Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Paul Wiedenau [a] & Siegfried Blechert [a]
[a] Institut für Organische Chemie, Technische Universität , Berlin, D-10623, Berlin
Published online: 22 Aug 2006.

To cite this article: Paul Wiedenau & Siegfried Blechert (1997) Facile Synthesis of 2-Benzylindoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:12, 2033-2039, DOI: 10.1080/00397919708006807

To link to this article: http://dx.doi.org/10.1080/00397919708006807

SYNTHETIC COMMUNICATIONS, 27(12), 2033-2039 (1997)

FACILE SYNTHESIS OF 2-BENZYLINDOLES

Paul Wiedenau and Siegfried Blechert*

Institut für Organische Chemie, Technische Universität Berlin, D-10623 Berlin

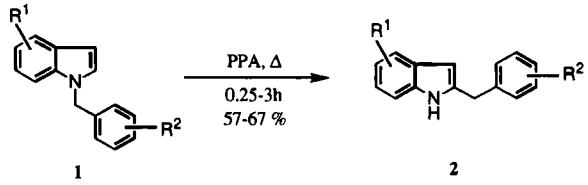
Abstract: A wide range of 2-Benzylindoles **2** are conveniently and efficiently prepared by heating *N*-benzylindoles **1** in polyphosphoric acid. Mechanistic studies suggest an intramolecular rearrangement via the corresponding 3-benzyl intermediates.

The indole nucleus is common to a large number of biologically active natural and synthetic compounds.[1] Their structural diversity and broad spectrum of pharmacological properties have attracted considerable attention in medicinal chemistry.[2] The particular interest for indoles substituted in the 2-position[3] and the limited availability of synthetic routes[4] towards them prompted us to disclose details about a novel rearrangement reaction, which we discovered in the course of the synthesis of the Trikentrin indole alkaloids.[5]

*To whom correspondence should be addressed

We found, that the benzyl group of *N*-benzylindole **1** migrates into the 2-position of the indole upon heating with polyphosphoric acid (PPA) (Scheme 1).[6]

Scheme 1



1 **2**

As shown in the table, a range of substituents on the indole as well as on the migrating benzyl group are tolerated under the reaction conditions.

1	**R^1**	**R^2**	**Yield (%) of 2**	**Time (h)**	**Temperature (°C)**
a	H	H	66	2	140
b	3-CH_3	H	60	1.5	120
c	7-Br	H	67	0.25	85
d	7-CO_2CH_3	H	58	0.75	80
e	H	2-Br	57	2.5	160
f	H	4-Br	60	3	130

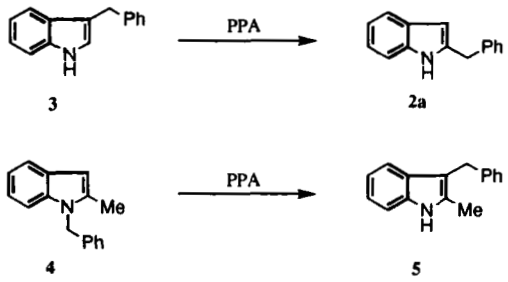
Formally, the rearrangement can be viewed as a [1,5]-benzyl shift around the pyrrole part of the indole. Thermal [1,5]-sigmatropic rearrangements of carbon are frequently found, but they usually require reaction temperatures betwen 300 and 500 °C.[7] In fact, the pyrolysis of *N*-benzylindoles at temperatures higher than 500 °C yields 2- and 3-benzylindoles.[8] Under these conditions however, a non-concerted radical mechanism is likely to operate. Similarily, when pericyclic reactions are catalysed by Lewis or Bronsted acids,[9] the mechanism shifts from a concerted one to a process involving ionic intermediates.

In order to elucidate the mechanism of our rearrangement, cross-over experiments were carried out. When submitting a mixture of *N*-benzylindoles **1b** and **1f** to PPA, only the rearrangement products **2b** and **2f** were obtained, and no products from intermolecular benzyl transfer were detected. This finding strongly suggests an intramolecular mechanism for the rearrangement.

Carrying out the rearrangement of **1a** to **2a** at various concentrations of **1a** did not affect the reaction rate. Hence we assume the rearrangement to be zero order, which represents additionally evidence for an intramolecular reaction mechanism.

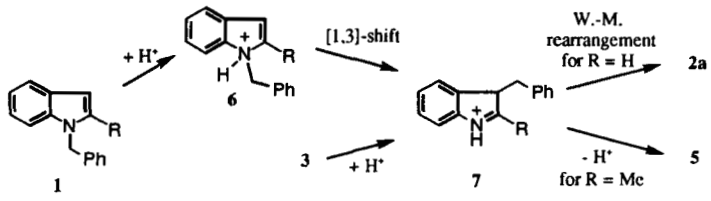
Furthermore, treatment of 3-benzylindole (**3**)[10] and *N*-benzyl-2-methylindole (**4**) afforded the rearrangement products **2a** and **5**, respectively in 55-60% yield (Scheme 2).

Scheme 2



From these results, we propose initial *N*-protonation of the indole by PPA followed by a [1,3]-shift of the benzyl group to give the indoleninium ion **7** (Scheme 3).

Scheme 3



Subsequent Wagner-Meerwein rearrangement would finally produce the 2-benzylindole **2a**.

In the case of the 2-methyl derivative **4**, the Wagner-Meerwein rearrangement of the corresponding intermediate **7** is thermodynamically not favoured, as it would give a product not capable of undergoing aromatisation to an indole. As a result, aromatisation occurs on the stage of intermediate **7** producing the 3-benzyl derivative **5**.

This report highlights a facile access to widely functionalised 2-benzyl indoles. These valuable building blocks are expected to find application in the synthesis of natural products and compounds of pharmacological interest.

EXPERIMENTAL

Melting points (m.p.) were determined on a Büchi SMO 20 apparatus and are not corrected. ^{1}H NMR spectra were recorded on Bruker AC 200 and WH 400 Spectrometers, respectively. The chemical shifts δ are reported in parts per million (ppm) relative to $CDCl_3$ as internal standard. Infrared spectra were recorded on a Perkin Elmer 881. Mass spectra as well as high-resolution mass spectra were recorded on a Varian MAT 711with an EI potential of 70 eV. Microanalyses were obtained from a Perkin Elmer CHNO/S-Analysator 2400. Flash chromatography was carried out with Baker or E.Merck silica gel (0.04-0.06 mm) using petroleum ether/*tert* butyl methyl ether as eluants. Reaction were monitored by thin layer chromatography on E.Merck Kieselgel 60 F 254 aluminium sheets. Solvents were distilled prior to use. Polyphosphoric acid was purchased from E.Merck, Germany.

N-benzyl indoles were prepared from the corresponding commercially available 1*H*-indoles and benzyl bromides with KOH in dimethylsulfoxide.[11] 7-Bromoindole was synthesised according to the Bartoli method,[12] and 7-carbomethoxyindole was prepared from 7-bromoindole by metallation with *n*-butyllithium and quenching with methyl chloroformate.

General procedure for the preparation of 2-benzyl indoles:

The *N*-benzylindole (0.5 mmol) was added to polyphosphoric acid (10 mL), which was prewarmed to the desired reaction temperature and vigorously stirred. Stirring and heating was continued until the starting material was consumed as indicated by tlc. Then the dark reaction mixture was cooled in an ice bath and treated carefully with ice water (40 mL). Extraction with *tert*-butyl methyl ether (3x30 mL) and washing the combined organic layers with saturated aqueous sodium bicarbonate solution and brine (30 mL each) was followed by drying over

magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography.

***N*-Benzylindole (1a):** m.p. 40°C. ^{1}H NMR ($CDCl_3$) δ = 7.66 (d, *J* = 7.8 Hz, 1H), 7.30-7.10 (m, 9H), 6.56 (d, *J* = 3, 1H), 5.34 (s, 2H). MS (EI) m/z (%) = 207 (M^+, 95), 91 (100).HRMS calculated for $C_{15}H_{17}N$: 207.1048, found: 207.1048.

***N*-Benzyl-3-methylindole (1b):** m.p. 65°C. ^{1}H NMR ($CDCl_3$) δ = 7.60 (d. *J* = 7.8 Hz, 1H), 7.30-7.10 (m, 9H), 6.90 (s, 1H), 5.27 (s, 2H). 2.35 (s, 3H). MS (EI) m/z (%) = 221 (M^+, 70), 130 (8), 91 (100). HRMS calculated for $C_{16}H_{15}N$: 221.1204, found: 221.1204.

***N*-Benzyl-7-bromoindole (1c):** m.p. 62°C. ^{1}H NMR ($CDCl_3$) δ = 7.58 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.34 (ddd, *J* = 7.7, 2.1, 1.1 Hz, 1H), 7.26 (m, 3H), 7.10 (dd, *J* = 3.5, 1 Hz, 1H), 7.01 (m, 2H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 5.82 (s, 2H). MS (EI) m/z (%) = 287 (M^++2, 17), 285 (M^+, 17), 204 (6), 91 (100). Anal. calculated for $C_{15}H_{12}NBr$: C 62.96, H 4.23, N 4.89, found: C 62.68, H 4.19, N 4.93.

***N*-Benzyl-7-carbomethoxyindole (1d):** obtained as an oil. ^{1}H NMR ($CDCl_3$) δ = 7.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.25-7.20 (m, 4H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.64 (d, *J* = 3 Hz, 1H), 5.61 (s, 2H), 3.71 (s, 3H). MS (EI) m/z (%) = 265 (M^+, 48), 233 (20), 204 (18), 188 (12), 91 (100). HRMS calculated for $C_{17}H_{15}NO_2$: 265.1121, found: 265.1121.

***N*-(2-Bromobenzyl)indole (1e):** m.p. 39°C. ^{1}H NMR ($CDCl_3$) δ = 7.68 (d, *J* = 8 Hz, 1H), 7.60 (m, 1H), 7.25-7.10 (m, 6 H), 6.60 (d, *J* = 3 Hz, 1H), 6.52 (m, 1H), 5.40 (s, 2H). MS (EI) m/z (%) = 287 (M^++2, 90), 285 (M+, 93), 206 (70), 204 (40), 171 (95), 169 (100). HRMS calculated for $C_{15}H_{12}NBr$: 285.0153, found: 285.0153.

***N*-(4-Bromobenzyl)indole (1f):** m.p. 63°C. ^{1}H NMR ($CDCl_3$) δ = 7.66 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.20-7.10 (m, 4H), 6.97 (d, *J* = 8 Hz, 1H), 6.57 (dd, *J* = 4, 1 Hz, 1H), 5.28 (s, 2H). MS (EI) m/z (%) = 287 (M^++2, 8), 285 (M^+, 8), 171 (10), 169 (10), 56 (100). HRMS calculated for $C_{15}H_{12}NBr$: 285.0153, found: 285.0153.

2-Benzylindole (2a): m.p. 78°C. IR (CCl_4) ν = 3476, 1457, 1289, 705. ^{1}H NMR ($CDCl_3$) δ = 7.77 (s, br, NH), 7.55 (d, *J* = 7.8 Hz, 1H), 7.35-7.25 (m, 6H), 7.12 (dt, *J* = 7, 1.3 Hz, 1H), 7.08 (dt, *J* = 7, 1 Hz, 1H), 6.34 (d, *J* = 1.5 Hz, 1H), 4.14 (s, 2H). MS (EI) m/z (%) = 207 (M^+, 100), 206 (65), 178 (6), 130 (58). HRMS calculated for $C_{15}H_{13}N$: 207.1048, found: 207.1048;

2-Benzyl-3-methylindole (2b): m.p. 89°C; IR (CCl_4) ν = 3476, 1463, 1241, 701. ^{1}H NMR ($CDCl_3$) δ = 7.57 (s, br, NH), 7.54 (m, 1H), 7.32-7.10 (m, 8H), 4.12 (s, 2H), 2.33 (s, 3H). MS (EI) m/z (%) = 221 (M^+, 100), 220 (40), 206 (40), 144 (40), 130 (25). HRMS calculated for $C_{16}H_{15}N$: 221.1204, found: 221.1204.

2-Benzyl-7-bromoindole (2c): m.p. 88°C; 3464, IR (CCl_4) ν = 1575, 1436, 1293, 711. ^1H NMR ($CDCl_3$) δ = 7.98 (s, br, NH), 7.47 (d, *J* = 7.8 Hz, 1H), 7.35-7.25 (m, 6H), 6.96 (t, *J* = 8 Hz, 1H), 6.37 (m, 1H), 4.16 (s, 2H). MS (EI) m/z (%) = 287 (M^++2, 24), 285 (M^+, 26), 221 (55), 91 (100). HRMS calculated for $C_{15}H_{12}NBr$: 285.0153, found: 285.0153. Anal. calculated: C 62.96, H 4.23, N 4.89, found: C 62.95, H 4.26, N 5.05.

2-Benzyl-7-carbomethoxylindole (2d): obtained as an oil. IR (CCl_4) ν = 3448, 1701, 1277, 1145. ^1H NMR ($CDCl_3$) δ = 9.55 (s, br, NH), 7.80 (dd, *J* = 7.5, 1 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.35-7.25 (m, 5 H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 4.17 (s, 3H), 3.94 (s, 2H). MS (EI) m/z (%) = 265 (M^+, 20), 233 (4), 175 (80), 143 (100), 115 (42). HRMS calculated for $C_{17}H_{15}NO_2$: 265.1121, found: 265.1121.

2-(2-Bromobenzyl)indol (2e): m.p. 73°C. IR (CCl_4) ν = 3476, 1457, 1287, 1027.^1H NMR ($CDCl_3$) δ = 7.97 (s, br, NH), 7.60 (d, *J* = 8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.23 (m, 2H), 7.15-7.05 (m, 3H), 6.33 (m, 1H), 4.26 (s, 2H). MS (EI) m/z (%) = 287 (M^++2, 50), 285 (M^+, 52), 206 (75), 204 (40), 130 (55), 55 (100). HRMS calculated for $C_{15}H_{12}NBr$: 285.0153, found: 285.0153.

2-(4-Bromobenzyl) indole (2f): m.p. 119°C. IR (CCl_4) ν = 3469, 1458, 1490, 1014. ^1H NMR ($CDCl_3$) δ = 7.77 (s, br, 1H), 7.54 (d, *J* = 7.5, 1H), 7.44 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.15-7.05 (m, 4H), 6.31 (m, 1H), 4.09 (s, 2H); MS (EI) m/z (%) = 287 (M^++2, 95), 285 (M^+, 100), 206 (20), 204 (30), 130 (55). HRMS calculated for $C_{15}H_{12}NBr$ 285.0153, found 285.0153.

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comparable (MSA) and considerably lower (TFA) yield, respectively.

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(Received in The Netherlands 23 January 1997)