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THE SYNTHESIS OF 7-ALKOXYINDOLES

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Abstract: A number of protected 7-hydroxyindoles was prepared by reaction of the protected 2-nitrophenols with vinylmagnesium bromide. Benzhydryl was shown to be the protecting group of choice, giving good yields of the indole and being readily removed for subsequent transformations of the 7-hydroxy function.

We wished to prepare a series of 7-alkoxyindoles as intermediates for chemical elaboration. Of the applicable procedures published[1a-g], the Gassmann synthesis[1b] appeared to present the most suitable approach to such compounds, but had the disadvantage of being a multistep route (FIG.I), requiring purification at each step. In our hands, synthesis of 7-benzyloxyindole by this method gave only 19% overall yield from 1-benzyloxy-2-nitrobenzene. Recently, Bartoli[2] has published a novel, short approach to 7-substituted indoles, whereby the nitrobenzene is reacted with 3 equivalents of vinyl magnesium bromide. Only one example of a 7-hydroxyindole derivative (7-trimethylsilyloxyindole)(FIG.II) was quoted, but we experienced difficulty in

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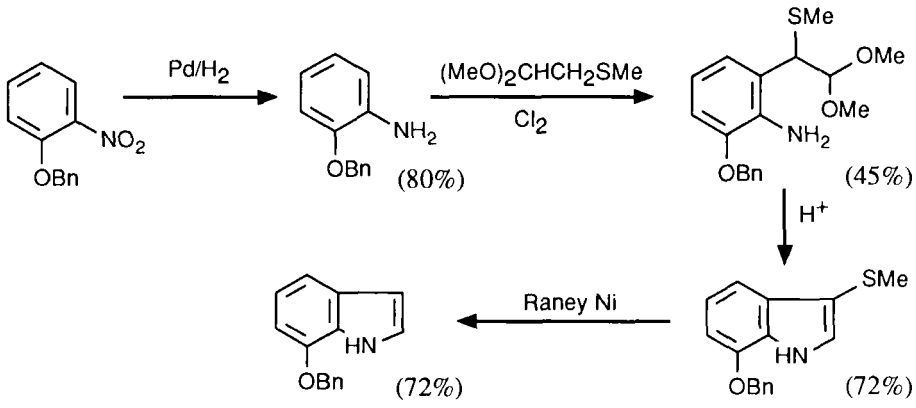


FIG.I

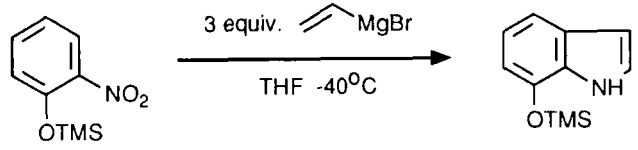


FIG.II

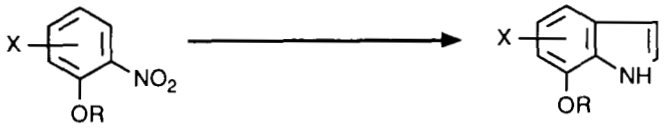
obtaining pure samples of the starting trimethylsilyloxynitrobenzene and in reproducing the reported yields of the resulting indole. However, if the general methodology could be extended, it would provide an attractive alternative to the Gassmann route.

We initially examined the reaction of 1-benzyloxy-2-nitrobenzene under Bartoli's general conditions but were disappointed in recovering only 13% of required product. However, replacement of the benzyl moiety by more bulky substituents improved the yield markedly (Table I), with benzhydryl giving the highest yield of 57%. The low recovered yield with a trityl protecting group was due to problems of isolation of the relatively labile product.

Table I

R	Yield
Benzyl	13%
Benzhydryl	57
9-Anthracenemethyl	53
Trityl	40 (62% by nmr before purification)

Table II



X	Yield R= Benzyl	Benzhydryl
H	13%	57%
4-Cl	31	50
4-CF_3	40	54
4-OBn	10	
4-CO_2Me	20	

We have also investigated the effect of a second substituent on the applicability of Bartoli's methodology to the synthesis of 7-alkoxyindoles (Table II). It appears that electron-withdrawing groups increase product formation and again, in the examples where we have compared a benzyloxy with a benzhydryl protecting group, the latter has given higher yields.

The utility of the benzhydryl protecting group in the synthesis of 7-alkoxyindoles is demonstrated by the formation of 7-cyanomethoxyindole.

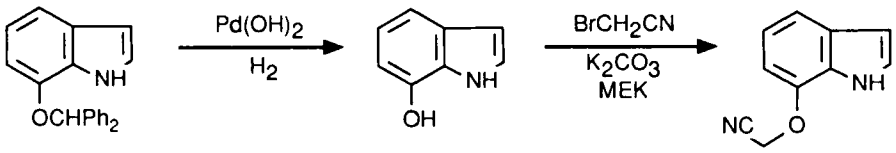


FIG.III

7-Benzhydryloxyindole was deprotected by hydrogenation over Pearlman's catalyst[3] and the crude 7-hydroxyindole isolated and immediately alkylated with bromoacetonitrile to give an overall yield of 88% of the purified 7-cyanomethoxyindole (FIG.III).

Experimental:

Melting points are uncorrected. ^1H n.m.r. spectra were obtained at 300 MHz on a Bruker AM300 instrument in $CDCl_3$ solution and data are given in p.p.m. (δ) relative to tetramethylsilane.

A typical experimental procedure is exemplified by the synthesis of 7-cyanomethoxyindole from 2-nitrophenol.

2-Benzhydryloxynitrobenzene:

A mixture of 2-nitrophenol (11.0g, 79 mmole)(dried by azeotroping with toluene), anhydrous potassium carbonate (17.6g, 127.4 mmole) and benzhydryl bromide (19.6g, 79 mmole) in acetone (220ml) was stirred at reflux under nitrogen for 5 hours. The cooled mixture was filtered and concentrated to dryness *in vacuo*. The residue was extracted with diethyl ether and solids removed by filtration. The filtrate was again concentrated to dryness and the residue triturated with 60-80°C petroleum ether. The resultant brown solid was

isolated by filtration, washed with petroleum ether and dried *in vacuo* at 30°C. Yield = 16.83g (70%). m.p. 96-98°C.

^{1}H nmr δ 6.36 (1H,s,OC<u>H</u>Ph$_2$), 6.96 (1H,t), 7.03 (1H,d), 7.2-7.4 (7H,m), 7.47 (4H,dd), 7.83 (1H,dd).

7-Benzhydryloxyindole:

To a stirred solution of 2-benzhydryloxynitrobenzene (3.05g, 10 mmole) in dry THF (100ml) at -40°C under nitrogen was added 1M vinyl magnesium bromide in THF (35ml) portionwise over a few minutes. After stirring for a further 40 mins. at -40°C, the reaction mixture was poured into aqueous ammonium chloride (200ml) and extracted into diethyl ether (2X100ml). The organic phases were combined, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to a yellow oil. The product was purified by column chromatography on silica eluting with 12.5% ethyl acetate in hexane to give a pale yellow solid. Yield = 1.72g (57%). m.p. 112-115°C.

^{1}H nmr δ 6.33 (1H,s,OC<u>H</u>Ph$_2$), 6.47 (1H,dd,H-3), 6.53 (1H,d,H-6), 6.85 (1H,t,H-5), 7.00 (1H,t,H-2), 7.1-7.5 (11H,m), 8.3 (1H,bs,NH).

7-Cyanomethoxyindole:

A solution of 7-benzhydryloxyindole (0.525g, 1.75 mmole) in methanol (10ml)/toluene (10ml) was hydrogenated at 50 p.s.i. and room temperature for 1 hour in the presence of Pearlman's catalyst (0.33g). The reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give an oil. The crude 7-hydroxyindole was taken up in methyl ethyl ketone (20ml), bromoacetonitrile (0.65g, 5.25 mmole) and anhydrous potassium carbonate (0.6g, 4.35 mmole) added, and the mixture heated at reflux under nitrogen for 1 hour. The cooled mixture was poured into 2.5M hydrochloric acid (40ml)/ice and extracted into dichloromethane. The organic phase was dried over magnesium sulphate, filtered and concentrated to low volume *in vacuo*, and then purified by column chromatography on silica, eluting with 20% ethyl

acetate in hexane. Yield = 0.264g (88%) - crystallised on cooling to give a bronze coloured solid, m.p. 63-65°C.

^{1}H nmr δ 4.76 (2H,s,OC$\underline{H}_2$CN), 6.53 (1H,dd,H-3), 6.63 (1H,d,H-6), 7.02 (1H,t,H-5), 7.14 (1H,t,H-2), 7.35 (1H,d,H-4), 8.47 (1H,bs,NH).

The following 7-substituted indoles were prepared by similar procedures:

7-Benzyloxyindole. ^{1}H nmr δ 5.20 (2H,s,OC$\underline{H}_2$Ph), 6.53 (1H,dd,H-3), 6.73 (1H,d,H-6), 7.03 (1H,t,H-5), 7.18 (1H,t,H-2), 7.2-7.5 (6H,m), 8.41 (1H,bs,NH).

7-Trityloxyindole. ^{1}H nmr δ 6.25 (1H,d,H-6), 6.42 (1H,dd,H-3), 6.60 (1H,t,H-5), 7.04 (1H,t,H-2), 7.10 (1H,d,H-4), 7.15-7.3 (9H,m), 7.46 (6H,m,H-2',6'), 8.17 (1H,bs,NH).

7-(9-Anthracenemethoxy)indole. ^{1}H nmr δ 6.12 (2H,s,OC$\underline{H}_2$Anthr), 6.53 (1H,dd,H-3), 7.05 (1H,t,H-2), 7.09-7.22 (2H,m,H-5,6), 7.37 (1H,d,H-4), 7.46-7.56 (4H,m,H-2',3',6',7'), 8.07 (2H,m,H-4',5'), 8.23 (1H,bs,NH), 8.31 (2H,m,H-1',8'), 8.56 (1H,s,H-10').

4,7-Dibenzyloxyindole. ^{1}H nmr δ 5.15 (2H,s,OC$\underline{H}_2$Ph), 5.19 (2H,s,OC$\underline{H}_2$Ph), 6.43 (1H,d), 6.57 (1H,d), 6.70 (1H,t,H-3), 7.11 (1H,t,H-2), 7.27-7.52 (10H,m), 8.42 (1H,bs,NH).

7-Benzyloxy-4-chloroindole. ^{1}H nmr δ 5.19 (2H,s,OC$\underline{H}_2$Ph), 6.63 (2H,m,H-3,6), 6.99 (1H,d,H-5), 7.22 (1H,t,H-2), 7.32-7.50 (5H,m), 8.51 (1H,bs,NH).

7-Benzhydryloxy-4-chloroindole. ^{1}H nmr δ 6.31 (1H,s,OC$\underline{H}$Ph$_2$), 6.46 (1H,d,H-6), 6.60 (1H,t,H-3), 6.86 (1H,d,H-5), 7.20 (1H,t,H-2), 7.25-7.45 (10H,m,Ph$_2$), 8.51 (1H,bs,NH).

7-Benzyloxy-4-trifluoromethylindole. ^{1}H nmr δ 5.24 (2H,s,OC$\underline{H}_2$Ph), 6.70 (1H,t,H-3), 6.71 (1H,d,H-6), 7.26 (1H,t,H-2), 7.3-7.53 (6H,m), 8.60 (1H,bs,NH).

7-Benzhydryloxy-4-trifluoromethylindole. ^{1}H nmr δ 6.37 (1H,s,OC$\underline{H}$Ph$_2$), 6.51 (1H,d,H-6), 6.66 (1H,m,H-3), 7.09 (1H,t,H-2), 7.17 (1H,d,H-5), 7.2-7.5 (10H,m,Ph$_2$), 8.51 (1H,bs,NH).

7-Benzyloxy-4-methoxycarbonylindole. ^{1}H nmr δ 3.96 (3H,s,$CO_2C\underline{H}_3$), 5.27 (2H,s,$OC\underline{H}_2Ph$), 6.75 (1H,d,H-6), 7.15 (1H,t,H-3), 7.30 (1H,t,H-2), 7.34-7.51 (5H,m), 7.91 (1H,d,H-5), 8.57 (1H,bs,NH).

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