Synthesis of Novel Indole Derivatives: Variations in the Bartoli Reaction

Adrian P. Dobbs,[1]* Martyn Voyle, Neil Whittall
SmithKline Beecham Pharmaceuticals, Old Powder Mills, Leigh, Tonbridge, Kent TN11 9AN, UK
E-mail: adrian@apdobbs.demon.co.uk; Neil_Whittall-1@sbphrd.com

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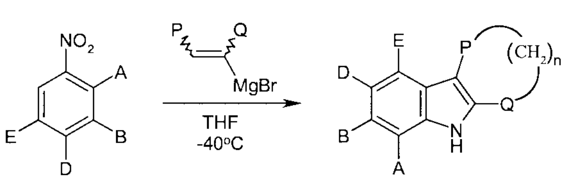
Abstract: The synthesis of a range of novel substituted indoles and tricyclic indole derivatives is described using an extension of the Bartoli methodology.

Key words: Grignard reactions, indoles, Bartoli reaction, regioselectivity

In the course of our work, it was necessary to prepare a range of novel di– and tri–substituted and fused indoles of varied substitution pattern. A number of methods already exist for the synthesis of such indoles from benzenoid or aniline precursors and these initially appeared attractive e.g. via palladium–mediated coupling and/or cyclisation reactions.[2] However due to the disappointing yields obtained with certain substrates via these methods, attention turned instead to the Bartoli method for indole synthesis.[3] This method involves treating an aromatic nitro–compound with three equivalents of a Grignard reagent (usually vinylmagnesium bromide) to form the indole but has so far been of limited use, generally being restricted to aromatic nitro–compounds bearing an *ortho*–substituent, thus giving selectivity in the cyclisation and an efficient route to 7–substituted indoles. (Indeed, the original work of Bartoli has shown that yields drop dramatically in the absence of an *ortho*–substituent[3a]).

However some interesting results have been encountered, which show that this methodology may be synthetically useful for other substrates (Scheme 1 and Table 1).

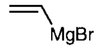
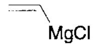
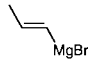
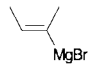
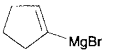
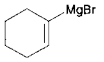
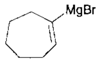


(1) (2)

Scheme 1

A range of simple substituted nitrobenzenes were first used in the reaction. As expected, both *ortho*–methyl (**1a**) and *ortho*–trifluoromethyl (**1c**) groups gave good yields of the corresponding 7–substituted indoles when treated with vinylmagnesium bromide in THF at ca. –40 °C for between 30 minutes and one hour. (Interestingly, the yield was lower with vinylmagnesium chloride by ca. 15% under identical conditions). Employing a further excess of Grignard reagent failed to push the reaction to completion and indeed a lowering of yield was observed (**1i**) while the levels of reduced products increased. It has been reported that using compounds with *meta*– or *para*–methyl groups gives drastically lower yields of indoles.[3a] It was found that employing either *meta*– or *para*–trifluoromethyl (**1d** and **1e**) groups failed to give any indole product but rather a complex mixture of compounds, including the corresponding reduced aniline and nitroso derivatives as well as azo–coupled products, but not the oxindole (a commonly reported side product of these reactions). In fact in all these reactions (even the high indole–yielding ones) the reduced aniline and nitroso compounds were always detected in varying levels and ratios by GCMS analysis, a result which is consistent with the proposed mechanism for this reaction.[3c] Yields were upheld using disubstituted nitrobenzenes (**1f**) where one substituent was still *ortho* to the nitro group, giving good yields of the indole as the major product.

Table 1 Results of the Bartoli Reaction employing various substrates and Grignard Reagents

	Nitrobenzene				RMgBr	Eq.	%Yield	Notes
(1)	A	B	D	E			Indole (2)	
a	Me	H	H	H		3	71	A
b	Me	H	H	H		3	58	
c	CF$_3$	H	H	H		3	56	
d	H	CF$_3$	H	H	“	3	0	
e	H	H	CF$_3$	H	“	3	0	
f	Br	H	H	Br	“	3	69	
g	H	CF$_3$	Me	H	“	3	36	
h	H	Br	Me	H	“	3	34	
i	H	CF$_3$	Me	H	“	5	29	
j	Me	H	H	H		3	59	A
k	Me	H	H	H		3	73	
l	Me	H	H	H		3	49	B
m	Me	H	H	H		3	47	B
n	Me	H	H	H		3	41	B

A) Consistent with literature yield[3a]; B) Prepared by treatment of the corresponding cycloalkene with bromine to give the di–bromocycloalkane followed by base–promoted hydrobromide elimination to the vinylbromide and finally treatment with magnesium turnings to generate the Grignard reagent.[4]

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The surprising results were obtained when combining some of these groups (particularly the methyl, trifluoromethyl and bromo groups) in the starting material. These groups on their own, in either the *meta*– or *para* positions, failed to yield any significant levels of indoles, vide supra. However, it was found that combinations of them in the 3 and 4 positions gave modest yields of the desired indoles, for example, 3–trifluoromethyl–4–methylnitrobenzene produced 5–methyl–6–trifluoromethylindole (**1g**) when treated with vinyl Grignard reagent (with only traces of the other possible regioisomer detected). Comparable levels of 5–methyl–6–bromoindole (**1h**) were similarly obtained from 3–bromo–4–methylnitrobenzene under the same conditions. The explanation for this is unclear at present, particularly since the simple *meta*– and *para*–trifluoromethylnitrobenzenes gave no indole products, although it could be due to a subtle interplay of steric and electronic effects favouring the cyclisation to the desired position on the aromatic nucleus.

In an attempt to improve the yields in these reactions the effects of solvent and temperature were investigated. It was found that warming the reaction (up to reflux in THF) gave lower yields of indole (15% at 0 °C and 0% at reflux). Similarly lowering the temperature to –78 °C also caused a decrease in indole yield (albeit less dramatic, to 16%) and –40 to –45 °C was found to be the optimum for these reactions. As far as the reaction solvent was concerned, only THF gave any significant levels of indole products, even when employing an *ortho*–substituent to assist in the reaction, as in the earlier examples. (Other solvents tested included dry diethyl ether, hexane and toluene at temperatures ranging from reflux down to –78 °C but none gave any appreciable levels of indoles). Longer reaction times had no effect on the yields of indole obtained and it is believed that these reactions are very rapid indeed, possibly proceeding via a radical/single electron transfer mechanism and being complete almost immediately.[3c]

Finally the effects of the Grignard reagent were investigated using more complex Grignards, (prepared by established literature procedures[4]). It was found that these carbocyclic Grignard reagents reacted with 2–nitrotoluene, thus affording very rapid synthesis of a range of fused tricyclic indole derivatives (**1 l**,**m**,**n**). (*N.B.* Although cyclic vinylbromide derivatives gave good yields, heteroaromatic Grignards, for example, thien–2–yl and *N*–methylpyrrolidin–2–yl reagents, failed to give any fused indoles, presumably due to the aromatic nature of these compounds).

In summary we have investigated the scope and extended the range of the Bartoli reaction to give a number of synthetically useful substituted indoles which are being further utilised in our studies.

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References and Notes

(1) Present Address: Department of Chemistry, The Open University, Walton Hall, Milton Keynes, MK7 6AA, England.

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(4) Giacomoni, J.C., Cambon, A., Rouvier, E. *Bull. Soc. Chim. France* **1970**, 3097–3098 (bromination) and Bandodakar, B.S., Nagendrappa, G. *Synthesis* **1990**, 843–844 (elimination).

(5) IR spectra were recorded neat or in solution on a Nicolet Avatar 360 FT–IR machine. ^{1}H and ^{13}C NMR spectra were recorded using either a Jeol GSX–400 or a Bruker DRX–400 using $CDCl_3$ as solvent and TMS or solvent peaks as internal references and are quoted in the form δ_H (integration, multiplicity, coupling constant(s), assignment) or δ_C (assignment). Coupling constants (*J* values) are quoted to one decimal place with values in Hz. Mass spectra were recorded on a HP–5890GC–VG–Masslab Trio–2 gas chromatography–mass spectrometer.

(6) ***Typical procedure for the Bartoli reactions:*** The nitro–compound (5 mmol) was placed in a two–necked round–bottomed flask fitted with a gas inlet (argon) and rubber septum. The flask was purged several times with argon before adding THF (35–40 ml) and cooling to between –40 and –45 °C. The Grignard reagent (3 eq.) was then added rapidly in one portion to the THF solution and stirring continued for a further 30 mins to 1 hour (exact length of time had little effect on yield). Saturated ammonium chloride solution was added to the reaction mixture (at ca. –40 °C) before allowing the mixture to warm to room temperature. The mixture was thoroughly extracted with diethyl ether (2 x 200 ml), the ether extracts combined and thoroughly washed with further ammonium chloride (300 ml), water (300 ml) and brine (300 ml) before drying ($MgSO_4$) and concentrating in vacuo to give a dark brown gum, which was purified by flash column chromatography (hexane:ethyl acetate 9:1) to give the *title compound*. Compounds were in good agreement with literature data; new compounds gave satisfactory

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spectroscopic and analytical data, as illustrated by the following representative compounds:***4,7–Dibromoindole (2f):*** Pale yellow oil, slowly crystallising to pale yellow/ brown solid; Found (M ^{79}Br, ^{79}Br)+272.8795. $C_8H_5N^{79}Br^{79}Br$ requires 272.8789; δ_H (400 MHz) 6.63 (1H, C(3)**H**), 7.15 (2H, m, C(5)**H** & C(6)**H**), 7.21 (1H, d, J C(2)**H**), 8.36 (1H, s (br), N–**H**); δ_C (100 MHz) 104.1 (**C**(7)Br), 104.8 (**C**(3)H), 114.3 (**C**(4)Br), 124.2 & 125.4 (**C**(5)H & **C**(6)H), 129.9 (**C**(3*a*)), 135.0 (**C**(7*a*)); ***5–Methyl–6–trifluoromethylindole (2g):*** Dark brown oil, crystallising to a dark brown/black solid; Found M+199.0619. $C_{10}H_8NF_3$ requires 199.0609; δ_H (400 MHz) 2.55 (3H, –C$\mathbf{H_3}$), 6.51 (1H, d, *J* 5.6, C(3)**H**), 7.28 (1H, d, *J* 5.6, C(2)**H**), 7.51(1H, s, C(4)**H**), 7.67(1H, C(7)**H**), 8.22 (1H, s (br), N–**H**); m/z:199.0 [(M)$^+$, 100%], 130.2 {(M–CF_3)$^+$, 68%]. (*N.B.* Care should be taken in these reactions as it has been reported[7] that the reaction between aromatic trifluoromethyl compounds and Grignards may be explosive in nature, although no such problems were encountered during the course of this work); ***2,3,7–Trimethylindole (2k):*** Yellow oil, slowly crystallising to pale yellow solid; Found M+159.1046. $C_{11}H_{13}N$ requires 159.1048; δ_H (400 MHz) 2.21 (3H, s, –C$\mathbf{H_3}$), 2.36 (3H, s, –C$\mathbf{H_3}$), 2.43 (3H, s, –C$\mathbf{H_3}$), 6.90 (1H, d, *J* 7.1, C(5)**H**), 7.00 (1H, dd, *J* 7.3, C(6)**H**), 7.32 (1H, d, *J* 7.5, C(4)**H**).

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