Synthesis of Bromoacetyl Derivatives by Use of Tetrabutylammonium Tribromide

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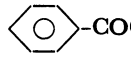
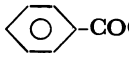
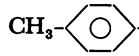
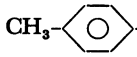
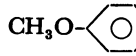
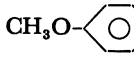
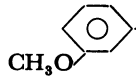
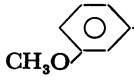
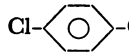
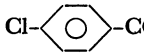
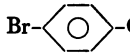
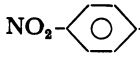
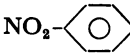
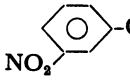
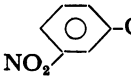
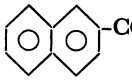
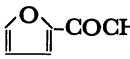
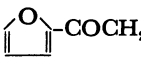
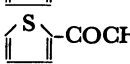
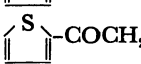
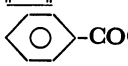
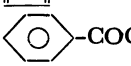
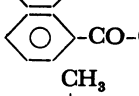
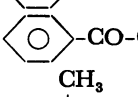
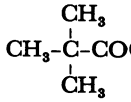
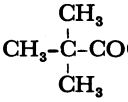
Synopsis. Orange crystalline tetrabutylammonium tribromide was prepared using a simple method. The reaction of acetyl derivatives with an equimolar amount of the tribromide in dichloromethane–methanol at room temperature gave bromoacetyl derivatives in fairly good yields.

In general, bromoacetyl derivatives **1** have been synthesized by a reaction of acetyl derivatives **2** with bromine in an appropriate solvent such as water, chloroform, carbon tetrachloride, acetic acid or *N*,*N*-dimethylformamide.[1] The reagents, copper(II) bromide,[2] 1,4-dioxane bromooxonium bromide,[3] tribromoacetophenone,[4] and *N*-bromosaccharin,[5] have been used as brominating agents instead of bromine for **2** having unsaturated bond or functional groups (hydroxyl group, enol ester, acetal etc.) which should react promptly with bromine or hydrobromic acid. It must be a merit that these reagents can be handled more easily than liquid bromine, because of their solid character.

Furthermore, the solid reagents, organic ammonium tribromides, such as pyridinium tribromide,[6] phenyltrimethylammonium tribromide,[7,8] and tetramethylammonium tribromide,[9] have also been used as selective brominating agents. Recently, Berthelot et al.[10] have shown that tetrabutylammonium tribromide (TBA Br_3) can be used as a brominating agent for the addition of bromine to the double bonds of alkenes and for the selective bromination of acetals. In this paper, we wish to report a facile synthetic procedure of **1** from **2** by the use of TBA Br_3.

Table 1. Bromoacetyl Derivatives **1** from Acetyl Derivatives **2**

	Starting material **2**	Product **1**	Reaction time/h	Yield[a] %	IR(KBr) νCO cm^{-1}	Mp (θm/°C) or Bp (θb/°C)(Torr) found	reported
a			1	78	1695	49—50	50[13]
b			1	83	1695	45—48	48—50[14]
c			1	79	1695	68—69	73[15]
d			1	80	1700	58—60	62—63[16]
e			3	85	1700	97—97.5	96—96.5[17]
f			3	86	1700	107.5—108	109—109.5[18]
g			5	75	1705	96—96.5	98[19]
h			5	71	1705	88—90	96[20]
i			2	75	1700	81—82	82.5—83.5[21]
j			2	85	1675	34.5—36	—
k			2	80	1665	35—35	—
l			1	99	1695	230—231/760	245—250/[22] 760
m			1	88	1695	49—52	54—55[23]
n			3	90	1725	129—130/760	—

a) Yield of isolated product. 1 Torr = 133.322 Pa.

Results and Discussion

TBA Br_3 have usually been prepared from tetrabutylammonium bromide and bromine in carbon tetrachloride.[11] We readily prepared TBA Br_3 by the addition of hydrobromic acid to an aqueous solution of tetrabutylammonium bromide and sodium bromate at room temperature in quantitative yield.

The reaction of **2** with an equimolecular amount of TBA Br_3 in a dichloromethane–methanol solution for 1—5 h at room temperature readily gave **1** containing a small amount of dibromoacetyl derivatives which could easily be removed by recrystallization. The results are summarized in the Table 1.

$$\underset{\mathbf{2}}{R\text{-}COCH_3} \xrightarrow[\text{in } CH_2Cl_2\text{-}CH_3OH \text{ rt}]{(C_4H_9)_4N^+Br_3^-} \underset{\mathbf{1}}{RCOCH_2Br}$$

These reactions should proceed via an ionic species rather than radical ones. In fact, the bromination of acetophenone with TBA Br_3 in dichloromethane, dichloromethane-containing peroxides, and dichloromethane-containing a free radical inhibitor (*m*-dinitrobenzene) all proceeded at the same rate. As shown by Marquet et al.[12] for the bromination of acetophenone with phenyltrimethylammonium tribromide, the mechanism of bromination of **2** with TBA Br_3, (it is suggested) is also considered to be a slow-stage enolization of the ketone and a fast-stage bromination.

We emphasize that the synthetic procedure for bromoacetyl derivatives will be a highly useful method because of its ease, simplicity, and mildness of conditions.

Experimental

Tetrabutylammonium Tribromide (TBA Br_3). To a solution of tetrabutylammonium bromide (9.7 g, 30 mmol) and sodium bromate (1.50 g, 10 mmol) in water (60 ml) was added dropwise hydrobromic acid (47%, 7 ml) under stirring at room temperature. After the mixture was stirred for a few minutes, the immediate orange precipitate was filtered and recrystallized from ether–dichloromethane (1:1) to give TBA Br_3 as orange crystals; yield 13.7 g (95%); mp 74—75 °C (lit,[11] mp 70—72 °C). Found: Br, 50.08%. Calcd for $C_{16}H_{36}NBr_3$: Br, 49.71%.

Phenacyl Bromide (1a). As a general procedure, the preparation of **1a** was as follows: To a solution of acetophenone (0.5 g, 4.16 mmol) in dichloromethane (50 ml)–methanol (20 ml) was added TBA Br_3 (2.2 g, 4.58 mmol) at room temperature. The mixture was stirred for 1 h until a decoloration of the orange solution took place. The solvent was then distilled and the obtained precipitate was extracted with ether (30 ml×4). The ether layer was dried with magnesium sulfate and evaporated in vacuo to give a residue which was recrystallized from ethanol–water (1:2) affording as colorless needles; yield 0.65 g (78%); mp 49—50 °C (lit,[13] mp 50 °C).

Bromomethyl 2-Furyl Ketone (1j). Compound **1j** was prepared similarly: Yield 85%; colorless crystals; mp 34.5—36 °C; IR (KBr) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.30 (2H, s, CH_2Br), 6.53 (1H, dd, J=1.8 and 3.6 Hz, O-CH=C<u>H</u>-CH=), 7.26 (1H, d, J=3.6 Hz, O-CH=CH-C<u>H</u>=), and 7.56 (1H, d, J=1.8 Hz, O-C<u>H</u>=CH-CH=); MS *m/z* 189 and 191 (M^+). Found: Br, 41.88%. Calcd for $C_6H_5O_2Br$: Br, 42.27%.

Bromomethyl Thienyl Ketone (1k). Compound **1k** was prepared similarly: Yield 80%; colorless crystals; mp 33—35 °C; IR (KBr) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.40 (2H, s, CH_2Br), 7.13 (1H, dd, J=4.9 and 4.0 Hz, S-CH=C<u>H</u>-CH=), 7.70 (1H, d, J=4.9 Hz, S-C<u>H</u>=CH-CH=), and 7.80 (1H, d, J=4.0 Hz, S-CH=CH-C<u>H</u>=); MS *m/z* 205 and 207 (M^+).

Bromomethyl *t*-Butyl Ketone (1n). Compound **1n** was prepared similarly: Yield 90%; colorless liquid; bp 129—130 °C/760 mmHg (1 mmHg=133.322 Pa); IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (9H, s, $C(CH_3)_3$), and 4.17 (2H, s, CH_2Br); MS *m/z* 179 and 181 (M^+). Found: Br, 44.79%. Calcd for $C_6H_{11}OBr$: Br, 44.59%.

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