) is added over 10 min, and the colourless mixture thus obtained is stirred at room temperature for 30 min. The mixture is then hydrolysed with water (60 ml) and extracted with ether (3 x 100 ml). The ether extract is dried with sodium sulphate and evaporated to give 3-hydroxy-2-methyl-1-oxotetrahydroisoquinoline (3); yield: 0.95 g (32%); m.p. 154 °C (from benzene/chloroform) (Ref.8, m.p. 150-152 °C).

I.R. (nujol): ν = 1635 (C=O); 3200 cm⁻¹ (br, OH) (cf. Ref.6).

1H N.M.R. (CDCl₃/TMS): δ = 4.01 (s, 3H, N—CH₃); 3.2 (m, 2H, 4,4-H); 5.07 (t, 1H, J = 2 Hz, 3-H); 7.3 (m, 3H, 5-H, 6-H, 7-H); 7.96 ppm (m, 1H, 8-H) (cf. Ref.6).

The aqueous layer is acidified with hydrochloric acid and extracted with ether (3 x 80 ml). The extract is dried with sodium sulphate and evaporated and the residual liquid distilled in vacuo to give 2-methyl-1-oxo-1,2-dihydroisoquinoline (2a); yield: 1.25 g (47%); b.p. 135-136 °C/0.5 torr; m.p. 38-40 °C (Ref.9, m.p. 38-40 °C; mixture m.p. 38-40 °C) (Ref.8, U.V., and 'H N.M.R. data in good agreement with those reported in Ref.6).

Dehydration of Compound 3 to 2-Methyl-1-oxo-1,2-dihydroisoquinoline (2a): compound 3 (0.18 g, 1 mmol) is stirred with 1 normal hydrochloric acid (2 ml) for 5 min and extracted with ether: yield: 0.15 g (93%); total yield of 2a from 1: 2 g (77%); m.p. 38-40 °C.

2,3-Dimethyl-1-oxo-1,2-dihydroisoquinoline (2b):
N,2-Dimethylbenzamide (1; 2.0 g, 0.013 mol) is lithiated as described above. A solution of N,N-dimethylacetamide (3.48 g, 0.04 mol) in ether (25 ml) is added, the mixture stirred at room temperature for 1 h, and then hydrolysed with water (60 ml). The aqueous layer is separated (the ether layer is discarded) and washed with ether (50 ml). It is then acidified with hydrochloric acid and extracted with ether (3 x 50 ml). All these phases are combined, dried with sodium sulphate, and evaporated to give 2b; yield: 1.35 g (58%); m.p. 105 °C from ethanol (Ref.10, m.p. 102-103 °C).

I.R. (nujol): ν = 1640 cm⁻¹ (C=O) (cf. Ref.11).

U.V. (methanol): The spectrum is identical with that reported in Ref.11.

1H N.M.R. (TMS): δ = 2.26 (s, 3H, 3'-CH₃); 3.44 (s, 3H, 2'-CH₃); 6.05 (s, 1H, 4'-H); 7.12 7.52 (m, 3H, 5-H, 6-H, 7-H); 8.2 ppm (m, 1H, 8-H) (cf. Ref.11).
2-Methyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline (2c):
N,N-Dimethylbenzamide (2; 1.3 g, 0.009 mol) is titrated as described above. A solution of N,N-dimethylbenzamide (5.96 g, 0.04 mol) in ether (30 ml) is added, the mixture refluxed for 2 h, then cooled to room temperature, and hydrolysed with water (60 ml). Work-up as for 2b affords 2c as a colourless solid; yield: 1.5 g (73%); m.p. 56°C (from light petroleum).

C₉H₈NO  
Calc.  C 81.68  H 5.57  
Found  81.95  5.57

I.R. (mujol): ν max 1645 cm⁻¹.
U.V. (methanol): λ max = 223 (log ε = 4.3), 247 (4.0), 288 (3.8), 326 (3.8), 342 nm (3.8).

¹H-N.M.R. (CDCl₃/TMS): δ = 3.29 (s, 3 H, 2-CH₃); 6.20 (s, 1 H, 4-H); 7.35 (m, 8.1, arom); 8.3 ppm (m, 1 H, 8-H).

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