An Efficient Synthesis of 4-Aryl-1,2,3,4-tetrahydroisoquinolines

Nurani S. Narasimhan* and Prakash A. Patil

Garware Research Centre, Department of Chemistry, University of Poona, Pune 411 007, India

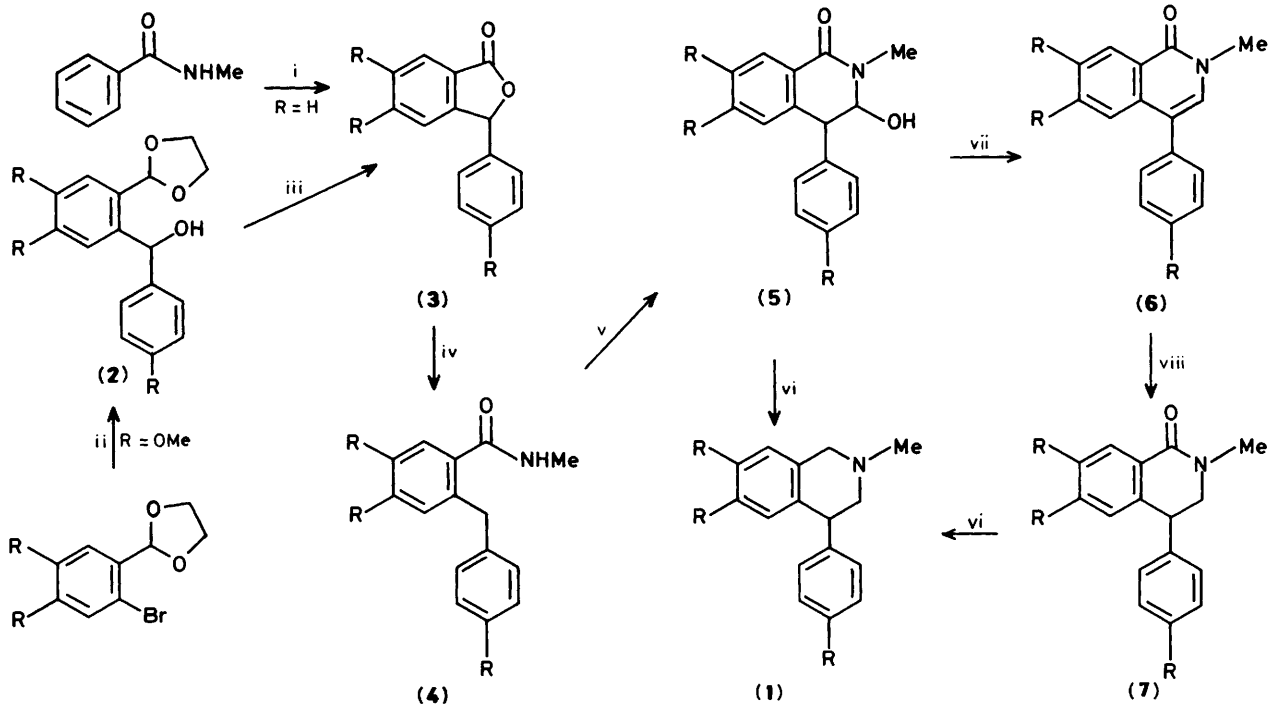
A general synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinolines from 3-aryl phthalides is described.

In this communication we describe a general synthesis of *N*-methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines. Our synthesis is illustrated for *N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**), which is an agonist for the dopamine receptor[1] and the methyl ether of cherylline (**1b**), a rare phenolic isoquinoline alkaloid[2] with an aryl substituent at the 4 position.

The starting compounds are the 3-aryl phthalides (**3**), which are obtained as shown.[3] On hydrogenolysis, the phthalides provided the *ortho*-benzyl benzoic acids. The *N*-methyl

Table 1.

		(2)	(3)	(4)	(5)	(6)	(7)	(1)
a; R = H	M.p./°C		114 (EtOH–C_6H_{14})	102—103 (C_6H_{14}–EtOAc)	135—136	181—182 (C_6H_{14}–EtOAc)	79—80	178—179 (HCl) (EtOH–Et_2O) Lit.,[5] 178—179
	% Yield		70	75	80	90	75	50
b; R = OMe	M.p./°C	106—108 (Et_2O)	128—129 (EtOH)	131—132 (C_6H_{14}–EtOAc)	123—126	179—180 (EtOAc)		227—228 (HCl) (MeOH–Et_2O) Lit.,[6] 228—229
	% Yield	80	65	80	75	90		45



Scheme 1. i, Bu^nLi–diethyl ether, tetrahydrofuran (THF), heat; PhCHO, 0 °C; 50% HCl; ii, Bu^nLi–diethyl ether, −78 °C; ArCHO, −78 °C; H_2O; iii, 1 M H_2SO_4, C_6H_6, room temp., 3 h; $Na_2Cr_2O_7$, room temp., 3 h; iv, H_2–Pd/C, 90 psi: for **a**, room temp., 18 h, for **b**, 80 °C, 3 h; $SOCl_2$: for **a**, 10 min, room temp., for **b**, THF, 0 °C, 1 h; aq. $MeNH_2$, 0 °C; v, Bu^nLi–diethyl ether, 0 °C; DMF, 0 °C; H_2O; vi, $LiAlH_4$–THF, room temp., 2 h; vii, 1 M H_2SO_4, heat, 10 min; viii, H_2–Pd/C, 90 psi, 80 °C, 3 h (only for **a**).

benzamides (**4**) of the acids, on lithiation with Bu^nLi followed by treatment with dimethylformamide (DMF), gave the *N*-methyl-3-hydroxy-1,2,3,4-tetrahydroisoquinolone (**5**), which on dehydration and reduction or direct reduction furnished the target compounds (Table 1).†

The synthesis described above is potentially very useful, since the 3-aryl phthalides, in which the aromatic ring may be unsubstituted or substituted at any position with methoxy groups, are readily available through aromatic lithiation reactions[3] or through halogen–metal exchange reactions.[4]

We thank C.S.I.R., New Delhi, for a fellowship to P. A. P.

Received, 22nd July 1986; Com. 1034

† Satisfactory i.r., ^1H n.m.r., and analytical data were obtained for all new compounds.

References

1 P. A. Dandridge, C. Kaiser, M. Brenner, D. Gaitanopoulos, L. D. Davis, R. Lee Webb, J. J. Foley, and H. M. Sarau, *J. Med. Chem.*, 1984, **27**, 28.

2 H. Hara, R. Shirai, O. Hoshino, and B. Umezawa, *Heterocycles*, 1983, **20**, 1945 and references cited therein.

3 Phthalides with different methoxy substitution patterns can be synthesised through aromatic lithiation reactions: W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 853; B. H. Bhide and N. S. Narasimhan, *Tetrahedron*, 1971, **27**, 6171; D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, 1976, **41**, 3653. For references to Professor V. Snieckus' work, see P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306.

4 H. P. Plaumann, J. G. Smith, and R. Rodrigo, *J. Chem. Soc., Chem. Commun.*, 1980, 354.

5 K. Freter, E. Dubois, and A. Thomas, *J. Heterocycl. Chem.*, 1970, **7**, 159.

6 A. Brossi, G. Grethe, and S. Teitel, *J. Org. Chem.*, 1970, **35**, 1100.