Selective bromination of acetophenone derivatives with bromine in methanol

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Acetophenone derivatives are selectively brominated in the acetyl side-chain with bromine in methanol at 0–5° by manipulating the electron density in the aromatic ring in good yield.

Bromination is a very important reaction in organic syntheses¹ particularly for the preparation of intermediate bromo compounds for different β -blockers², such as atypical adrenoreceptor agonists SR58611A, denopamine, tembamide, formoterol, salmeterol etc. Although several aromatic ring as well as side-chain bromination methods appeared in the literature^{3,4} none of these methods give exclusively side-chain brominated products. Moreover, stringent conditions, long reaction time and excess requirement of reagents³ are some of the extra disadvantages of the reported methods.

In our program for synthesis of commercially important cardiovascular drug *R*(–)denopamine and highly potent bronchodilator *R*(–)salmeterol, we have carried out several bromination reactions for preparation of different ω -bromo substituted acetophenone derivatives. We observed that when bromination was carried out with molecular bromine in methanol containing 0.5% conc. hydrochloric acid the site of bromination depends upon the electron density in the aromatic ring (Scheme 1). The acidic condition of the reaction was advocated to facilitate bromination through acid-catalyzed enolization. If the electron density is sufficiently high the attack by the bromonium electrophile (the attacking species for bromo derivatives) takes place in the aromatic ring rather than the acetyl side-chain. On the other hand, when the electron density in the ring is sufficiently low in that case bromination in either site is very very poor. Thus in case of hydroxyacetophenone ring bromination takes place whereas in case of *m*-chloroacetophenone bromination is remarkably poor. It means that a moderate electron density is required to facilitate bromination in the acetyl side-chain. If the hydroxyl group in hydroxyacetophenones is blocked, bromination takes place exclusively in the acetyl side-chain. However, the amount of bromine should be restricted to a little less than the stoichiometry, otherwise the reaction will end up with di- or tribrominated products.

Scheme 1

1 $R_1 = R_2 = R_3 = H$	8 $R_1 = R_2 = R_3 = H,$
$X_1 = H, X_2 = Br$
2 $R_1 = R_2 = H, R_3 = Cl$	9 $R_1 = R_2 = H, R_3 = Cl, X_1 = H,$
$X_2 = Br$
3 $R_1 = R_3 = H, R_2 = OCH_2Ph$	10 $R_1 = R_3 = H, R_2 = OCH_2Ph,$
$X_1 = H, X_2 = Br$
4 $R_1 = H, R_2 = OCH_2Ph,$
$R_3 = CH_2OH$	11 $R_1 = H, R_2 = OCH_2Ph,$
$R_3 = CH_2OH, X_1 = H,$
$X_2 = Br$
5 $R_1 = H, R_2 = R_3 =$
$-OCH_2-O-CH_2-$	12 $R_1 = H, R_2 = OCH_2Ph,$
$R_3 = CH_2OH, X_1 = X_2 = Br$
6 $R_1 = OCH_2Ph, R_2 = H,$
$R_3 = Me$	13 $R_1 = H, R_2 = R_3 =$
$-OCH_2-O-CH_2-,$
$X_1 = H, X_2 = Br$
7 $R_1 = H, R_2 = OCH_2Ph,$
$R_3 = Me$	14 $R_1 = OCH_2Ph, R_2 = H,$
$R_3 = Me, X_1 = H, X_2 = Br$
	15 $R_1 = H, R_2 = OCH_2Ph,$
$R_3 = Me, X_1 = H, X_2 = Br$

Experimental

M.ps. were recorded on a Buchi apparatus and are uncorrected. IR spectra (KBr) were obtained on a Perkin-Elmer 237B spectrophotometer, ¹H NMR spectra on a Varian T-60 NMR spectrometer using Me₄Si as internal standard (δ ppm) and mass spectra on a AEI MS 30 Finnigan Mat spectrometer at 70 eV. Microanalytical data were obtained on a Perkin-Elmer series II 2400 instrument.

6-Acetyl-1,3-benzodioxan (5) : To 4-hydroxyacetophenone (0.01 mol) in HCl (50 ml), was added conc. sulfuric acid (~5 ml) followed by 15.4% formaldehyde (0.03 mol) solution at room temperature with stirring. The reaction was continued for 6 h. Then the mixture was extracted with 5%

benzene in petroleum ether (3 × 30 ml). The extract was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to get the product (1.01 g, 58%), m.p. 75° (Found : C, 65.9; H, 4.1. $C_{10}H_{10}O_3$ requires : C, 67.4; H, 5.7%), $\nu_{\max}$ (KBr) 1690, 2900 cm^{-1} ; δ_H ($CDCl_3$) 2.3 (3H, s, CH_3CO), 4.7 (2H, s, CH_2Ph), 5.06 (2H, s, OCH_2O), 6.6 (1H, d, J 8 Hz, aromatic 8-H), 7.3 (1H, d, J 2 Hz, aromatic 5-H), 7.5 (1H, dd, J 8 and 2 Hz, aromatic 7-H), δ_C ($CDCl_3$) 26.27 ($COCH_3$), 65.58 ($ArCH_2O-$), 91.30 (OCH_2O-), 114.37 (aromatic 8-C), 123.90 (aromatic 6-C), 127.85 (aromatic bridge 10-C), 130.14 (aromatic 7-C), 130.30 (aromatic 5-C), 161.57 (aromatic bridge 9-C), 196.87 ($C=O$); m/z 178 (M^+).

2-Benzyloxy-5-methylacetophenone (6) : To 2-hydroxy-5-methylacetophenone (3 mmol) in dry acetonitrile (30 ml) was added equimolar amount of KOH followed by benzyl chloride (3.3 mol) and 0.5% tetraethylammonium iodide (PTC). The mixture was refluxed with stirring for 3 h, and the progress of the reaction was monitored by TLC. After complete conversion, the mixture was filtered and washed with acetonitrile. The solvent was removed under reduced pressure. The residue thus obtained was taken in dichloromethane and washed with water (3 × 20 ml). The organic layer was dried over anhydrous sodium sulfate. It was then purified by crystallization from benzene (89%), m.p. 81° (Found : C, 79.78; H, 6.07. $C_{16}H_{16}O_2$ requires : C, 80; H, 6.7%), $\nu_{\max}$ (KBr) 1680, 2960 cm^{-1} ; δ_H ($CDCl_3$) 1.9 (3H, s, $Ar-CH_3$), 2.2 (3H, s, $COCH_3$), 4.0 (2H, s, $Ar-CH_2$), 6.3–7.1 (8H, m, ArH), δ_C ($CDCl_3$) 20.75 ($ArCH_3$), 28.29 ($COCH_3$), 70.65 (OCH_2Ph), 112.30 (aromatic 3-C), 126.88 (aromatic 4'-C), 127.80 (aromatic 2'- and 6'-C), 128.00 (aromatic 1-C), 128.45 (aromatic 3'- and 5'-C), 130.00 (aromatic 6-C), 130.91 (aromatic 5-C), 135.14 (aromatic 4-C), 136.66 (aromatic 1'-C), 157.58 (aromatic 2-C), 199.60 ($C=O$); m/z 240 (M^+).

4-Benzyloxy-3-hydroxymethylacetophenone (4) : It was prepared as above from 4-hydroxy-3-hydroxymethylacetophenone⁵ (88%), m.p. 125° (Found : C, 74.53; H, 5.83. $C_{16}H_{16}O_3$ requires : C, 75; H, 6.3%), $\nu_{\max}$ (KBr) 1685, 2950, 3300 cm^{-1} ; δ_H ($CDCl_3$) 2.16 (3H, s, $COCH_3$), 2.4 (1H, b s, OH), 4.36 (2H, s, CH_2OH), 4.7 (2H, s, CH_2OPh), 6.3–7.6 (8H, m, ArH), δ_C ($CDCl_3$) 26.27 ($COCH_3$), 60.21 ($Ar-CH_2OH$), 71.65 ($-OCH_2Ph$), 114.37 (aromatic 5-C), 126.88 (aromatic 4-C), 127.80 (aromatic 2'- and 6'-C), 127.85 (aromatic 3-C), 128.45 (aromatic 3'- and 5'-C), 123.90.22 (aromatic 1-C), 130.14 (aromatic 6-C), 130.30 (aromatic 2-C), 136.66 (aromatic 1'-C), 161.57 (aromatic 4-C), 196.87 ($C=O$); m/z 256 (M^+).

Similarly, other benzyloxy derivatives (3, 7) were pre-

pared and characterized and found to be similar with the data available in the literature⁶.

General procedure for bromination of acetyl side-chain of acetophenone derivatives :

Preparation of 14 : To 2-benzyloxy-5-methyl acetophenone (6; 2.08 mmol) in methanol (50 ml) was added conc. HCl (1 ml) solution followed by dropwise addition of bromine (2 mmol) in methanol (10 ml) at 0–5°. The solution was stirred for ~1 h at that temperature and then at room temperature for another 1 h. The solvent was then removed under reduced pressure and neutralized with 10% sodium bicarbonate solution. It was then extracted in ethyl acetate (3 × 25 ml), the organic layer washed with brine water and dried over anhydrous sodium sulfate. Solvent was then removed under reduced pressure and the product was crystallized from benzene-dichloromethane (1 : 1), (89%), m.p. 115° (Found : C, 60.0; H, 4.4. $C_{16}H_{15}BrO_2$ requires : C, 60.2; H, 4.7%), $\nu_{\max}$ (KBr) 1670, 2950 cm^{-1} , δ_H (CCl_4) 2.2 (3H, s, $Ar-CH_3$), 4.1 (2H, s, $Ar-CH_2Br$), 4.8 (2H, s, $Ar-OCH_2$), 7.1 (5H, s, Ph), 6.3–7.1 (8H, m, ArH), m/z 318 and 320 (M^+ isotopic cluster). Similarly, other acetophenone derivatives were brominated in the acetyl side-chain.

Phenacyl bromide (8) : Yield 87%, m.p. 48° (Found : C, 47.84; H, 3.32. C_8H_7BrO requires : C, 48.24; H, 3.52%), $\nu_{\max}$ (KBr) 1730, 2925 cm^{-1} , δ_H ($CDCl_3$) 2.3 (3H, s, CH_3), 4.1 (2H, s, CH_2Br), 7.45 (5H, m, ArH), m/z 198, 200 (M^+ isotopic cluster).

3-Chloro- ω -bromoacetophenone (9) : Yield 11%, oil (Found : C, 40.03; H, 2.2. C_8H_6BrClO requires : C, 41.15; H, 2.6%), $\nu_{\max}$ (film) 1750, 3050 cm^{-1} , δ_H ($CDCl_3$) 4.2 (2H, s, CH_2Br), 7.2–7.6 (4H, m, ArH); m/z 232, 234, 236 (M^+ isotopic cluster).

4-Benzyloxy- ω -bromoacetophenone (10) : Yield 90%, m.p. 82° (Found : C, 58.79; H, 3.99. $C_{15}H_{13}BrO_2$ requires : C, 59.02; H, 4.26%), $\nu_{\max}$ (KBr) 1700, 2970 cm^{-1} , δ_H ($CDCl_3$) 4.1 (2H, s, CH_2Br), 4.9 (2H, s, CH_2Ph), 7.1 (5H, s, Ph), 7.15 (4H, m, ArH), m/z 304, 306 (M^+ isotopic cluster).

4-Benzyloxy-3-hydroxymethyl- ω -bromoacetophenone (11) : Yield 70%, m.p. 130° (Found : C, 56.89; H, 4.1. $C_{16}H_{15}BrO_3$ requires : C, 57.3; H, 4.5%), $\nu_{\max}$ (KBr) 1695, 3000 cm^{-1} , δ_H ($CDCl_3$) 4.2 (2H, s, CH_3Br), 4.5 (2H, s, CH_2OH), 7.1 (5H, s, Ph), 6.7–7.6 (3H, m, ArH), δ_C ($CDCl_3$) 31.10 (CH_2Br), 60.21 ($-CH_2OH$), 71.65 (OCH_2Ph), 114.37 (aromatic 5-C), 126.88 (aromatic 4-C), 127.80 (aromatic 2'- and 6'-C), 127.85 (aromatic 3-C), 128.45 (aromatic 3'- and 5'-C), 129.22 (aromatic 1-C), 130.00 (aromatic 6-C), 130.30 (aromatic 2-C), 136.66 (aromatic 1'-C), 161.57 (aro-

matic 4-C), 190.30 (C=O), m/z 334, 336 (M^+ isotopic cluster).

4-Benzoyloxy-3-hydroxymethyl- ω,ω -dibromoacetophenone (12) : Yield 25%, m.p. 110° (Found : C, 45.8; H, 3.3. $C_{16}H_{14}Br_2O_3$ requires : C, 46.3; H, 3.6%), $\nu_{\max}$ (KBr) 1685, 2976 cm^{-1} , δ_H ($CDCl_3$) 4.4 (2H, s, CH_2OH), 5.0 (2H, s, OCH_2), 6.4 (1H, s, $CHBr_2$), 7.2 (5H, s, Ph), 6.6–7.9 (3H, m, ArH), m/z 413, 415 (M^+ , isotopic cluster)

6- ω -Bromoacetyl-1,3-benzodioxan (13) : Yield 69%, oil (Found : C, 45.55; H, 3.02. $C_{10}H_9BrO_3$ requires : C, 46.7; H, 3.5%), $\nu_{\max}$ (film) 1760, 3000 cm^{-1} , δ_H ($CDCl_3$) 4.0 (2H, s, CH_2OH), 4.3 (2H, s, CCH_2O), 5.0 (2H, s, $-OCH_2O-$), 6.5–7.6 (3H, m, ArH), δ_C ($CDCl_3$) 31.10 (CH_2Br), 65.58 ($-CH_2O-$), 91.30 ($-OCH_2O-$), 114.37 (aromatic 8-C), 127.85 (aromatic bridge 10-C), 129.72 (aromatic 6-C), 130.00 (aromatic 7-C), 130.30 (aromatic 5-C), 161.57 (aromatic bridge 9-C), 190.30 (C=O), m/z 256, 258 (M^+ isotopic cluster).

4-Benzoyloxy-3-methyl- ω -bromoacetophenone (15) : Yield 71%; m.p. 170° (Found : C, 40.63; H, 2.2. $C_{16}H_{15}BrO_2$ requires : C, 41; H, 2.6%), $\nu_{\max}$ (film) 1730, 3050 cm^{-1} , δ_H ($CDCl_3$) 4.2 (2H, s, CH_2Br), 7.2–7.6 (4H, m, ArH), δ_C ($CDCl_3$) 15.93 (CH_3), 31.10 (CH_2Br), 70.65 (CH_2Ph), 114.37 (aromatic 5-C), 126.88 (aromatic 4'-C), 127.80 (aromatic-2'- and 6'-C), 128.45 (aromatic 3'- and 5'-C), 128.61 (aromatic 3-C), 129.72 (aromatic 1-C), 136.66

(aromatic 1'-C), 161.57 (aromatic 4-C), 190.30 (C=O), m/z 318, 320 (M^+ isotopic cluster).

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