ONE-STEP SYNTHESIS OF SUBSTITUTED 2-ARYL-2-BROMOALKYL-1,3-DIOXOLANES*

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Substituted phenones *II* reacted with ethylene glycol and pyridinium perbromide, phenyltrimethylammonium tribromide, or dioxane dibromide give the corresponding α-bromoacetals *I*. The highest yields are obtained with dioxane dibromide, and a route is suggested in which the agent is generated *in situ*. The mass spectra of the compounds *I* are interpreted.

Acetals of α-bromocarbonyl compounds are significant intermediates in the synthesis of a number of important substances[1]. Recently, these compounds were used on a technological scale for a simple, elegant synthesis of antirheumatics based on 2-arylpropionic acids[2].

The acetals are commonly prepared by two-stage procedures, either by halogenation of the corresponding ketone followed by acetalization[2-6], or the other way round, by halogenation of the previously prepared acetal[1,7,8]. The yields of the products thus obtained are moderate only. The one-step synthesis of the acetals[9] working with high excess of copper dibromide does not suit to technological applications.

Recently, a convenient one-step synthesis of α-bromoacetals of aliphatic ketones has been reported[10], using phenyltrimethylammonium tribromide as the brominating agent. This inspired[11] us to examine the experimental conditions for the formation of acetals of α-bromophenones. We investigated the effect of pyridinium perbromide, dioxane dibromide, and phenyltrimethylammonium tribromide as brominating agents in tetrahydrofuran and dioxane, substances binding the hydrogen bromide formed.

The results are given in Table I. The yields of the products are fairly high, in particular if dioxane dibromide is employed. We found it convenient to use a simple route adding the phenone *II* and ethylene glycol to dioxane dibromide directly prepared *in situ* in dioxane; the yields of the products *I* are unaffected by this modification. The low yield of acetal *If* be can explained in terms of the steric shielding

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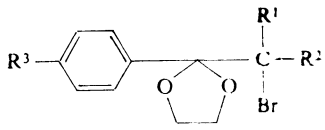
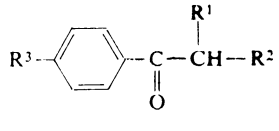
of the carbonyl group by the bulky substituents, in accordance with the results[5] obtained in the acetalization of α-bromoisobutyrophenone.



I



II

Ia, IIa; $R^1 = R^2 = R^3 = H$
Ib, IIb; $R^1 = R^2 = H$, $R^3 = (CH_3)_2CHCH_2$
Ic, IIc; $R^1 = R^2 = H$, $R^3 = C_6H_5$
Id, IId; $R^1 = R^3 = H$, $R^2 = CH_3$
Ie, IIe; $R^1 = H$, $R^2 = CH_3$, $R^3 = (CH_3)_2CHCH_2$
If, IIf; $R^1 = R^2 = CH_3$; $R^3 = H$

The ^1H NMR data (Table II) are consistent with the suggested molecular structures The data of the mass spectra are as follows (the superscripts refer to the ionic species shown in the fragmentation pathway suggested later): *Ia*: 163[h] (0·2), 149[b] (100) 105[d] (48·2), 77[e] (18·5), 51 (10·3); *Ib*: 283/285[f] (0·2), 255/257[g] (0·2), 254/256[c] (0·2), 219[h] (0·5), 205[b] (100), 161[d] (46·3), 133[e] (2·1), 118 (2·0), 103 (2·1), 91 (5·3), 89 (3·0), 43 (3·1); *Ic*: 318/320[a] (0·6), 239[h] (0·4), 225[b] (100), 181[d] (27·2), 153[e] (10·6), 152 (12·8),

TABLE I
Substituted 1,3-dioxolanes synthesized, their physical constants and reaction yields

Substance	B.p., °C/Pa (m.p., °C)		Yield[a], %		
	this work	published value	A	B[b]	C
Ia	(59–60)	(61)[10]	62	83	77
Ib[c]	107–109/40	—	79	84 (85)	—
Ic	(77–79)	(77–78)[5]	69	83 (82)	—
Id	70–73/53	112/93[8]	44	85 (82)	79
Ie[d]	103–105/66	—	42	80 (81)	72
If	(73–75)	(74–76)[5]	35	32	—

[a] A pyridinium perbromide, B dioxane dibromide, C phenyltrimethylammonium tribromide, all in tetrahydrofuran; [b] data obtained with the brominated agent generated *in situ* in dioxane are given in parentheses; [c] for $C_{14}H_{19}BrO_2$ (299·2) calculated: 56·20% C, 6·40% H, 26·70% Br; found: 56·09% C, 6·52% H, 26·45% Br; [d] for $C_{15}H_{21}BrO_2$ (313·2) calculated: 57·52% C, 6·76% H, 25·51% Br; found: 57·38% C, 6·70% H, 25·36% Br.

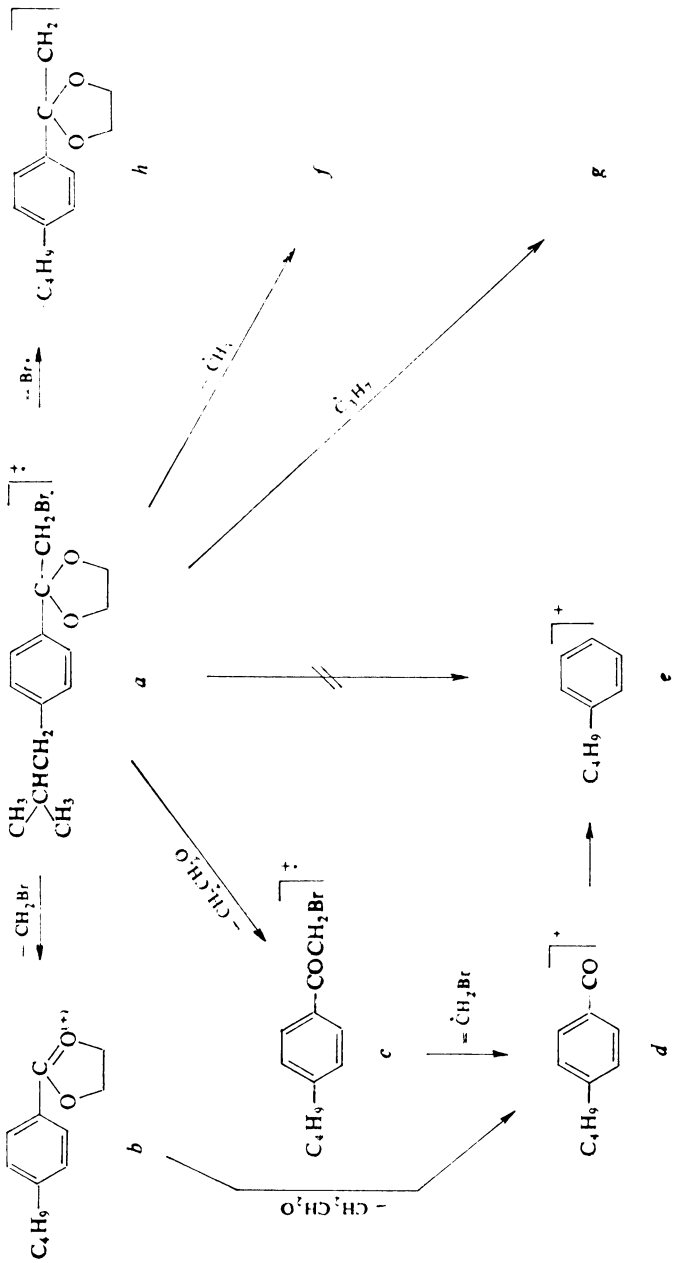
76 (10·5), 51 (2·3); *Id*: 212/214[c] (0·1), 177[h] (0·8), 149[b] (100), 105[d] (61·7), 77[e] (12·3) 51 (10·6); *Ie*: 297/299[f] (0·2), 268/270[c] (0·2), 269[g] (0·3), 235[h] (0·6), 205[b] (100), 179/181 (0·5), 161[d] (38·2), 133[e] (2·1). Based on these data, the fragmentation pathway was elucidated, and is shown here for 1-(bromomethyl)-2-(4-isobutylphenol)-1,3-dioxolane (*Ib*).

Basically the fragmentation proceeds as with 2,2-dialkyl-1,3-dioxolanes[12,13]. The molecular ion of the structure *a* has not been detected at all except for derivative *Ic*. The main fragmentation of the molecular ion *a* begins with the elimination of the bromoalkyl radical, giving rise to the stable ionic species *b* (100% rel. int.), from which the CH_2CH_2O particle is eliminated to give the ion fragment *d*. A competitive fragmentation of the molecular ion *a* starts with the cleavage of the 1,3-dioxolane grouping whereupon the neutral CH_2CH_2O particle is split off and the low-intensity ionic species *c* emerges, yielding the high-intensity ionic species *d* on the elimination of the bromoalkyl radical. The occurrence of ion *e* can be interpreted, in analogy with the fragmentation of phenone[14], in terms of the elimination of carbon monoxide from the phenacyl ion *d*. The fragmentation of the substituent in position 4 of the aromatic ring is of little diagnostic utility. The relative abundances of the species $(M-15)^+$, $(M-43)^+$, and $(M-Br)^+$ (hence, *f*, *g*, and *h*) are low indeed (0·1 to 1% rel. int.).

TABLE II

^1H NMR spectral patterns of substances *Ia*—*If* (signal positions in ppm, interaction constants in Hz)

Substance	Spectral patterns
Ia	3·60 s (2 H, CH_2Br), 3·84 m (2 H, CH_2), 4·14 m (2 H, CH_2), 7·27 m and 7·93 m (5 H, aromatic ring)
Ib	0·89 d (6 H, CH_3), 1·84 m (1 H, CH), 2·45 d (2 H, CH_2) $^3J_{HH}$ 7, 3·65 s (2 H, CH_2Br), 3·85 m (2 H, CH_2), 4·15 m (2 H, CH_2), 7·11 d and 7·38 d (4 H, aromatic ring) $^3J_{HH}$ 7
Ic	3·70 s (2 H, CH_2Br), 3·93 m (2 H, CH_2), 4·23 m (2 H, CH_2), 7·40—7·58 m (9 H, aromatic rings)
Id	1·88 d (3 H, CH_3) $^3J_{HH}$ 6·5, 3·84 m (2 H, CH_2), 4·14 m (2 H, CH_2), 5·28 q (1 H, CH), 7·50 m and 8·03 m (5 H, aromatic ring)
Ie	0·91 d (6 H, CH_3), 1·84 m (1 H, CH), 1·88 d (3 H, CH_3) $^3J_{HH}$ 6, 2·45 d (2 H, CH_2), 3·86 m (2 H, CH_2), 4·14 m (2 H, CH_2), 5·28 q (1 H, CH) $^3J_{HH}$ 7, 7·25 d and 7·96 d (4 H, aromatic ring) $^3J_{HH}$ 8
If	2·00 s (6 H, CH_3), 3·45 m (2 H, CH_2), 3·66 m (2 H, CH_2), 7·38 m and 8·05 m (5 H, aromatic ring)



SCHEME 1

EXPERIMENTAL

Apparatus. The ^{1}H NMR spectra were scanned on a Varian XL-100-15 spectrometer using tetramethylsilane as the internal standard, the mass spectra were measured on a single-focussing JEOL DX-200 instrument (electron energy 70 eV) interfaced to a DA 2000 computer unit.

The temperature data have not been corrected.

Chemicals. Pyridinium perbromide, m.p. 132–134°C, was prepared according to[15], phenyltrimethylammonium tribromide, m.p. 112–115°C, by a modified procedure after[16], and dioxane dibromide, m.p. 60–61°C, according to[17]. 4-Isobutylacetophenone (*IIb*, b.p. 151–155°C/3·3 kPa), 4-phenylacetophenone (*IIc*, m.p. 119–121°C), propiophenone (*IId*, b.p. 110–115°C/3·3 kPa), 4-isobutylpropiophenone (*IIe*, b.p. 124–127°C/0·8 kPa), and isobutyrophenone (*IIf*, b.p. 112–115°C/3·3 kPa) were synthesized by acylation of the corresponding substituted aromatics[18].

Synthesis of 2-(1-Bromoalkyl)-2-(4-substituted phenyl)-1,3-dioxolanes *Ia–If*

A) Ketone *II* (10 mmol) was dissolved in tetrahydrofuran (10 ml) and ethylene glycol (10 ml), and the brominating agent was added to the constantly stirred system. The stirring was continued for 12 h at room temperature, the mixture was diluted with saturated sodium hydrogencarbonate solution (50 ml) and with 5% sodium thiosulphate solution (25 ml), and extracted with ether (2 × 50 ml). The extract was dried with anhydrous magnesium sulphate, the ether was removed by evaporation, and the residue was distilled or crystallized.

B) Bromine (1·6 g) was added to dioxane (10 ml) with stirring. The mixture was stirred constantly, and after 5 min, ethylene glycol (10 ml) and ketone *II* (10 mmol) were added. The stirring was continued for 12 h at room temperature, and the product was isolated as *sub A*.

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