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NOVEL 1-SUBSTITUTED -2,3-DIHYDRO-1H-ISOINDOLES: SYNTHESIS VIA MEYERS' METHODOLOGY

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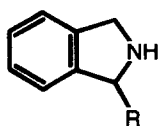
Summary: A variety of novel 1-substituted-2,3-dihydro-1H-isoindoles have been synthesised in three steps from 2,3-dihydro-1H-isoindole via metallation and alkylation of its tert-butylformamidino derivative.

In the course of our work we required a series of 1-substituted-2,3-dihydro-1H-isoindoles 1. Methods of preparing compounds of this type include the electrolytic reduction of phthalimidines[1] and the Clemmensen reduction of phthalazines[2]. Neither of these procedures appeared to us to be of general synthetic utility due to the limited availability of suitable precursors and the incompatability of the reaction conditions towards functionalized substituents.



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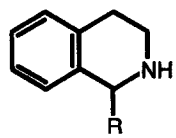
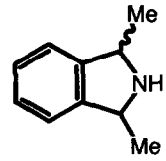


2

However, A.I. Meyers et al[3] have shown that substituents can be introduced into 1,2,3,4-tetrahydroisoquinolines via metallation of the corresponding N-tert-butylformamidino derivatives. The resultant amidines are readily converted into the α-substituted amines 2, by a variety of reagents. By application of this methodology to 2,3-dihydro-1H-isoindole 4, we have been able to prepare a series of novel 1-substituted derivatives 1, (Table) via a single intermediate 5 (Scheme).

Furthermore, alkylation of the monosubstituted intermediate 6a gave, the 1,3-disubstituted analogue 3 as a 1:1 mixture of cis and trans isomers. This is in contrast to the tetrahydroisoquinoline series, in which further alkylation gave 1,1-disubstituted analogues[3].



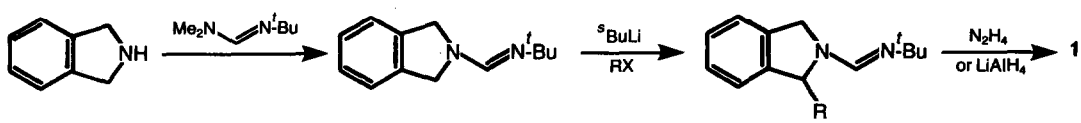
3

The synthetic route (see Scheme) involved treatment of 2,3-dihydro-1H-isoindole[4] 4 with N'-tert-butyl-N,N-dimethylformamidine[5] (1.5 equiv.) and ammonium sulphate (catalytic) in refluxing toluene (4.5h). Evaporation and purification by dry flash chromatography (EtOAc/5% Et_3N) yielded the formamidine[6] 5 (93%, mp 226°C). Metallation of 5 was accomplished using sec - butyllithium (1.1 equiv.) in dry THF (-78°C, 0.25h) followed by addition of the electrophile (1.1 equiv.) and allowing the solution to warm to -20°C (0.5-1h), before quenching with water. Extraction into dichloromethane, evaporation and purification as before furnished the 1-substituted intermediate 6. Cleavage of the formamidine was effected by either treatment with hydrazine (3 equiv.) and acetic acid (3 equiv.) in 60% aqueous ethanol (60°C, 1.5-5h, 6a-g) or lithium aluminium hydride (3 equiv.) in refluxing THF overnight[7](6h). The crude 1-substituted-2,3-dihydro-1H-isoindole 1 was purified either by distillation (Kugelrohr) or by dry flash chromatography (EtOAc/5% Et_3N).

Preparation of 2,3-dihydro-1,3-dimethyl-1H-isoindole 3, was accomplished by treatment of the formamidine 6a with sec-butyllithium and iodomethane in the usual manner to afford the 1,3-disubstituted formamidine (80%). Subsequent heating with potassium hydroxide (7.5 equiv.) in 60% aqueous methanol, (60°C,2h), then concentration and extraction as before yielded the product 3 in 57% yield[8].

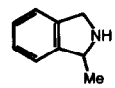
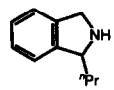
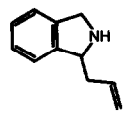
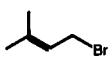
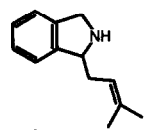
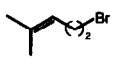
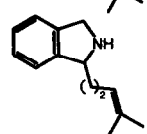
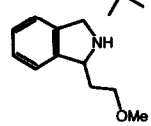
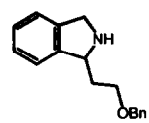
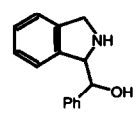
In conclusion, a variety of 1-substituted-2,3-dihydro-1H-isoindoles have been synthesised in three steps from 2,3-dihydro-1H-isoindole 4 via metallation and alkylation of the formamidino derivative 5. Further substitution occurs regioselectively to afford the 1,3-disubstituted analogue as a mixture of cis and trans isomers. This facile synthesis replaces the more tedious routes which have been applied to compounds of this type.

Scheme



4 5 6

Table

Electrophile	Formamidine	Yield[9], %	Amine 1	Yield[9], %, (Bp°C,mm/Hg)
MeI	6a	91		84(55,0.2)[10]
*n*PrI	6b	80		61(95,0.5)[11]
	6c	54		72(130,0.1)
	6d	44		73(147,0.1)
	6e	76		79(170,0.2)
	6f	80		35(145,0.1)
	6g	56		55(-)
PhCHO	6h[12]	61		42(-)
 [13]	6i	42	-[14]	

Acknowledgement - We thank Dr J.M. Berge for useful discussions.

References and Notes

1. S. Sugasawa and H. Shigehara, J. Pharm. Soc. Jpn., 1943, 63, 98.
2. D.G. Parsons and A.F. Turner, J. Chem. Soc. (C), 1966, 2016.
3. A.I. Meyers, S. Hellring and W.T. Hoeve, Tetrahedron Lett., 1981, 22, 5115 and A.I. Meyers, Aldrichimica Acta, 1985, 18, 59 (Review).
4. J. Bornstein, S.C. Lashua and A.P. Boiselle, J. Org. Chem., 1957, 22, 1255.
5. Available from Aldrich Chemical Company.
6. All new products gave satisfactory analytical and/or spectroscopic data.
7. A.I. Meyers and S. Hellring, Tetrahedron Lett., 1981, 22, 5119.
8. Attempted hydrazinolysis or reductive cleavage with $LiAlH_4$ of the 1,3-disubstituted formamidine resulted in recovered starting material only, presumably due to steric interference of the 1- and 3-substituents.
9. Yields have not been optimized.
10. R.P. Linstead and E.G. Noble, J. Chem. Soc., 1937, 933, reported bp 94°C, (6mm/Hg).
11. O. Bromberg, Ber., 1896, 29, 1434.
12. 1:1 Mixture of diastereomers, separable by chromatography.
13. When 1.1 equiv. of ethyl chloroformate were employed, the 1,1-di(ethoxycarbonyl) derivative was isolated (35%)alongside 6i (15%), presumably via deprotonation of the monoalkylated product. This side reaction was minimized by using a large excess (20 fold) of the electrophile.
14. Characterized as the formamidine.

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