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

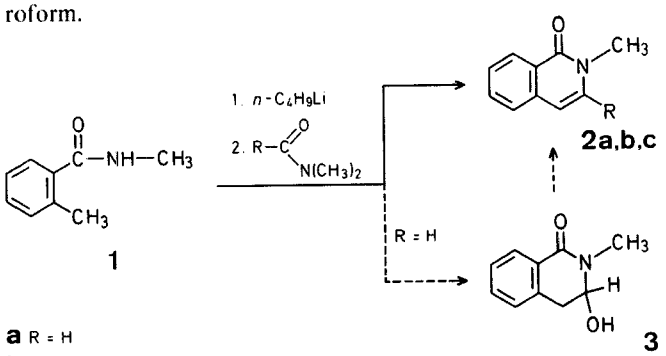
R. S. Mali*, B. K. Kulkarni, K. Shankaran

Department of Chemistry, University of Poona, Pune - 411007, India

The isoquinolone (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 indenoisoquinolines[3], protoberberins[4,5], and dibenzoquinolizine derivatives[5]. Isoquinolones are also of interest in medicinal chemistry[6].

Several methods have been reported for the synthesis of isoquinolones[2]. 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 isoquinolium salts and their oxidation with different reagents[7], or by the photolysis of isoquinoline *N*-oxides[8]. Homophthalic acids are transformed into isoquinolones via isocoumarins or isoquinolone-4-carboxylic acid[9], or via homophthalimide[5].

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[10] (**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 ^{1}H-N.M.R. measurements in deuteriochloroform.



a R = H
b R = CH_3
c R = C_6H_5

2-Methyl-1-oxo-1,2-dihydroisoquinoline (2a) and 3-Hydroxy-2-methyl-1-oxotetrahydroisoquinoline (3):

A solution of *N*,2-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 (2 × 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. 145 °C (from benzene/chloroform) (Ref.[5], m.p. 150–152 °C).

I.R. (nujol): ν = 1635 (C=O); 3200 cm^{-1} (br, OH) (cf. Ref.[5]).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 3.01 (s, 3 H, N—CH_3); 3.2 (m, 2 H, 4,4-H_2); 5.07 (t, 1 H, J = 2 Hz, 3-H); 7.3 (m, 3 H, 5-H, 6-H, 7-H); 7.96 ppm (m, 1 H, 8-H) (cf. Ref.[5]).

The aqueous layer is acidified with hydrochloric acid and extracted with ether (3 × 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). [I.R., U.V., and ^{1}H-N.M.R. data in good agreement with those reported in Ref.[9]].

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 × 50 ml). All ether phases are combined, dried with sodium sulphate, and evaporated to give **2b**; yield: 1.35 g (58%); m.p. 105 °C (from ethanol) (Ref.[11], 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.[12].

^{1}H-N.M.R. (CCl_4/TMS): δ = 2.26 (s, 3 H, 3-CH_3); 3.44 (s, 3 H, 2-CH_3); 6.05 (s, 1 H, 4-H); 7.12–7.52 (m, 3 H, 5-H, 6-H, 7-H); 8.2 ppm (m, 1 H, 8-H) (cf. Ref.[11]).

0039-7881/82/0432-0329 $ 03.00

2-Methyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline (2c):
N,2-Dimethylbenzamide (**2**; 1.3 g, 0.009 mol) is lithiated 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).

$C_{16}H_{13}NO$	calc.	C 81.68	H 5.57
(235.3)	found	81.95	5.57

I.R. (nujol): $\nu = 1645$ cm^{-1}.

U.V. (methanol): $\lambda_{max} = 223$ (log$\varepsilon = 4.3$), 247 (4.0), 288 (3.8), 326 (3.8), 342 nm (3.7).

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 3.29$ (s, 3H, 2-CH_3); 6.20 (s, 1H, 4-H); 7.35 (m, 8H$_{arom}$); 8.3 ppm (m, 1H, 8-H).

Received: August 6, 1981

[1] S. W. Pelletier, *Chemistry of the Alkaloids*, Van Nostrand Reinhold Co., New York, 1970, p. 77.
[2] M. Shamma, J. L. Moniot, *Isoquinoline Alkaloid Research*, Plenum Press, New York, 1978, p. 57.
[3] S. F. Dyke et al., *Tetrahedron* **27**, 281 (1971).
[4] D. W. Brown, S. F. Dyke, *Tetrahedron* **22**, 2429 (1966).
[5] H. Iida, K. Kawano, T. Kikuchi, F. Yoshimizu, *Yakugaku Zasshi* **96**, 176 (1976); *C. A.* **84**, 135898 (1976).
[6] T. S. Sulkowski, M. A. Wille, *U. S. Patent* 3452027 (1969), American Home Products Corp.; *C. A.* **71**, 112830 (1969).
W. E. Coyne, J. W. Cusic, *U. S. Patent* 3600394 (1971), Searle & Co.; *C. A.* **75**, 118241 (1971).
[7] N. I. Fisher, F. M. Hamer, *J. Chem. Soc.* **1934**, 1905.
S. Ruchirawat, S. Sunkul, Y. Thebtaranonth, N. Thirasasna, *Tetrahedron Lett.* **1977**, 2335.
[8] M. Ishibawa, S. Yamada, H. Hotta, C. Kaneko, *Chem. Pharm. Bull.* **14**, 110 (1966).
[9] V. H. Belgaonkar, R. N. Usgaonkar, *Tetrahedron Lett.* **1975**, 3849.
[10] R. L. Vaulx, W. H. Puterbaugh, C. R. Hauser, *J. Org. Chem.* **29**, 3514 (1964).
[11] D. E. Korte, L. S. Hegedus, R. K. Wirth, *J. Org. Chem.* **42**, 1329 (1977).
[12] E. J. Mariconi, F. J. Creegan, *J. Org. Chem.* **31**, 2090 (1966).

0039-7881/82/0432-0330 $ 03.00