Ring Bromination of Aryl Methyl Ketones with Hypobromous Acid

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The reaction of hypobromous acid, generated *in situ*, with a variety of aryl methyl ketones in aqueous acetic acid containing perchloric acid catalyst, produces ring-brominated products in a rapid reaction at room temperature.

THE bromination of acetophenone and like compounds has been extensively studied and, with one exception, occurs in the side-chain. Treatment with molecular bromine in the presence of an excess of aluminium chloride has been developed [1] as a useful means of carrying out ring bromination. For example, acetophenone gives exclusively *m*-bromoacetophenone under these conditions. We report here that treatment with hypobromous acid, under certain rather milder conditions, also results in ring rather than side-chain bromination.

A number of deactivated benzenes have previously been successfully brominated by acid-catalysed reaction with acetophenone in aqueous dioxan to produce either 2-bromoacetophenone or ring-brominated products, with formation of the latter being favoured by high water content in the solvent and high concentration of added acid. The acid produces a greater increase in the rate of ring bromination than it does in the rate of keto–enol interconversion, the rate-determining step in side-chain bromination. The generation of a positive bromine species from the hypobromous acid is apparently highly dependent on the acidity of the medium.

In the preparative work described here, we used aqueous acetic acid and *ca.* 1·3M-perchloric acid. Ring bromination proceeds in the presence of a higher proportion of acetic acid than of dioxan in the solvent. Solubility problems are therefore lessened in larger scale reactions. The hypobromous acid was generated *in situ*. Under these conditions, ring bromination was rapid at, or below, room temperature. The

[1] D. E. Pearson and H. W. Pope, *J. Org. Chem.*, 1958, **23**, 1412.
[2] P. B. D. de la Mare and I. C. Hilton, *J. Chem. Soc.*, 1962, 997.

use of sulphuric acid in place of perchloric acid gave rise to some 2-bromoacetophenone. The results are summarised in the Table.

Products from the bromination of aromatic ketones

Ketone	Position of bromination	Yield (%)	M.p. [B.p.] (°C)	Recovered ketone (%)
Acetophenone	*m* + *o* (6 : 1)	49	[136—140] [a]	12
4′-Methylacetophenone	3′	60 [b]	38—40 [c,d]	
4′-Chloroacetophenone	3′ [e]	66 [b]	74—76 [e,f]	
2-Acetylthiophen	5 [g]	31	[140—150] [a] 90—92 [e,h]	35
2′-Methoxyacetophenone	5′ [i]	34	[120] [j,k]	22
3′-Methoxyacetophenone	6′		[115—125] [j,m]	12
	2′,6′ [n] 4′,6′ [p]	17	[142—146] [j,o]	

[a] At 15 mmHg. [b] Isolated by recrystallisation of the crude product mixture. [c] From light petroleum (b.p. 40—60°). [d] Lit.,[1] 42—43°. [e] δ(CCl_4) 2·54 (Me), 7·46 (d, *J* 9 Hz, H-5′), 7·75 (q, H-6′), and 8·10 (d, *J* 2 Hz, H-2′). [f] Lit. (B. K. Diep, N. P. Buu-Hoï, and N. D. Xuong, *J. Chem. Soc.*, 1963, 2784), 75°. [g] δ(CCl_4) 2·46 (Me), 7·0 (d, *J* 4 Hz), and 7·35 (d). [h] Lit. (M. W. Farrar and R. Levine, *J. Amer. Chem. Soc.*, 1950, **72**, 3695), 94—95°. [i] δ(CCl_4) 2·4 (Ac), 3·76 (OMe), 6·6 (d, *J* 9 Hz, H-3′), 7·22 (q, H-4′), and 7·45 (d, *J* 2·5 Hz, H-6′). [j] At 1·5 mmHg. [k] Semicarbazone, m.p. 204—206° [Lit. (R. Quelet and R. Golse, *Compt. rend.*, 1946, **223**, 159), 205°]. [l] δ(CCl_4) 2·3 (Ac), 3·5 (OMe), 6·5 (m, H-2′ and -4′), and 7·15 (d, *J* 9 Hz, H-5′). [m] Purified *via* oxime, m.p. 125—126° (from EtOH–H_2O) [lit. (W. J. Horton and D. E. Robertson, *J. Org. Chem.*, 1960, **25**, 1016), 131—132°]. [n] Major component (for isolation see Experimental section), δ(CCl_4) 2·5 (Ac), 3·85 (OMe), 6·75 (d, *J* 9 Hz, H-4′), and 7·32 (d, H-5′). [o] Found: C, 35·45; H, 2·7; Br, 52·2. $C_9H_8Br_2O_2$ requires C, 35·1; H, 2·6; Br, 51·9%. [p] Oxime, m.p. 163—165°; δ($CDCl_3$) 2·25 (Ac), 3·85 (OMe), 6·80 (s, H-2′), and 7·70 (s, H-5′).

Bromination of acetophenone produced both *m*- and *o*-bromoacetophenones (6 : 1) and there was no evidence (g.l.c.) for the presence of any *p*-isomer. This preference for *o*- over *p*-substitution is normal for reaction of deactivated benzenes with reactive electrophiles.[3] No *o*-bromoacetophenone is produced in the Br_2–$AlCl_3$ reaction.[1] Evidently, the positive bromine species in the reaction reported here is rather smaller than the brominating species in the Br_2–$AlCl_3$ reaction and the *o*-position is therefore accessible. The two isomers are readily separable by g.l.c. and thus, while the method is not as satisfactory for preparing pure *m*-bromoacetophenone as the Br_2–$AlCl_3$ reaction, it can provide a direct synthesis of the *o*-bromo-isomer.

In both *p*-methyl- and *p*-chloro-acetophenone, the effect of the additional substituent is to decrease reactivity *ortho* to the acetyl group relative to that in the *meta*-position. As expected, only one product was formed from each.

The reaction was also successful when applied to 2-acetylthiophen. Some dibromo-compound was also formed, even though a substantial amount of starting material was recovered.

The advantages of the mild reaction conditions were shown by the bromination of *o*-methoxyacetophenone. (Presumably, reaction in the presence of an excess of aluminium chloride would lead to significant *O*-demethylation.) In this case the directing effects of the two substituents reinforce one another and 5′-bromo-2′-methoxyacetophenone was isolated. A small amount of a second monobromo-compound (identified as such from g.l.c. retention time) was also formed. This was not isolated in a pure state but the n.m.r. spectrum suggested that it was another ring bromo-compound.

Bromination of *m*-methoxyacetophenone produced an unexpected result in that, under the same conditions as for the *o*-methoxy-compound, the extents of di- and mono-bromination were about equivalent, even though starting material remained. Two monobromo-isomers were formed and the major one was identified as 2′-bromo-5′-methoxyacetophenone. Two compounds were present in the dibromo-fraction also. These were separated and identified as 2′,6′-dibromo-3′-methoxyacetophenone and 2′,4′-dibromo-5′-methoxyacetophenone. Thus the strong *p*-directing effect of the methoxy-group causes predominant bromination *ortho* to the acetyl group. The resulting *o*-bromo-group apparently interacts sterically with the acetyl group, twisting it sufficiently to reduce its deactivating effect and making reaction possible at the activated positions *ortho* to the methoxy-group.

These results show that this rapid reaction under mild conditions is useful for the preparation of a variety of ring-brominated aryl methyl ketones.

EXPERIMENTAL

The general bromination method is described for acetophenone. Bromine (13 g) was added dropwise with stirring to a solution of acetophenone (8·0 g) and silver nitrate (15 g) in acetic acid (130 ml), water (70 ml), and aqueous 72% perchloric acid (40 g). The mixture was stirred for 0·5 h at room temperature and the precipitated silver bromide was filtered off and washed with water and ether. The filtrate was poured into water (*ca.* 300 ml) and the solution was extracted three times with ether. The combined extracts were washed with water, 5% sodium hydroxide (until the washing was alkaline), and water, dried ($MgSO_4$), and concentrated. (On an analytical scale, the extraction was done with benzene, and the washing with dilute sodium hydrogen carbonate solution, so as to retain any 2-bromoacetophenone.) The residue (10·4 g) was distilled at 20 mmHg through a 4 in vacuum-jacketed Vigreux column.

G.l.c. analysis was generally carried out on a 6 ft glass column packed with 15% GE-SE30 on Chromosorb W, programmed from 140 to 190°. Preparative separation of the two bromoacetophenones was not feasible on this column. However, the isomers were well separated on a 20% Apiezon L column at 160°. They were identified by comparison of retention times with those of authentic samples.

The monobromo-fraction (23%) from reaction of *m*-methoxyacetophenone contained two compounds (*ca.* 3 : 1 by g.l.c.) and the major component only was purified *via* the oxime. The dibromo-fraction, which also contained two compounds (6 : 1), was treated with hydroxylamine hydrochloride–pyridine–ethanol to give the oximes. The mixture was poured into water and extracted with ether. The extract was washed with dilute acid and water, dried, and concentrated. A small amount of carbon tetrachloride

[3] R. O. C. Norman and R. Taylor, ' Electrophilic Substitution in Benzenoid Compounds,' Elsevier, Amsterdam, 1965, p. 305.

was added. After two days at 0°, the oxime of the minor component was filtered off and the ketone was identified as 2′,4′-dibromo-5′-methoxyacetophenone. The filtrate contained 2′,6′-dibromo-3′-methoxyacetophenone (almost free of the other isomer).

N.m.r. spectroscopy was used to identify the various bromo-methoxy-compounds: protons adjacent to the methoxy-group resonated *ca.* 40 Hz upfield of those adjacent to the bromine.

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