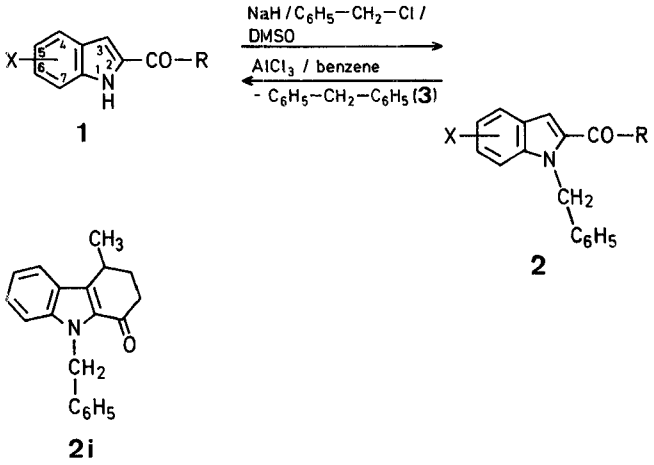
A Novel Method for the Debenzylation of Protected Indole Nitrogen

Yasuoki MURAKAMI*, Toshiko WATANABE, Atsushi KOBAYASHI, Yuusaku YOKOYAMA

School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274, Japan

The protection of the NH group of indoles is important in synthetic indole chemistry, and several methods for the protection of indole nitrogen have been developed[1-6]. Among these, the benzyl group is found to be the most stable protecting group; it can only be deprotected[1] by reduction with sodium in liquid ammonia[7]. However, this method can not be used for an indole derivative with reactive functional groups such as an ester, aromatic ether, halide, or an acyl group. In this paper we report a novel method for the debenzylation of the protected indole nitrogen atom.

Most debenzylation processes, including the *O*-benzyl group, involve a Lewis acid(aluminum chloride[8,9] and boron trifluoride[10])-catalyzed reaction besides the reduction with sodium in liquid ammonia and catalytic hydrogenation. However, no debenzylation catalyzed by Lewis acid has yet been applied to the *N*-benzyl group. We have now investigated the Lewis acid-catalyzed debenzylation of indoles by using 2-acylindoles **(2)** as substrates. These are stable under acidic conditions; the synthetic applications of ethyl indole-2-carboxylates as stable equivalents of indoles are being investigated[11].



1 **2** **2i**

The starting *N*-benzylindoles **(2)** are prepared in good yields (Table 1) from the corresponding sodium salt of indoles **(1)** with benzyl chloride in dimethyl sulfoxide. The *N*-benzylindoles **(2)** are treated with aluminum chloride (4 eq.) in benzene under mild conditions. Benzene serves as a solvent and as a trapping agent of the benzyl cation thus generated. Each reaction mixture is chromatographed on silica gel to give the deprotected product **1** (Table 2) and diphenylmethane **(3)**, the anticipated by-product. The products **1** and oily diphenylmethane **(3)**, are found to be identical with authentic samples on the basis of the ^{1}H-N.M.R., I.R., and M.S. spectra, but the yields of **3** are liable to variation because of its volatility.

The advantages of the present debenzylation reaction are that the reaction can be carried out under mild conditions in a period from several minutes to several hours at 0 °C or at room temperature and that in all cases, with the exception of the 5-nitro compound **2h**, the yields are satisfactory (50–80%) independent of the substituent on the benzene moiety of the indole nucleus. The 5-nitroindole **(2h)** gives only tarry products. The reaction of the 7-methoxyindole **(2c)** gives only a 18% yield of the desired product **1c** in benzene solution accompanied by much more of a rearranged product **4c**; however, benzene can satisfactorily be replaced by anisole.

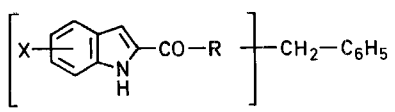


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Table 1. *N*-Benzylindoles **2** prepared

Product No.	X	R	Yield [%]	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	M.S. *m/e* (M^+)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm] Ar—CH_2—N
2a	H	OC_2H_5	62	58–60°	61–62°[13]	279	5.80
2b	5-H_3CO	OC_2H_5	78	64–66°	$C_{19}H_{19}NO_3$ (309.4)	309	5.77
2c	7-H_3CO	OC_2H_5	84	77–78.5°	$C_{19}H_{19}NO_3$ (309.4)	309	6.18
2d	5-Cl	OC_2H_5	86	69–72.5°	$C_{18}H_{16}ClNO_2$ (313.8)	313	5.80
2e	7-Cl	OC_2H_5	66	74–76°	$C_{18}H_{16}ClNO_2$ (313.8)	313	6.34
2f	5-H_3C—CO	OC_2H_5	80	126.5–129°	$C_{20}H_{19}NO_3$ (321.4)	321	5.83
2g	H	CH_3	62	130–131.5°	$C_{17}H_{15}NO$ (249.3)	249	5.81
2h	5-O_2N	OC_2H_5	75	120–122°	$C_{18}H_{16}N_2O_4$ (324.3)	324	5.87
2i	–	–	84	oil	$C_{20}H_{19}NO$ (289.4)[b]	289	5.76

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.09, N ±0.13.
[b] Purity checked by high resolution mass spectrum; *m/e* (M^+) = calc. 289.1468; found 289.1480.

Table 2. Debenzylation of *N*-Benzylindoles **2** with Aluminum Chloride in Benzene

N-Benzyl-indole	Debenzylated product	Reaction conditions Temperature/Time	Yield [%]	m.p. [°C] found	m.p. [°C] reported
2a	**1a**	r.t./3 min	62	123–124°	123–124°[14,15]
2b	**1b**	r.t./2 h	51	156–160°	158–162°[16]
2c[a]	**1c**	0°C/15 min	62	112–114°	115–117°[14]
2d	**1d**	0°C/15 min	83	167–169°	172–173°[16]
2e	**1e**	r.t./30 min	87	111–112°	113.5–114°[16]
2f	**1f**	r.t./4 h	67	137–139°	138–139°[17]
2g	**1g**	0°C/12 min	77[b]	152–154°	154–155°[18]
2h	**1h**	r.t./3 h	0	–	225–226°[19]
2i	**1i**	0°C/20 min	71[b]	130–133°	145–146°[20]

[a] Anisole was used in place of benzene.
[b] Compound **4**, in which the position of the benzyl group is uncertain, was obtained in 16% and 11% yields, respectively.

The debenzylation of **2b** and **2c** is safely carried out without demethylation under these conditions, although aluminum chloride[12] is known to be a reagent used for the cleavage of ether. The substrates are limited to 2-acylindoles at this stage, but this method should also be applicable to other indoles which are stable under acidic conditions.

Consequently, the present method provides a new methodology for the debenzylation of protected indole nitrogen under mild conditions, compensates for defects in the vigorous reduction using sodium in liquid ammonia, which has actually been the sole method in these cases, and enhances the value of benzyl group for the *N*-protection of indoles. We are now performing investigations aimed at its further improvement and application.

The melting points were determined on a Yanagimoto micro-melting-point apparatus and are uncorrected. All experiments were carried out under argon. The structures of all the new compounds were established by means of the analytical data or high resolution mass spectrum, ^{1}H-N.M.R., M.S., and I.R. spectra.

Ethyl 1-Benzyl-7-chloroindole-2-carboxylate(2e); Typical Procedure:
A mixture of 50% sodium hydride (79 mg, 1.65 mmol) and ethyl 7-chloroindole-2-carboxylate (**1e**; 336 mg, 1.50 mmol) in dimethyl sulfoxide (3 ml) is stirred at 50°C for 30 min. Benzyl chloride (0.17 ml, 1.50 mmol) is then added, and the resulting mixture is stirred at 80°C for 30 min. The mixture is poured into water (50 ml) and extracted with benzene (3 × 50 ml). The organic layer is washed successively with 5% aqueous hydrochloric acid (70 ml), brine (70 ml), dried with magnesium sulfate, and evaporated to dryness in vacuo. The resulting pale yellow solid is purified by column chromatography on silica gel (3:1 *n*-hexane/dichloromethane) to give colorless needles of **2e**; yield: 310 mg (66%); m.p. 74–76°C (methanol).

$C_{18}H_{16}ClNO_2$ (313.8) calc. C 68.90 H 5.14 N 4.46
found 68.89 5.05 4.43

I.R. (Nujol): ν = 1658 cm^{-1} (C=O); (ν_{NH} absent).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.31 (t, 3H, J = 8 Hz, CH_3); 4.30 (q, 2H, J = 8 Hz, O—CH_2); 6.34 (s, 2H, N—CH_2); 6.80–7.75 ppm (m, 9H_{arom}).

M.S.: *m/e* = 315 (M^+ + 2, 7.4%), 313 (M^+, 20), 91 (100).

Debenzylation of 2e; Formation of Ethyl 7-Chloroindole-2-carboxylate (1e); Typical Procedure:
To anhydrous aluminum chloride (534 mg, 4.0 mmol) is added a solution of ethyl 1-benzyl-7-chloroindole-2-carboxylate (**2e**; 315 mg, 1.0 mmol) in benzene (2.5 ml). The mixture is stirred at room temperature for 30 min, then poured into water (50 ml), and extracted with benzene (3 × 50 ml). The organic layer is washed successively with 5% aqueous sodium hydrogen carbonate (70 ml) and brine (70 ml), dried with magnesium sulfate, and evaporated to dryness in vacuo to give a pale yellow residue. The residue is chromatographed on a silica gel column using *n*-hexane/dichloromethane (3:1) as eluent to give diphenylmethane (**3**) as a colorless oil in the first fraction; yield: 125 mg (74%).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 3.92 (s, 2H, CH_2); 7.15 ppm (s, 10H_{arom}).

M.S.: *m/e* = 168 (M^+).

The second fraction affords colorless needles of **1e**; yield: 195 mg (87%); m.p. 111–112°C (benzene/*n*-hexane) (Lit.[16], m.p. 113.5–114°C). This compound is identical with the starting authentic sample in all respects.

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* Address for correspondence.

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