

A General Method for the Preparation of 2-Benzylpyrroles by Modified Borohydride Reduction of Azafulvenium Salts

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2-Benzylpyrroles (5a–h) can be prepared in high yield from pyrroles by reduction, with modified borohydride reagents, of the corresponding 1-azafulvenium salts (3a–h) generated *in situ* in the presence of excess of phosphoryl trichloride. The procedure is compatible with ester groups.

Even though the chemistry of pyrroles has been widely studied,^{1,2} no general method is available for the preparation of 2-benzylpyrroles, important precursors in the synthesis of pharmaceutically useful compounds.³ Methods involving direct alkylation,⁴ homolytic benzylation,⁵ or rearrangement of *N*-benzylpyrroles^{6,7} are unsatisfactory and low yields (*ca.* 30%) are obtained from benzylation of pyrrolylmagnesium halides^{8,9} and pyrrolyl-lithiums^{9,10}. The most widely used approach is the Wolff-Kishner reduction of 2-benzoylpyrroles^{3,11–13} with yields of up to 73% being reported;¹¹ lithium aluminium hydride-reduction^{14,15} and high-pressure catalytic hydrogenation¹⁶ of the same compounds have found only limited application. Recently, the preparation of 2-benzylpyrroles in high yield by alkylation-reduction of 2-formylpyrroles was reported.¹⁷ However, all the above reduction procedures are incompatible with a number of functional groups, in particular ester groups, and they require prior isolation of the corresponding benzoyl- or formylpyrrole.

Preliminary studies showed that the Wolff-Kishner reduction of 2-benzoylpyrrole (4a) (91% yield) was superior to lithium aluminium hydride-reduction (61%) or reduction with sodium borohydride in aqueous ethanol¹⁸ (42%) for the preparation of 2-benzylpyrrole (5a). Compounds (5b), (5c), and (5d) were also prepared by Wolff-Kishner reduction in 85, 89, and 78% yield, respectively. However, these yields were obtained only when starting materials of high purity were used and reaction conditions were carefully controlled.

We have shown¹⁹ that 2-benzoylpyrroles (4) can be prepared in high yield by hydrolysis of the corresponding 6-aryl-6-morpholino-1-azafulvenium salt, (3), generated *in situ* in 1,2-dichloroethane (DCE) from a pyrrole (2) and the appropriate Vilsmeier complex (1) [Scheme, path (a)]. As *NN*-dialkyliminium salts are generally more reactive than ketones, it was predicted that hydride reduction [Scheme, path (b)] of the 1-azafulvene salts (3) without isolation would provide an expeditious route, under mild conditions, to the 2-benzylpyrroles (5). Furthermore this procedure would avoid the necessity of isolating and purifying the corresponding 2-benzoylpyrroles (4). The hydride reduction of iminium salts has been used as a method for converting amides into amines.²⁰

The preparation of ethyl 5-benzyl-2,4-dimethylpyrrole-3-carboxylate (5e) was chosen for the initial investigation as this fully substituted pyrrole is more stable than 2-benzylpyrrole (5a). The reduction of the 1-azafulvenium salt (3e) was investigated by adding a solution in DCE, containing an excess of phosphoryl trichloride, to a suspension of an excess of sodium borohydride in various solvents at room temperature. The reaction showed a marked solvent dependence and the best results were obtained using a tetrahydrofuran (THF)-ethyl acetate mixture (9 : 1). The results are given in Table 1. The reaction using this solvent system was therefore applied to the preparation of compounds (5e–h) on a 20 mmol scale. The results, which are given in Table 2, show

Table 1. Effect of solvent on the reduction of compound (3e) to give compound (5e) with excess of sodium borohydride

Solvent ^a	Yield (%) ^b
THF	75
DCE	74
EtOAc	82
THF-EtOAc (9 : 1)	89
DCE-EtOAc (9 : 1)	85
Toluene	10
DMF	15
DME ^c	9
Diglyme	7

^a DCE (20% of total volume) and phosphoryl trichloride (1 mol equiv.) present in all cases owing to the procedure used for the preparation of compound (3e). ^b Determined by g.l.c. after 4 h. ^c 1,2-Dimethoxyethane.

Table 2. Preparation of compounds (5e–h) by reduction of the salts (3e–h) with excess of sodium borohydride in THF-EtOAc^a

Product	Yield (%) ^b
(5e)	90 (98)
(5f)	80 (90)
(5g)	91 (99)
(5h)	75 (84)

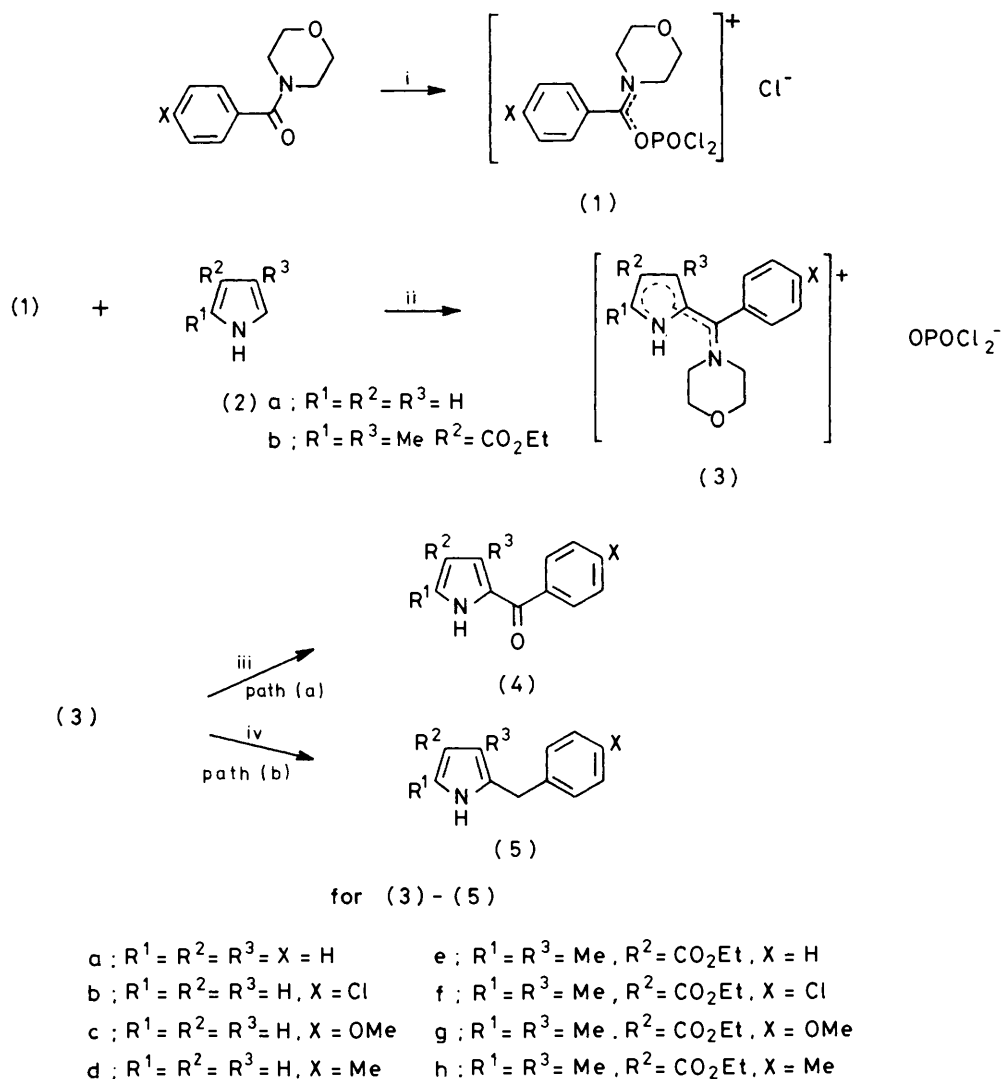
^a DCE and phosphoryl trichloride present in all cases. ^b Isolated (determined by g.l.c.).

the efficiency of the procedure and also show that it is compatible with the presence of an ester group in the molecule.

Extension of the procedure to the synthesis of the less stable 2-benzylpyrrole (5a) led to a disappointingly low yield (15%). The reaction was therefore examined using a variety of solvents and temperature conditions. The results are given in Table 3.

The best yields were obtained in *NN*-dimethylformamide (DMF) but were still unsatisfactorily low and a number of experimental factors were investigated using the reaction in DMF at 0 °C for 4 h as a standard. The use of dry DMF under argon led to no improvement in the yield. Highest yields (50%) were obtained using aqueous sodium carbonate or aqueous sodium hydroxide during work-up; hydrochloric acid (33%), acetic acid (35%), and refluxing methanol (40%) were less effective. Adding the solution of the 6-aryl-6-morpholino-1-azafulvenium salt to the reducing agent at a rate of 1 ml min⁻¹ gave a slightly higher yield (51%) than the reverse addition (47%). Faster rates of addition gave lower yields (35–45%). Hence, none of these changes gave any significant improvement in yield.

The addition of 5% palladium-charcoal to the reaction mixture markedly increased the yield to 78%. As the addition



Scheme. Reagents and conditions: i, POCl₃; ii, ClCH₂CH₂Cl (solvent); iii, aqueous Na₂CO₃; iv, hydride reduction

of metal salts is known to influence the reactions of sodium borohydride²¹⁻²³ the effect of certain salts on the reaction was studied. The results are given in Table 4. In contrast to the previous observations, the reactions in the presence of metal salts were very susceptible to moisture and the yields reported were obtained only when the reactions were carried out under both an inert atmosphere and anhydrous conditions. The highest yield was obtained using sodium borohydride and CdCl₂·1.5DMF in THF at 0 °C and the procedure was tested, on a 5 mmol scale, for the preparation of the 2-benzylpyrroles (5a-d). The results, given in Table 5, indicate that this is a satisfactory procedure for the preparation of these unstable compounds.

As the role of the metal salts in the above reactions could be to modify the reducing agent^{21,22} the effect of other, commercially available, borohydride reducing agents was investigated. Reduction of the azafulvenes (3a-d) with both lithium borohydride and sodium cyanoborohydride in THF at 0 °C took place in high yield. Moreover, strictly anhydrous conditions and use of an inert atmosphere proved to be unnecessary. Results for the preparation of the 2-benzylpyrroles (5a-d) are given in Table 6 (entries 1-8).

Because of the efficiency of the reactions with lithium borohydride and sodium cyanoborohydride in THF these

procedures were also applied to the preparation of the tetra-substituted pyrroles (5e-h). The yields obtained [Table 6, entries 9-16] show an improvement on those obtained in the sodium borohydride-reduction in THF-ethyl acetate (Table 2). However, the yields are sufficiently high in the latter reaction for it to be satisfactory for use in large-scale preparations.

The results indicate that this is an efficient and simple procedure for preparing 2-benzylpyrroles and it is compatible with ester groups.

Experimental

G.l.c. analyses were carried out on a Perkin-Elmer Sigma 3 gas chromatograph (flame ionization detector) coupled to a Spectra-Physics Minigrator using a 10% OV 101 on Chromosorb W AW/DMCS column (2 m × 6.4 mm) and nitrogen as carrier gas (60 ml min⁻¹) at 230 °C and 250 °C for compounds (5a-d) and (5e-h), respectively. ¹H N.m.r. spectra (data in Table 7) were recorded in CDCl₃ solutions on a Perkin-Elmer R12B 60 MHz spectrometer with SiMe₄ as internal standard. M.p.s. were determined on a Kofler hot stage and are uncorrected. Purification by liquid chromatography (medium pressure) was carried out using the apparatus described by Meyers *et al.*,²⁴ and a Kugelrohr apparatus was used for

Table 3. Effect of solvent and temperature on the yield (%)^a obtained during the reduction of the salt (3a) to give compound (5a) with excess of sodium borohydride

Solvent ^b	Reflux	Temperature			
		25 °C	0 °C	-25 °C	-78 °C
THF-EtOAc	<1	15	20	22	21
THF	<1	16	30	34	34
DCE	<1	13	19	21	20
DMF	<1	24	50	53	51
Diglyme	<1	20	38	43	42
DME	<1	10	31	32	30
EtOAc	<1	10	25	28	30
Pr ⁱ OH	<1	7	15	18	20

^a Determined by g.l.c. after 4 h. ^b DCE and phosphoryl trichloride present in all cases.

Table 4. Effect of added metal salts on the reduction^a of the salt (3a) to give compound (5a) with excess of sodium borohydride at 0 °C

Metal salt	Solvent ^b	Yield (%) ^c
None	DMF	50
CuCl ₂	DMF	85
ZnCl ₂	DMF	— ^d
CdCl ₂	DMF	96
CdCl ₂ ·1.5DMF	THF	98
CdCl ₂ ·1.5DMF	THF (moist)	51

^a All reactions carried out under argon, using strictly anhydrous solvents, except the last entry. ^b DCE and phosphoryl trichloride present in all cases. ^c Determined by g.l.c. after 4 h. ^d Isolation and detection of the product were unreliable.

distillations (only oven temperatures are reported). Elemental analyses were performed at the National Chemical Research Laboratories, C.S.I.R., Pretoria.

THF was distilled from lithium aluminium hydride, DCE was distilled from phosphorus pentoxide, and other solvents were dried over molecular sieves which had been activated at ca. 250 °C and 3 mmHg pressure. Light petroleum was of boiling range 62–65 °C. CdCl₂·1.5DMF was prepared by recrystallizing cadmium chloride from DMF.²¹ Pyrrole was dried over sodium hydroxide pellets, distilled from molecular sieves, and stored under argon in sealed ampoules. Reducing agents and other reagents were of good commercial quality and were used without further purification. The 2-benzoylpyrroles (4a–d) were prepared as previously described.¹⁹

Ethyl 2,4-Dimethylpyrrole-3-carboxylate (2b).—*t*-Butyl 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylate²⁵ (5 g, 19 mmol) was heated at 200 °C in the presence of formic acid (2 ml) for 30 min. Purification by recrystallization (light petroleum, charcoal) followed by sublimation gave the required pyrrole (2b) as crystals (2.59 g, 83%), m.p. 76–77 °C (lit.,²⁶ 75–76 °C).

6-Aryl-6-morpholino-1-azafulvenium Salts (3a–h).—0.2M Solutions of these salts in DCE were prepared as previously described.¹⁹

Reductions Monitored by Gas-liquid Chromatography.—A solution of the azafulvenium salt (5 ml; 1 mmol) containing anthracene (178 mg, 1 mmol) as internal standard, was added to a stirred suspension of the reducing agent (0.5 g, ca. 100-fold molar excess) and the added salt (1 g) where applicable in the solvent under investigation (25 ml) at the required temperature. At appropriate intervals samples (0.5 ml) were

Table 5. Preparation of compounds (5a–d) by reduction^a of the salts (3a–d) with excess of NaBH₄ and CdCl₂·1.5DMF in THF^b at 0 °C

Product	Yield (%) ^c
(5a)	80
(5b)	79
(5c)	85
(5d)	71

^a Carried out under argon using strictly anhydrous solvents. ^b DCE and phosphoryl trichloride present. ^c Isolated.

Table 6. Preparation of compounds (5a–h) by reduction of the salts (3a–h) in THF^a at 0 °C

Entry	Product	Reducing agent ^b	Yield (%) ^c
1	(5a)	LiBH ₄	90 (99)
2	(5a)	NaCNBH ₃	92 (99)
3	(5b)	LiBH ₄	82 (91)
4	(5b)	NaCNBH ₃	80 (90)
5	(5c)	LiBH ₄	91 (98)
6	(5c)	NaCNBH ₃	92 (99)
7	(5d)	LiBH ₄	79 (87)
8	(5d)	NaCNBH ₃	80 (89)
9	(5e)	LiBH ₄	90
10	(5e)	NaCNBH ₃	93
11	(5f)	LiBH ₄	89
12	(5f)	NaCNBH ₃	90
13	(5g)	LiBH ₄	91
14	(5g)	NaCNBH ₃	93
15	(5h)	LiBH ₄	87
16	(5h)	NaCNBH ₃	88

^a DCE and phosphoryl trichloride present. ^b Present in excess. ^c Isolated (determined by g.l.c.).

treated with 10% aqueous Na₂CO₃ or by other work-up procedures under investigation, and the organic phase was analysed by g.l.c.

General Procedures for the Preparation of the 2-Benzylpyrroles (5a–h).—(a) LiBH₄. A solution (25 ml) of the azafulvenium salt (3a–h; 5 mmol) in DCE was added dropwise (1 ml min⁻¹) to a stirred suspension of LiBH₄ (2.5 g) in THF (100 ml) at 0 °C. After 2 h the reaction mixture was poured into aqueous Na₂CO₃ (10%; 100 ml) and the product was extracted with diethyl ether. The combined ethereal phases were washed with brine, dried (Na₂CO₃), and the solvent was removed under reduced pressure. The crude product was purified by vacuum distillation, recrystallization from aqueous ethanol or medium-pressure liquid chromatography (ethyl acetate–light petroleum 1:2 as eluant), to give the required 2-benzylpyrrole (5a–h). Yields are given in Table 6 and details of physical data and analyses in Table 7.

(b) NaCNBH₃. Reduction of the azafulvenium salt (3a–h) was carried out as described in (a) above except that NaCNBH₃ (2.5 g) was used as reducing agent and the reaction mixtures were worked up after 20 min. Yields of the 2-benzylpyrroles (5a–h) are given in Table 6.

(c) NaBH₄. A solution (100 ml) of the azafulvenium salt (3e–h; 20 mmol) in DCE was added dropwise to a stirred suspension of NaBH₄ (10 g) in a mixture of THF (90 ml) and ethyl acetate (10 ml) at room temperature; the mixture was then stirred for a further 6 h. The reaction mixture was poured into aqueous Na₂CO₃ (10%; 100 ml) and was extracted with DCE. The solvent was removed under reduced pressure and

Table 7. Physical data and analyses of the 2-benzylpyrroles (5a—h)

Compound	M.p. or b.p. (lit. m.p. or b.p.)	δ_{H} of benzyl CH_2^a	Formula	Analyses (%) Found (Required)			Ref.
				C	H	N	
(5a)	130 °C at 2.5 mmHg (85—89 °C at 0.12—0.15 mmHg)	3.85					11
(5b)	150 °C at 2.5 mmHg	3.8					3
(5c)	150 °C at 3 mmHg (140—145 °C at 2.5 mmHg)	3.9					16
(5d)	145 °C at 4 mmHg	3.85	$\text{C}_{12}\text{H}_{13}\text{N}$	84.1 (84.15)	7.7 (7.65)	8.2 (8.2)	
(5e)	119 °C (120 °C)	3.9					10
(5f)	glass ^b	3.85	$\text{C}_{16}\text{H}_{18}\text{ClNO}_2$	65.85 (65.85)	6.25 (6.2)	4.8 (4.8)	
(5g)	glass ^b	3.95	$\text{C}_{17}\text{H}_{21}\text{NO}_3$	71.0 (71.05)	7.4 (7.35)	4.85 (4.85)	
(5h)	glass ^b	3.85	$\text{C}_{17}\text{H}_{21}\text{NO}_2$	75.3 (75.25)	7.8 (7.8)	5.6 (5.2)	

^a N.m.r. spectra of all compounds were consistent with their assigned structures. ^b Could not be induced to crystallize; purified by medium-pressure liquid chromatography.

the crude product was purified by recrystallization from aqueous ethanol or medium-pressure liquid chromatography to give the required 2-benzylpyrrole (5e—h). Yields are given in Table 2.

(d) NaBH_4 and $\text{CdCl}_2 \cdot 1.5\text{DMF}$. Reduction of the azafulvenium salts (3a—d) was carried out as described in (a) above except that NaBH_4 (2.5 g) in the presence of $\text{CdCl}_2 \cdot 1.5\text{DMF}$ (5 g) was used as reducing agent; the reactions were carried out under strictly anhydrous conditions under argon and the mixtures were worked up after 4 h. Yields of the 2-benzylpyrroles (5a—d) obtained after vacuum distillation are given in Table 5.

Reduction of the 2-Benzoylpyrroles (4a—d).—(a) *Wolff-Kishner reduction.* The 2-benzoylpyrroles (4a—d) were reduced by the standard procedure^{11,12} using hydrazine hydrate and triethylene glycol to give, after distillation, the corresponding 2-benzylpyrroles (5a—d) in 91, 85, 89, and 78% yield, respectively.

(b) *Lithium aluminium hydride reduction.* 2-Benzoylpyrrole (4a; 1.71 g, 10 mmol) was reduced by the published procedure¹⁵ to give, after distillation, 2-benzylpyrrole (5a) (0.96 g, 61%).

(c) NaBH_4 in aqueous ethanol. 2-Benzoylpyrrole (4a) (2 g) was reduced by the published procedure¹⁸ to give, after distillation, 2-benzylpyrrole (5a) (0.77 g, 42%).

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