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α-AMINONITRILES—I
A SIMPLE SYNTHESIS OF DEOXYBENZOINS

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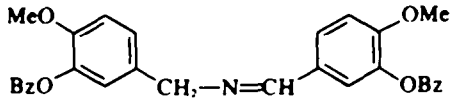
Abstract—A method is described, involving an acyl anion equivalent, for the preparation of deoxybenzoins that are inaccessible by the more usual methods.

Although several different methods exist for the preparation of deoxybenzoins,[1-6] none of them is satisfactory for unsymmetrically substituted derivatives in which the aromatic rings carry OH, OMe or methylenedioxy groups. Indeed, deoxybenzoins which carry a phenolic hydroxyl group in one ring and a methylenedioxy group in the other do not seem to have been described. Recently in connection with some syntheses in the pavine,[7] isopavine[8,9] and protoberberine[10,11] groups of alkaloids, we required some deoxybenzoins as starting materials, and we have examined several methods of obtaining them.[12] One method that was developed[9,13] involves the alkylation of a symmetrically substituted Schiff base, e.g. **1**, with the benzyl chloride in the presence of NaH/DMF, followed by hydrolysis. This procedure may be regarded as involving an acyl carbanion equivalent.[14]



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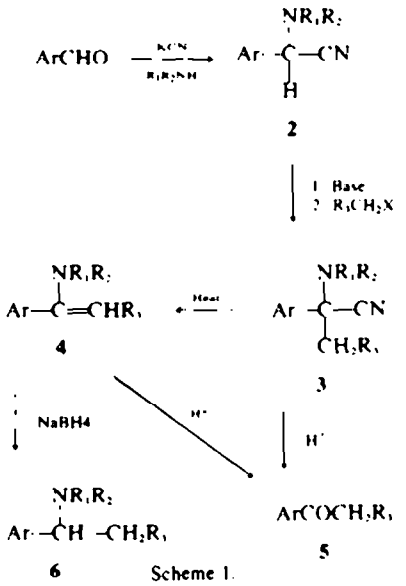
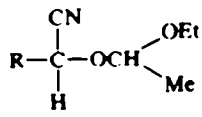


Scheme 1.

However, we were attracted to the work of Hauser *et al.*[15] in which it was shown that anions can be formed from α-aminonitriles (**2**, Ar = C_6H_5; $R_1 = R_2$ = Me) with KNH_2 in liquid ammonia, then alkylated and hydrolysed to ketones (Scheme 1). The alkylated α-aminonitriles **3** were isolated in some cases and a brief examination was made of the enamines **4**, derived from **3** by thermolysis. Acid hydrolysis of **3** or **4** gave good overall yields of ketones **5**. Although Hauser suggested that the method showed promise as a route to deoxybenzoins, no further work seems to have been done in this direction. Kirby *et al.*[16] have found that the anion can be conveniently generated from (**2**, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$) with NaH/DMF and they prepared some deuterated aldehydes. The anion from (**2**, Ar = 3-pyridyl; $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$) has been added to acrylonitrile[17] as the key step in a new synthesis of myosmine. A brief review of the preparation and some properties of α-aminonitriles appeared recently.[18] Although Seebach[14] recognised α-aminonitriles as potential acyl carbanion equivalents, he felt that they do not fulfil the desirable criteria that he listed. Stork and Maldonado[19] have listed the advantages of protected cyanohydrins of the type **7** as acyl anion equivalents in the preparation of aliphatic ketones; derivatives of the type **8** have also been used.[20]

Our method for the preparation of deoxybenzoins is essentially that summarised in Scheme 1, although it is better to generate the anion from **2** with NaH/DMF.

Several α-aminonitriles were examined (Table 1), and high overall yields of deoxybenzoins (Table 2) were realised in one isolated step from **2**. Only on one occasion was the alkylated aminonitrile (**3**, Ar = 3,4-methylenedioxyphenyl; $R_1 = R_2$ = Et; R_3 = 3,4-dimethoxyphenyl) isolated and characterised. Usually it



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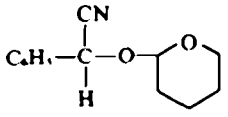

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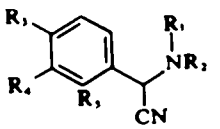
was hydrolysed directly with dilute mineral acid, or was converted into the enamine **4** during removal of DMF, and this was hydrolysed *in situ* to the ketone. We have established that the morpholinonitriles (**2**, $R_1 + R_2 = -CH_2CH_2OCH_2CH_2-$) offer no advantage over the N,N-diethylamino derivatives (**2**, $R_1 = R_2$ = Et). It is apparent from the Tables that the character of R_3 can be varied over wide limits, and that heterocyclic aldehydes as well as aromatic ones can be utilised. The deoxybenzoin (**5**, Ar = 3,4-dimethoxyphenyl; R_3 = α-pyridyl) was prepared originally[22] in much lower yields from α-picolyllithium and 3,4-dimethoxybenzonitrile. Deoxybenzoins containing phenolic hydroxyl groups are best prepared through their O-benzyl ethers. Debenzylation can be achieved catalytically in high yield without reducing the ketone carbonyl group.

Table 1. α-aminonitriles



R_1	R_2	R_3	R_4	R_5	% Yield	M.p.	NMR δ Value ArCHCN	Found C	Found H	Found N		Required C	Required H	Required N
Et	Et	OMe	OMe	H	88	OIL[21]	4·98							
Et	Et	H	OMe	OMe	94	55	5·38	67·3	8·1	11·4	$C_{14}H_{20}N_2O_2$	67·7	8·1	11·3
Et	Et	OBz	OMe	H	86	68	4·93	74·0	7·3	8·3	$C_{20}H_{24}N_2O_2$	74·1	7·5	8·6
Et	Et	OMe	OBz	H	80	57	4·90	74·0	7·5	8·4	$C_{20}H_{24}N_2O_2$	74·1	7·5	8·6
Et	Et	O–CH_2–O		H	81	OIL[21]	4·92	65·3	7·0	11·6	$C_{12}H_{16}N_2O_2$	65·5	7·3	12·7
Me	$CH_2CH(OMe)_2$	OMe	OBz	H	90	OIL.	5·02	M$^+$ 398·2207			$C_{23}H_{30}N_2O_4$		398·2206	
Me	$CH_2CH(OMe)_2$	OBz	OMe	H	87	OIL.	5·01	M$^+$ 398·2207			$C_{23}H_{30}N_2O_4$		398·2206	
H	$CH_2CH(OMe)_2$	OMe	OMe	H	92	OIL.	4·83	M$^+$–HCN 253·1300			$C_{15}H_{19}NO_4$		253·1314	
					84	OIL.	5·03	67·2	7·8	15·4	$C_{10}H_{14}N_2O$	67·4	7·9	15·7

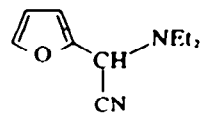
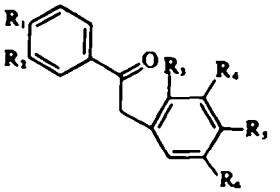
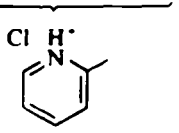
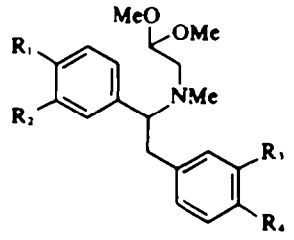


Table 2. Deoxybenzoins



R_1	R_2	R_3	R_4	R_5	R_6	% Yield	M.p.	NMR δ Value $ArCOCH_2$–	IR cm^{-1} Nujol	Found C	Found H	Found -	Required	Required C	Required H	Required -
OMe	OMe	Cl	H	H	H	78	98	4·40	1680	65·8	5·1	Cl, 12·5	$C_{16}H_{15}O_3Cl$	66·0	5·2	Cl, 12·2
OMe	OMe	H	H	Cl	H	91	128	4·25	1675	66·0	5·0	Cl, 11·9	$C_{16}H_{15}O_3Cl$	66·0	5·2	Cl, 12·2
OMe	OMe	H	H	NO_2	H	83	129	4·40	1680	63·4	5·0	N, 4·9	$C_{16}H_{15}NO_5$	63·8	5·0	N, 4·7
OMe	OMe	H	H	OMe	H	69	107	4·15	1690	71·2	5·8	—	$C_{17}H_{18}O_4$	71·4	6·3	—
OMe	OMe	NO_2	H	H	H	75	134	4·70	1685	64·1	5·3	N, 4·8	$C_{16}H_{15}NO_5$	63·8	5·0	N, 4·7
OMe	OMe	H	H	H	H	68	82	4·23	1678	74·1	6·2	—	$C_{16}H_{16}O_3$	75·0	6·3	—
OBz	OMe	H	O–CH_2–O		H	61	98	4·10	1668	73·5	5·4	—	$C_{23}H_{20}O_5$	73·4	5·4	—
OMe	OBz	H	O–CH_2–O		H	74	144	4·10	1670	73·1	5·6	—	$C_{23}H_{20}O_5$	73·4	5·4	—
OMe	OBz	H	OMe	OMe	OMe	63	131	4·10	1680	71·0	6·2	—	$C_{25}H_{26}O_6$	71·1	6·2	—
O–CH_2–O		H	OBz	OMe	H	45	113	4·00	1670	73·7	5·5	—	$C_{23}H_{20}O_5$	73·4	5·4	—
O–CH_2–O		NO_2	H	O–CH_2–O		56	171	3·70	1670	58·3	3·5	N, 4·2	$C_{16}H_{11}NO_7$	58·4	3·7	N, 4·3
OMe	OMe	NO_2	H	O–CH_2–O		49	158	4·80	1680	59·1	4·4	N, 4·1	$C_{17}H_{15}NO_7$	58·8	4·9	N, 4·0
OMe	OMe	H	OMe	OMe	H	66	105	4·20	1670	Ref 24						
O–CH_2–O		H	OMe	OMe	H	75	110–111	—	1670	Ref 8						
OMe	OMe					87	198	5·1	1670	61·3	5·4	N, 4·7 Cl, 12·1	$C_{15}H_{16}NO_3Cl$	61·5	5·5	N, 4·8 Cl, 12·1

In the alkaloid syntheses referred to,[7-9,11] the deoxybenzoin is condensed with aminoacetal to give, after reduction and N-methylation, the substituted benzylaminoacetals **9**. A far superior method for obtaining **9** involves the use of N-methylaminoacetal as the secondary base in the formation of the α-aminonitriles **2**



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(Scheme 1) then trapping the enamine **4** by reduction with $NaBH_4$, instead of subjecting it to acid hydrolysis.[9]

EXPERIMENTAL

M.ps are uncorrected. UV data refer to 95% EtOH solns and absorption maxima are expressed in nm. IR spectra were measured as Nujol mulls unless otherwise stated and absorption maxima are expressed in cm^{-1}. NMR spectra were determined at 60 MHz and chemical shifts are expressed as ppm downfield from internal TMS. Mass spectra were measured with an AEI MS 12 instrument.

Preparation of the α-aminonitriles **2** [*Table* 1]. The aldehyde (0·05 moles) in a minimum of MeOH was added over 1 h to a soln of the amine hydrochloride (0·06 moles) and NaCN (0·06 moles) in H_2O (10 ml). The soln was stirred at 30° for 4 h, quenched with H_2O (200 ml) and extracted into ether (4 × 50 ml). The combined ether extracts were washed with H_2O (4 × 30 ml), saturated sodium metabisulphite soln (4 × 20 ml) and H_2O (2 × 20 ml). After drying ($MgSO_4$) the ether extracts were evaporated to afford the α-aminonitriles **2** as pale yellow oils. (NB: The benzyl ethers of vanillin and isovanillin are insoluble in aqueous sodium metabisulphite soln).

The IR spectra of the reported α-aminonitriles show weak C≡N absorption in the region of 2230 cm^{-1}, and the mass spectra of **2** are consistent with the aminonitrile structures. The molecular ions are evident in the mass spectra, and a facile loss of the amine function is a predominant feature. For typical UV, mass and NMR spectral data refer to *α - cyano - N,N - diethyl - 3 - benzyloxy - 4 - methoxybenzylamine*. λ_{max} (ϵ_{max}) 232 (10,000), 281 (3,340), 311 (900); mass *m/e* 324 (M^+) [16%], 252 [24%], 242 [9%], 207 [34%], 91 [100%]; NMR ($CDCl_3$), 7·6–6·8 complex [8] (aromatic H); 5·18 s [2] ($PhCH_2O$); 4·90 s [1] ($ArCHCN$); 3·89 s [3] $ArOCH_3$); 2·59 q [2] J = 7Hz; and 2·50 q [2] J = 7Hz ($N-CH_2CH_3$)$_2$); 1·02 t [6] J = 7Hz (NCH_2CH_3).

Preparation of the deoxybenzoins **5** [*Table* 2]. Sodium hydride (60% suspension in oil, 0·02 moles NaH) was washed with petrol and suspended in dry DMF (10 ml), under N_2. A soln of the aminonitrile (2), (0·015 moles) in dry DMF (20 ml) was added. The resulting red suspension was stirred under N_2 at RT for 1 h and the appropriate benzyl chloride (0·015 moles) added over a further 1 h. After stirring overnight, the excess NaH was destroyed with MeOH (5 ml) and the solvent removed under 1 mm pressure at 90°, over 6 h. The resulting red oil was stirred in 6N HCl for 16 h, and extracted into $CHCl_3$ (3 × 30 ml). The combined extracts were washed (H_2O), dried ($MgSO_4$) and evaporated to leave an oil. In each case the deoxybenzoin crystallised on trituration with ether. The samples were recrystallised from either MeOH or EtOH.

4-Hydroxy-3-methoxyphenyl-3,4-methylenedioxybenzyl ketone. A solution of 4-benzyloxy-3-methoxyphenyl-3',4'-methylenedioxybenzyl ketone (190 mg) in 95% EtOH (50 ml) was hydrogenated over 10% Pd/C at RT and atmospheric pressure for 1·5 h. Removal of the catalyst and solvent afforded the required ketone (125 mg; 87%) m.p. 132–133° from ether/ethanol. NMR ($CDCl_3$) 7·7–6·72 complex [6] (aromatic H), 5·90 s [2] (OCH_2O), 6·1–5·5 broad s (OH, removed by D_2O), 4·10 s [2] ($ArCH_2CO$); 3·88 s [3] ($ArOCH_3$); ν_{max} 3400 broad, 1672, 1494, 1268, 1253, 1162; λ_{max} (ε) 233 (19,500), 287 (13,000), 310 sh (10,040); λ_{max} (ε) EtOH/NaOH 250 (10,000), 293 (6,360), 355 (26,000); mass *m/e* 286 (M^+) [10%], 151 [100%], 135 [12%]. (Found: C, 66·9; H, 5·1. $C_{16}H_{14}O_5$ requires: C, 67·1; H, 4·9%).

α - Cyano - α - (3,4 - dimethoxybenzyl) - N,N - diethyl - 3,4 - methylenedioxybenzylamine (3, *Ar* = *3,4-methylenedioxy*; R_1 = R_2 = *Et*; R_3 = *3,4-dimethoxy*). NaH (0·66 g, 60% suspension in oil, 16·5 mmoles) was washed with petrol and suspended in dry DMF (50 ml). To this was added N,N - diethyl - α - cyano - 3,4 - methylenedioxy benzylamine (3·5 g, 15 mmoles) in DMF. After stirring for 16 h, and removal of the solvent, the red oil was stirred for 2 h in dichloromethane (100 ml) and 2N HCl (100 ml). The organic phase was washed with aqueous $NaHCO_3$ (50 ml), H_2O and dried ($MgSO_4$), then evaporated. Trituration from ether afforded the title compound (1·61 g, 28%) m.p. 127–9° NMR ($CDCl_3$) 7·0 m [1] (aromatic H), 6·75–6·95 complex [2] (2 × aromatic H), 6·70 d [1] J = 8·5 Hz (aromatic H), 6·47 d of d [1] J = 2 Hz and J = 8·5 Hz (C_6H on veratryl), 6·17 d [1] J = 2 Hz, (C_2–H on veratryl), 5·93 s [2] (OCH_2O), 3·80 s [3] ($Ar-OCH_3$), 3·63 s [3] ($ArOCH_3$), 3·49 d [1] J = 13 Hz (Ar–CH(H)–), 2·82 d [1] J = 13 Hz (Ar–CH(H)–); 2·80 q [2] J = 7·5 Hz ($-CH_2CH_3$), 2·77 q [2] J = 7·5 Hz ($-CH_2CH_3$), 1·14 t [6] J = 7·5 Hz (2 × $-CH_2CH_3$); ν_{max} ($CHBr_3$) 2850, 2795, 945 (Found: C, 68·9; H, 6·85; N, 7·5. $C_{22}H_{26}N_2O_4$ requires C, 69·1; H, 6·85; N, 7·3%).

Further acid treatment of this material (0·38 g) in dichloromethane (50 ml) and 2N HCl (50 ml) for 48 h afforded 3,4-methylenedioxyphenyl 3,4-dimethoxybenzyl ketone (0·24 g; 80%) m.p. 110–111°.

The benzyl chlorides were prepared by treating the corresponding benzyl alcohols with excess of $SOCl_2$ in $CHCl_3$.[23]

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