Cesium Carbonate Promoted N-Alkylation of Indoles

David M. Fink*

Aventis Pharmaceuticals, Department of Medicinal Chemistry, Route 202-206, Bridgewater, NJ 08807, USA
E-mail: david.fink@aventis.com.

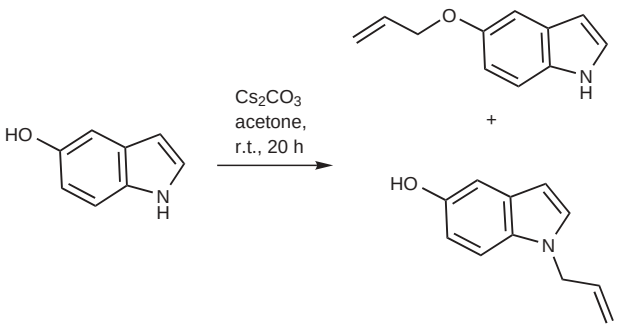
Received 24 April 2004

Abstract: The N-alkylation of indoles with alkyl halides and epoxides, using cesium carbonate as the base in DMPU, is reported.

Key words: cesium carbonate, indoles, alkylation, epoxides, alkyl halides

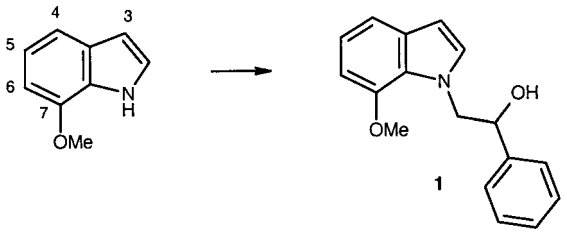
Numerous methods for the N-alkylation of indoles have been reported.[1] The usual methods employ bases such as sodium hydride or sodium amide in dipolar aprotic solvents to effect this transformation. The use of *n*-butyllithium in THF,[2] tetraalkylammonium salts[3] or crown ethers[4] under phase-transfer conditions and potassium hydroxide in acetone[6] have been reported. Indoles substituted by electron withdrawing groups may be alkylated using weak bases such as potassium carbonate or lithium cyanide[5] or using the Mitsunobu reaction.[7,8]

As part of an ongoing research program, we were investigating the alkylation of 7-methoxyindole with styrene oxide. Reactions using NaH as the base under a variety of conditions provided poor results. While investigating other reported procedures,[9] we noted a report that the allylation of 5-hydroxyindole with allyl bromide using cesium carbonate as the base in acetone provided a 10% yield of 1-allyl indole, in addition to the expected *o*-allylation product (Equation 1).[10]



Equation 1

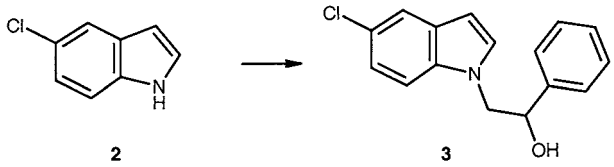
As indicated above, weak bases such as potassium carbonate have only been successfully used in cases where the indole is activated by the presence of electron withdrawing groups. Nonetheless, this report led us to try the reaction (Equation 2).



Equation 2

Treatment of 7-methoxyindole with cesium carbonate and styrene oxide in acetone at reflux provided only a trace of the desired product. However, replacement of the acetone with DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone],[11] and heating the mixture at 80 °C for 18 hours provided the desired product in 78% yield. This was particularly gratifying due to the electron rich nature of this indole. It remained possible that the presence of the oxygen functionality at the 7-position of the indole was activating the indole via chelation, holding the base in proximity to the acidic proton. In order to test this and to probe the effects of solvent and counterion on the alkylation, 5-chloroindole and styrene oxide were treated with carbonate bases in a number of solvents at 80 °C for four hours (Table 1).

Table 1 Synthesis of Indole **3** Using Carbonate Bases and Polar Aprotic Solvents



2 **3**

Entry	Conditions	Ratio 2:3 (4 h)[a]	Ratio 2:3 (18 h)
1	K_2CO_3, DMPU, 80 °C	92:8	64:36
2	Rb_2CO_3, DMPU, 80 °C	23:77	0:100
3	Cs_2CO_3, DMPU, 80 °C	2:98	
4	$CsHCO_3$, DMPU, 80 °C	100:0	
5	Cs_2CO_3, MeCN, 80 °C	19:81	0:100
6	Cs_2CO_3, 2-butanone, 80 °C	43:57	13:87

[a] Ratios determined by HPLC analysis.

SYNLETT 2004, No. 13, pp 2394–2396
Advanced online publication: 24.09.2004
DOI: 10.1055/s-2004-832836; Art ID: S03704ST

As expected, the use of potassium carbonate as the base provided almost none of the addition product after four hours (entry 1), while the starting material was almost completely consumed in the reaction using cesium carbonate as the base (entry 3). Rubidium carbonate provided an intermediate result, with the reaction proceeding to almost 80% completion in four hours (entry 2). After 18 hours, this reaction was complete. The reaction with potassium carbonate also proceeded slowly upon continued heating. Cesium bicarbonate proved to be a poorer base than potassium carbonate in this reaction, affording none of the alkylation product (entry 4). Either acetonitrile or 2-butanone can be used in place of DMPU as the solvent for the alkylation, although in both cases the reaction proceeds at a slower rate (entries 5 and 6). To test the generality of the methodology, the alkylation conditions were applied to several different indoles and alkylating agents, as shown in Table 2.[12]

As can be seen the reaction appears to be general. Unactivated indoles (Y = H, entries 2 and 3) and deactivated indoles (Y = 7-OMe and 5-OMe, entries 1 and 8), participate in the reaction. Although an exhaustive survey of alkylation agents was not attempted, the reaction appears to behave as expected. Reactive electrophiles such as benzyl bromide provide product in high yield (entry 5), as do somewhat less reactive ones such as propyl bromide (entry 6). Less reactive halides such as *iso*-propyl iodide (entry 7) gave a lower yield, presumably due to instability of the electrophile under the reaction conditions.

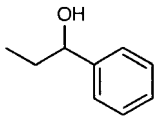
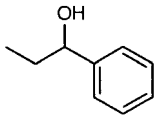
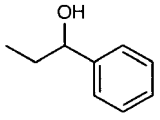
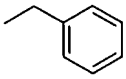
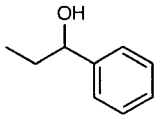
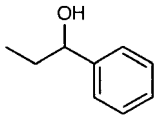
In summary, cesium carbonate is a suitable base for the N-alkylation of indoles in dipolar aprotic solvents. The method should prove useful in situations where the use of stronger bases is prohibited.

2-(5-Chloroindol-1-yl)-1-phenylethanol (3):
A suspension of 5-chloroindole (250 mg, 1.65 mmol), styrene oxide (257 mg, 2.14 mmol) and cesium carbonate (1.1 g, 3.3 mmol) in 4 mL of DMPU was heated with stirring at 80 °C for 4 h. The mixture was allowed to cool to ambient temperature, diluted with Et_2O, and filtered. The filtrate was washed with H_2O (3×) and brine, dried over $MgSO_4$, filtered and the filtrate concentrated in vacuo to leave the crude product as an oil. Column chromatography (silica gel, 10 g pre-packed from ISCO, gradient elution with heptane to 1:3 EtOAc–heptane) provided 375 mg (84%) of the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (br s, 1 H), 4.21–4.32 (m, 2 H), 4.99–5.03 (m, 1 H), 6.41 (d, *J* = 3.0 Hz, 1 H), 7.06 (d, *J* = 3.0 Hz, 1 H), 7.12 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.29–7.37 (m, 5 H), 7.56 (d, *J* = 1.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.2, 73.6, 101.0, 110.3, 120.2, 121.7, 125.1, 125.6, 128.2, 128.6, 129.4, 129.8, 134.4, 140.7 ppm. HRMS (ESI+): *m/e* calcd for $C_{16}H_{14}ClNOH$ (MH^+): 272.0842; found: 272.0833.

2-(7-Methoxyindol-1-yl)-1-phenylethanol (1):
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, *J* = 3.2 Hz, 1 H), 3.95 (s, 3 H), 4.17 (dd, *J* = 14.1, 8.7 Hz, 1 H), 4.78 (dd, *J* = 14.1, 3.1 Hz, 1 H), 5.00–5.05 (m, 1 H), 6.37 (d, *J* = 3.0 Hz, 1 H), 6.62 (d, *J* = 7.6 Hz, 1 H), 6.9 (d, *J* = 3.0 Hz, 1 H), 6.98 (t, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 7.8 Hz, 1 H), 7.25–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 57.2, 74.6, 101.2, 102.3, 113.9, 119.8, 125.3, 125.6, 127.6, 128.3, 129.9, 131.1, 141.3, 147.0 ppm. HRMS (ESI+): *m/e* calcd for $C_{17}H_{17}NO_2$ (MH^+): 268.1338; found: 268.1332.

Table 2 Synthesis of *N*-Alkyl Indoles[a]

1, 3, 4a–g

Entry	Y	Alkylating agent	R	Yield (%)
1	7-OMe	Styrene oxide	 **1**	78
2	H	Styrene oxide	 **4a**[13]	82
3	H	Propyl bromide	 **4b**[14]	67
4	5-Cl	Styrene oxide	 **3**	84
5	5-Cl	Benzyl bromide	 **4c**[15]	91
6	5-Cl	Propyl bromide	 **4d**	75
7	5-Cl	*iso*-Propyl iodide	 **4e**	35
8	5-OMe	Styrene oxide	 **4f**	79
9	7-F	Styrene oxide	 **4g**	76

[a] Cs_2CO_3, DMPU, 80 °C.

5-Chloro-1-propyl-1*H*-indole (4d):
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3 H), 1.75 (app sextet, *J* = 7.2 Hz, 2 H), 4.12 (t, *J* = 6.9 Hz, 2 H), 6.40 (d, *J* = 3.1 Hz, 1 H), 7.09 (dd, *J* = 8.7, 2.0 Hz, 1 H), 7.42 (d, *J* = 3.1 Hz, 1 H), 7.50 (d, *J* = 8.7 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 23.6, 48.2, 100.4, 110.2, 120.0, 121.4, 124.7, 128.9, 129.3, 134.2 ppm. HRMS (ESI+): *m/e* calcd for $C_{11}H_{12}ClNH$ (MH^+): 194.0736; found: 194.0734.

5-Chloro-1-*iso*propyl-1*H*-indole (4e):
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.75 Hz, 6 H), 4.62 (sept, *J* = 6.8 Hz, 1 H), 6.43 (d, *J* = 2.9 Hz, 1 H), 7.12 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.21–7.27 (m, 2 H), 7.56 (d, *J* = 2.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 47.4, 100.7, 110.2, 120.1, 121.3, 124.7, 129.3, 133.7 ppm. HRMS (ESI+): *m/e* calcd for $C_{11}H_{12}ClNH$ (MH^+): 194.0736; found: 194.0733.

2-(5-Methoxyindol-1-yl)-1-phenylethanol (4f):
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.14–4.28 (m, 2 H), 4.94 (dd, *J* = 7.9, 4.2 Hz, 1 H), 6.37 (d, *J* = 3.1 Hz, 1 H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.00 (d, *J* = 3.1 Hz, 1 H), 7.06 (d, *J* = 2.4 Hz, 1 H), 7.22–7.37 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.5, 56.0, 73.7, 101.2, 102.8, 110.3, 112.1, 126.0, 128.3, 128.8, 129.2, 129.3, 131.6, 141.2, 154.2 ppm. HRMS (ESI+): *m/e* calcd for $C_{17}H_{17}NO_2$ (MH^+): 268.1338; found: 268.1327.

2-(7-Fluoroindol-1-yl)-1-phenylethanol (4g):
^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.28 (dd, *J* = 14.0, 8.5 Hz, 1 H), 4.42 (dd, *J* = 14.0, 4.0 Hz, 1 H), 4.87–4.92 (m, 1 H), 5.62 (d, *J* = 4.8 Hz, 1 H), 6.43 (t, *J* = 2.7 Hz, 1 H), 6.86–6.97 (m, 2 H), 7.12–7.34 (m, 8 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 55.8, 72.5, 101.0, 106.4 (J_{CF} = 8.1 Hz), 116.4 (J_{CF} = 3.0 Hz), 119.0 (J_{CF} = 6.6 Hz), 123 (J_{CF} = 9.2 Hz), 125.6, 127.1, 127.9, 131.3, 132.2 (J_{CF} = 5.8 Hz), 142.6, 149.3 (J_{CF} = 241 Hz) ppm. HRMS (ESI+): *m/e* calcd for $C_{16}H_{14}FNO$ (MH^+): 256.1138; found: 256.1134.

References

(1) Gilchrist, T. L. *Heterocyclic Chemistry*; John Wiley and Sons: New York, **1985**, 67–168.
(2) Epling, G. A.; Kumar, A. *Synlett* **1991**, 347.
(3) See, for example: Galons, H.; Miocque, M.; Combet-Farnoux, C.; Bensaid, Y.; Decodts, G.; Bram, G. *Chem. Pharm. Bull.* **1985**, *33*, 5108.
(4) Schmolka, S. J.; Zimmer, H. *Synthesis* **1984**, 29.
(5) (a) Kalir, A.; Szara, S. J. *J. Med. Chem.* **1966**, *9*, 793. (b) Kurihara, T.; Fujimoto, T.; Harusara, S.; Yoneda, R. *Synthesis* **1987**, 396.
(6) Kikugawa, Y.; Miyake, Y. *Synthesis* **1981**, 461.
(7) Bhagwat, S. S.; Gude, C. *Tetrahedron Lett.* **1994**, *35*, 1847.
(8) Alkylation of 5-bromoindole under Mitsunobu-like conditions was recently reported. See: Bombrun, A.; Casi, G. *Tetrahedron Lett.* **2002**, *43*, 2187.
(9) Using *n*-butyllithium as the base in THF as in ref. 2 resulted in a slow but clean conversion to product (24% conversion at reflux for 18 h). However, if DMPU was used as solvent, then the product was formed at r.t. over 48 h.
(10) Macor, J. E.; Ryan, K.; Newman, M. E. *Tetrahedron* **1992**, *48*, 1039.
(11) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
(12) The products exhibited satisfactory ^{1}H NMR spectra.
(13) Sundberg, R. *J. Org. Chem.* **1973**, *38*, 3324.
(14) Shim, S. C.; Youn, Y. Z.; Lee, D. Y.; Kim, T. J.; Cho, C. S. *Synth. Commun.* **1996**, *26*, 1349.
(15) Hary, U.; Roettig, U.; Paal, M. *Tetrahedron Lett.* **2001**, *42*, 5187.