Anomalous Halogenation of *N*-(2-Acetylbenzofuran-3-yl)acetamide

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N-(2-Acetylbenzofuran-3-yl)acetamide (6) reacts with sulphuryl chloride or chlorine to give *N*-(2-chlorobenzofuran-3-yl)acetamide (9) in high yield. Experiments with radical inhibitors suggest the reaction with sulphuryl chloride to be electrophilic in nature. In contrast, the acetamide (6) reacts with bromine or phenyltrimethylammonium tribromide (PTAT) to give a high yield of the bromoacetyl derivative (2). 3-Methylbenzofuran-2-yl methyl ketone (8) reacts with sulphuryl chloride or PTAT to give the corresponding halogenoacetyl derivative (3) or (4).

In connection with another study we required the chloroacetylbenzofuran (1). The 3-aminobenzofuran (5) [1,2] was treated with acetic anhydride to give a mixture of the mono- and di-acetamido derivatives (6) and (7). After purification, the benzofuran (6) was treated with 1 mol. equiv. of sulphuryl chloride [3] in chloroform at room temperature. T.l.c. showed the presence of one major product, which was isolated by crystallisation in 60% yield. The n.m.r. spectrum of the product, $C_{10}H_8ClNO_2$, showed no methyl ketone resonance and as

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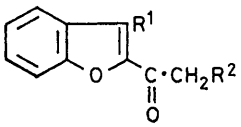
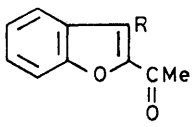
there was no signal corresponding to a 2-H, the product was assigned structure (9), in which the 2-acetyl group has been replaced by chlorine.

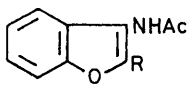
Controlled hydrogenation of the product over palladium–carbon furnished the known benzofuran (10).[2] The 2-H signal of this compound was clearly visible in the n.m.r. spectrum as a singlet at δ 8.38. Hydrogenation of the 2-chlorobenzofuran (9) with an excess of hydrogen furnished the dihydrobenzofuran (12).



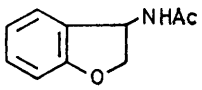
(1) R^1 = NHAc, R^2 = Cl
(2) R^1 = NHAc, R^2 = Br
(3) R^1 = Me, R^2 = Cl
(4) R^1 = Me, R^2 = Br



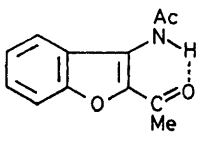
(5) R = NH_2
(6) R = NHAc
(7) R = NAc_2
(8) R = Me



(9) R = Cl
(10) R = H
(11) R = Br



(12)



(13)

Sulphuryl chloride is known to react by both free radical [4-6] and electrophilic pathways.[3,7,8] In order to elucidate the mechanism of this reaction, the chlorination was repeated in the dark and in the presence of radical inhibitors (see Table). The reaction was essentially unaffected by the absence of light or the presence of radical inhibitors (nitrobenzene,[9] anisole,[10] and norbornadiene [11]). The same product could be isolated using tetrahydrofuran or 90% acetic acid as solvent, or in the presence of an excess of anhydrous potassium carbonate to remove hydrogen chloride. These results suggest that the chlorination is electrophilic in nature. Ionic chlorination is known to be favoured in aqueous acetic acid,[12] and this probably accounts for the improved yield of the 2-chlorobenzofuran (9) in this solvent. Substitution of chlorine gas for sulphuryl chloride gave the same 2-chlorobenzofuran (9), and in improved yield (see Table). Sulphuryl chloride is therefore probably acting as a source of electrophilic chlorine.

These results are in marked contrast to the reaction of the 2-acetylbenzofuran (6) with bromine in tetrahydrofuran, which gave none of the 2-bromo-derivative (11), but instead a good yield of the bromoacetylbenzofuran (2). The yield of the bromoacetylbenzofuran (2) could be improved by using phenyltrimethylammonium tribromide [13] in place of bromine.

In contrast to the 3-acetamidobenzofuran (6), the 3-methyl analogue (8) [14,15] reacted with sulphuryl chloride in chloroform giving the 2-chloroacetylbenzofuran (3) [16] in high yield. Similarly, bromination of the 3-methylbenzofuran (8) with phenyltrimethylammonium tribromide gave a high yield of the 2-bromoacetyl derivative (4).

Reaction of *N*-(2-acetylbenzofuran-3-yl)acetamide (6) and 3-methylbenzofuran-2-yl methyl ketone (8) with halogenating agents

Compound	Reagents	Solvent	Product	% Yield *
(6)	SO_2Cl_2(1.0 equiv.)	$CHCl_3$	(9)	59.5
(6)	SO_2Cl_2 (1.0 equiv.) in the dark	$CHCl_3$	(9)	61
(6)	SO_2Cl_2 (1.0 equiv.) + $PhNO_2$ (0.1 equiv.)	$CHCl_3$	(9)	51
(6)	SO_2Cl_2 (1.0 equiv.) + PhOMe (0.1 equiv.)	$CHCl_3$	(9)	56.5
(6)	SO_2Cl_2 (1.0 equiv.) + norbornadiene (0.1 equiv.)	$CHCl_3$	(9)	55.5
(6)	SO_2Cl_2 (1.0 equiv.)	THF	(9)	44.5
(6)	SO_2Cl_2 (1.1 equiv.) + anhyd. K_2CO_3 (excess)	$CHCl_3$	(9)	65.5
(6)	SO_2Cl_2 2.0 equiv.)	90% AcOH	(9)	78
(6)	Cl_2 (excess)	$CHCl_3$	(9)	70.5
(6)	Br_2 (1.5 equiv.)	THF †	(2)	50.5
(6)	$PhN^+Me_3\ Br_3^-$ (1.0 equiv.)	THF	(2)	58.5
(8)	SO_2Cl_2 (1.1 equiv.)	$CHCl_3$	(3)	70
(8)	$PhN^+Me_3\ Br_3^-$ (1.05 equiv.)	THF	(4)	80

* Isolated after one crystallisation.
† Tetrahydrofuran.

Hydrogen bonding between the acetamido and oxo-groups [see structure (13)] may be responsible for slowing the enolisation, and therefore halogenation, of the 2-acetyl group in (6). This can be clearly demonstrated by comparing the i.r. and n.m.r. spectra of the mono- and di-acetamidobenzofurans (6) and (7) (see Experimental section).

Electronegative substituents have previously been reported to be displaced during aromatic electrophilic substitution. For example, formyl or acetyl groups in the 3-position of 2-methylindoles are readily displaced

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by a nitro-group during nitration with concentrated nitric acid.[17,18]

EXPERIMENTAL

Column chromatography was carried out on silica gel [Kieselgel 60 (Merck)]. Merck Kieselgel 60 F_{254} (0.25 mm) plates were used for t.l.c., and Anachem Uniplate (2.0 mm) plates were used for preparative layer chromatography (p.l.c.).

M.p.s were determined with a Büchi Tottoli apparatus. U.v. spectra were measured for solutions in ethanol with a Unicam SP 1800 spectrophotometer. I.r. spectra were obtained for Nujol mulls with a Unicam SP 1000 spectrophotometer, and n.m.r. spectra for solutions in deuteriochloroform with Varian T60 and XL 100/15 spectrophotometers (internal tetramethylsilane). Mass spectra were determined with an A.E.I. MS902 instrument.

Tetrahydrofuran was first filtered through a column of alumina (grade I) and then distilled from sodium. Sulphuryl chloride (B.D.H.) was used as supplied. The term ' recovery ' means that the organic fraction was washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness *in vacuo*.

Acetylation of 3-Aminobenzofuran-2-yl Methyl Ketone (5).[1,2]—A solution of the amine (5) (5.35 g) in pyridine (50 ml) and acetic anhydride (10.5 g) was heated under reflux for 8.5 h. The mixture was poured into an excess of ice and 2N-hydrochloric acid and extracted with dichloromethane. The recovered product was chromatographed on silica gel (100 g). Elution with dichloromethane–hexane (1 : 1) gave N-(2-*acetylbenzofuran*-3-*yl*)*diacetamide* (7) (1.2 g), which crystallised from chloroform–hexane; m.p. 93—96° (Found: C, 64.7; H, 4.9; N, 5.3. $C_{14}H_{13}NO_4$ requires C, 64.85; H, 5.05; N, 5.4%); $\nu_{max.}$ 1 724, 1 708, and 1 685 cm^{-1}; δ 2.4 [6 H, s, $N(COMe)_2$], 2.62 (3 H, s, COMe), and 7.5 (4 H, m, aromatic H); *m/e* 259 (8%), 217 (56), 175 (100), and 43 (90).

Elution of the column with ether–chloroform (1 : 9) gave N-(2-*acetylbenzofuran*-3-*yl*)*acetamide* (6) (3.29 g), which crystallised from chloroform–hexane; m.p. 138—140° (lit.,[1] 135—137°) (Found: C, 66.1; H, 5.05; N, 6.45. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%); $\nu_{max.}$ 3 310, 1 678, 1 600, and 1 573 cm^{-1}; δ 2.26 (3 H, s, NHCO*Me*), 2.58 (3 H, s, 2-COMe), 7.5 (3 H, m, aromatic H), 8.65 (1 H, d, *J* 8 Hz, 4-H), and 10.35br (1 H, s, N*H*COMe); *m/e* 217 (25%), 175 (100), 160 (70), and 43 (40).

General Conditions for the Reaction of N-(2-*Acetylbenzofuran*-3-*yl*)*acetamide* (6) *with Sulphuryl Chloride* (*see Table*).—The acetamide (6) (0.2 g) in chloroform (10 ml) (or solvent and additive specified in the Table) was treated with sulphuryl chloride (amount specified in the Table) at room temperature, and the mixture was stirred for 30 min. T.l.c. [ether–chloroform (1 : 9] showed one major product with R_F 0.4. The chloroform solution was washed with 2N-sodium carbonate (5 ml) and water (5 ml), and then dried and evaporated to dryness *in vacuo*. For reactions in tetrahydrofuran or 90% acetic acid, the mixture was first evaporated to dryness *in vacuo*, then diluted with water, and extracted with chloroform as described above.

The product was crystallised from chloroform–hexane to give N-(2-*chlorobenzofuran*-3-*yl*)*acetamide* (9), (yield specified in the Table), m.p. 180—181° (Found: C, 57.1; H, 3.8; Cl, 16.75; N, 6.65. $C_{10}H_8ClNO_2$ requires C, 57.3; H, 3.8; Cl, 16.9; N, 6.7%), $\nu_{max.}$ 3 260, 1 665, and 1 625 cm^{-1}; $\lambda_{max.}$ 254, 275, 279, 282, and 284 nm (ε 11 570, 3 950, 4 090, 2 070, and 3 120); δ[$(CD_3)_2SO$] 2.15 (3 H, s, NHCO-*Me*), 7.4 (4 H, m, aromatic H), and 9.8br (1 H, s, N*H*COMe); *m/e* 211 (16%), 209 (46), 169 (34), 167 (100), 139 (56), 138 (60), 104 (40), 102 (56), 76 (52), and 43 (90).

Reaction of N-(2-*Acetylbenzofuran*-3-*yl*)*acetamide* (6) *with Chlorine*.—A slow stream of chlorine gas was passed through a solution of the acetamide (6) (0.5 g) in chloroform (40 ml) at room temperature for 1 min. The solution was stirred for a further 30 min, then evaporated to dryness *in vacuo*, and the residue was crystallised from chloroform–hexane to give *N*-(2-chlorobenzofuran-3-yl)acetamide (9) (0.34 g), identical (m.p. and i.r. and mass spectra) with the sample described above.

Hydrogenation of N-(2-*Chlorobenzofuran*-3-*yl*)*acetamide* (9).—(a) *With excess of hydrogen*. The acetamide (9) (0.5 g) in ethanol (20 ml) was hydrogenated over 5% palladium–carbon (0.25 g) until uptake ceased (2 h). The recovered product was recrystallised from chloroform–hexane to give N-(2,3-*dihydrobenzofuran*-3-*yl*)*acetamide* (12) (0.27 g), m.p. 141—142° (Found: C, 67.6; H, 6.3; N, 7.85. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%); $\nu_{max.}$ 3 300 and 1 650 cm^{-1}; $\lambda_{max.}$ 243, 280, 285, and 287 nm (ε 230, 3 010, 2 580, and 2 640); δ 1.98 (3 H, s, β-NHCO*Me*), 4.28 (1 H, dd, *J* 10 and 4 Hz, 2α-H), 4.63 (1 H, dd, *J* 10 and 8 Hz, 2β-H), 5.48 (1 H, m, 3α-H), 6.38br (1 H, d, N*H*-COMe), and 6.7—7.4 (4 H, m, aromatic H); *m/e* 177 (12%), 135 (10), 134 (8), 118 (100), 91 (8), and 43 (8).

(b) *With 1 mol. equiv. of hydrogen*. The acetamide (9) (0.5 g) in ethanol (30 ml) was hydrogenated over 5% palladium–carbon (0.15 g) until 1 mol. equiv. of hydrogen (55 ml) had been absorbed. The recovered product was subjected to p.l.c. Development with ether–dichloromethane (1 : 9) and recovery of the most polar band gave *N*-(benzofuran-3-yl)acetamide (10) (0.1 g), which crystallised from benzene–hexane; m.p. 173.5—175° (lit.,[3] 173.5—175°); $\nu_{max.}$ 3 300 and 1 665 cm^{-1}; $\lambda_{max.}$ 237 and 245 nm (ε 7 150 and 7 350); δ 2.2 (3 H, s, NHCO*Me*), 7.3 (3 H, m) and 7.85 (1 H, m) (aromatic H), 8.38 (1 H, s 2-H), and 9.7br (1 H, s, N*H*COMe); *m/e* 175 (60%), 133 (100), 105 (18), 104 (48), and 43 (42).

Bromination of N-(2-*Acetylbenzofuran*-3-*yl*)*acetamide* (6).—(a) *With phenyltrimethylammonium tribromide*. The acetamide (6) (10 g) in dry tetrahydrofuran (270 ml) was treated with phenyltrimethylammonium tribromide (17.3 g) and the solution was stirred at room temperature for 2 h. The mixture was poured into a large excess of water and extracted with dichloromethane. The recovered product crystallised from chloroform–hexane to give N-[2-(*bromoacetyl*)*benzofuran*-3-*yl*]*acetamide* (2) (8.0 g), m.p. 151—153° (Found: C, 48.55; H, 3.4; Br, 27.35; N, 4.75. $C_{12}H_{10}BrNO_3$ requires C, 48.65; H, 3.4; Br, 27.0, N, 4.75%); $\nu_{max.}$ 3 280, 1 702, 1 660, and 1 600 cm^{-1}; δ 2.30 (3 H, s, NHCO*Me*), 4.46 (2 H, s, CH_2Br), 7.4 (3 H, m, aromatic H), 8.54 (1 H, d, *J* 8 Hz, 4-H), and 10.05br (1 H, s, N*H*-COMe); *m/e* 297 (8%), 295 (8), 255 (32), 253 (32), 175 (32), 160 (100), and 43 (48).

(b) *With bromine*. The acetamide (6) (1.0 g) in dry tetrahydrofuran (25 ml) was treated with bromine (1.1 g) in tetrahydrofuran (20 ml) and the solution was stirred for 2 h at room temperature. The mixture was poured into a large excess of water and extracted with chloroform.

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The recovered product crystallised from chloroform–hexane to give *N*-[2-(bromoacetyl)benzofuran-3-yl]acetamide (2) (0.69 g.), m.p. 152—154°, identical (n.m.r., i.r., and mass spectra) with the sample described above.

Reaction of 3-Methylbenzofuran-2-yl Methyl Ketone (8) *with Sulphuryl Chloride*.—The benzofuran (8) (20 g) in chloroform (70 ml) at 0 °C was treated with sulphuryl chloride (17 g) over 1 h and the solution was stirred for another 2 h at room temperature. The mixture was poured into an excess of water and extracted with chloroform. The recovered product crystallised from ethanol to give chloromethyl 3-methylbenzofuran-2-yl ketone (3) (16.8 g), m.p. 106—107° (lit.,[16] 54—56°), $\nu_{max.}$ 1 695 cm^{-1}; δ 2.6 (3 H, s, Me), 4.75 (2 H, s, $CO{\cdot}CH_2Cl$), and 7.5 (4 H, m, aromatic H); *m/e* 210 (8%), 208 (20), 159 (100), and 103 (18).

Reaction of 3-Methylbenzofuran-2-yl Methyl Ketone (8) *with Phenyltrimethylammonium Tribromide*.—The benzofuran (8) (17 g) in dry tetrahydrofuran (50 ml) was treated with phenyltrimethylammonium tribromide (27.3 g) and the solution was stirred at room temperature for 3 h, poured into a large excess of water, and extracted with chloroform. The recovered product crystallised from ethanol to give *bromomethyl 3-methylbenzofuran-2-yl ketone* (4) (14.0 g), m.p. 111—113° (Found: C, 52.1; H, 3.5; Br, 31.4. $C_{11}H_9BrO_2$ requires C, 52.2; H, 3.6; Br, 31.6%); $\nu_{max.}$ 1 692 cm^{-1}; δ 2.64 (3 H, s, Me), 4.50 (2 H, s, CH_2Br), and 7.5 (4 H, m, aromatic H); *m/e* 254 (10%), 252 (10), 174 (18), 173 (36), and 59 (100).

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