SYNTHETIC COMMUNICATIONS, 25(10), 1433-1439 (1995)

A SIMPLE DEBENZYLATION OF O-SUBSTITUTED PHENOL ETHERS USING HYDROBROMIC ACID IN PRESENCE OF PHASE TRANSFER CATALYST

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Abstract : A simple methodology for the debenzylation of ortho substituted phenol ethers in two phase system with aqueous hydrobromic acid in the presence of tetrabutylammonium bromide as a phase transfer catalyst is described.

Protective groups have an important role in organic synthesis, hence there is always a demand for selective newer reagents for smooth removal of the protecting groups. The utility of the benzyl group as a protecting group for phenols and a variety of debenzylating agents such as Lewis acidic reagents[1,2], substituted boron halides[3], Me_2BBr for acetals, ethers including benzyl ether[4] and α-chloro ethyl chloro formate[5] are well documented in the literature.

Here we wish to report O-debenzylation of phenol ethers using aqueous hydrobromic acid (46%) in the presence of tetrabutylammonium

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IICT Communication No. : 3389

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bromide (25 molar %) as a phase transfer catalyst which we observed during our studies on total halogen exchange of active methylene chloro compounds. Phenols of the type **1** having an active methylene chloro substituent, when subjected to benzylation with benzyl bromide gave the benzyl derivative as a mixture of chloro and bromo derivatives in a 60/40 ratio (**2a**)[6]. In order to bring about the total conversion to a bromo derivative when compound **2a** was refluxed with aqueous HBr in presence of tetrabutylammonium bromide the product obtained was the debenzylated product **2b** (Fig. 1).

To study the utility of this reagent various benzyl ethers (**3a** to **8a**) were synthesised and subjected to debenzylation. Results reported in Table-I describes the scope and selectivity of the methodology. From the results obtained this methodology seems to be useful for O-substituted phenols. Special mention may be made about Bromovanilline (**7a**) benzyl ether where debenzylation is selective without effecting the methoxy group.

We believe that the present procedure offers an attractive alternative to the currently available methods.

In a typical experimental procedure a mixture of 2-chloro/bromo-3'-5'-dimethyl-4'-benzyloxy acetophenone (**2a**) (0.200 g; 0.69 mmoles), HBr (46% solution, 1.22 g; 6.9 mmoles) and tetrabutylammonium bromide (25 molar %; 0.056 g) was refluxed in methylene chloride (5 ml) for 24 hrs. After the reaction, the contents were cooled and diluted

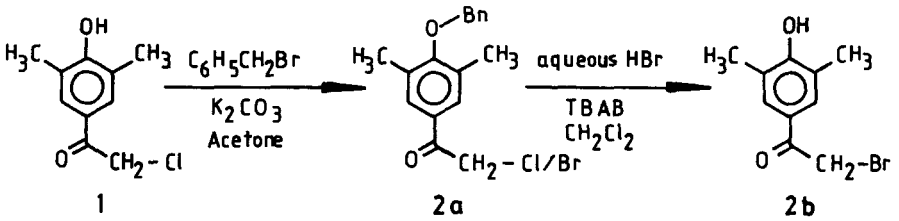


Fig.I

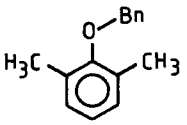
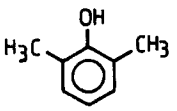
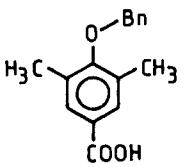
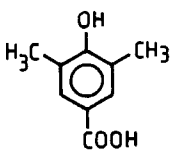
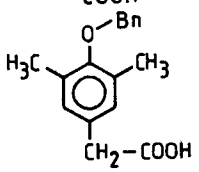
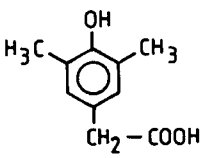
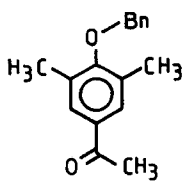
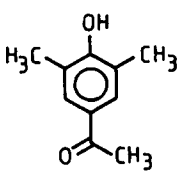
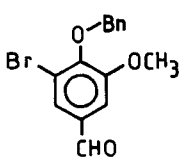
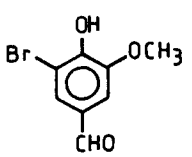
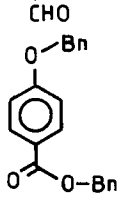
with an additional 25 ml of methylene chloride. The organic layer was separated, washed with water, dried over sodium sulphate, concentrated and purified by column chormatography over silica gel using hexane to remove benzylbromide and then with chloroform to give 2-bromo-3'-5'-dimethyl-4'-hydroxy aceto phenone (**2b**, 0.140 g; 83% yield).

Characterisation data of compounds 2a, 2b; 4a, 4b; 5a, 5b; 6a, 6b

NOTE : Melting points were obtained on a Mettler FPS melting point apparatus and are uncorrected. The elemental analysis were in satisfactory agreement with the calculated values. Melting points and other physical data (NMR, IR & Mass) were in agreement with those reported in the literature.

Compounds **3a**, **7a** and **8a** were prepared by benzylation of commercially available corresponding phenols. Compounds **4a** and **5a** were the products of oxidation, from 3',5'-dimethyl-4'-benzyloxy-3-phenyl

TABLE-1

Compd. No.	Substrate (a)	Product (b)	Yield (%)
3			60
4			87.3
5			64.6
6			53.2
7			63.2
8*		—	—

* 8a was recovered, no debenzylation observed

prop-1-ene obtained as per the reported procedure[7], with potassium permanganate. Compound **6a** was prepared by the reduction of compound **1**, followed by benzylation.

2-Chloro/bromo-3',5'-dimethyl-4'-benzyloxy acetophenone (2a)

m.p. : 95.5°; ^{1}H-NMR ($CDCl_3$) : δ 2.34 (s, 6H, $2CH_3$), 4.37, 4.62 (s, s, 2H, CH_2Br + CH_2Cl); 4.82 (s, 2H, OCH_2); 7.37 (s, 5H, aromatic); 7.59 (s, 2H, aromatic); IR ($CHCl_3$); 1670, 1600, 1320, 1300 & 1150 cm^{-1}; mass : m/e 332, 334 & 288, 290 (M^+).

2-Bromo-3',5'-dimethyl-4'-hydroxyacetophenone (2b)

m.p. 130.6°, ^{1}H-NMR ($CDCl_3$) : δ 2.31 (s, 6H, $2CH_3$); 4.37 (s, 2H, $-CH_2Br$); 5.31 (s, 1H, OH); 7.68 (s, 2H, aromatic). IR ($CHCl_3$) : 3400, 1660, 1600, 1320 & 1150 cm^{-1}, mass : m/e 242, 244 (M^+).

3-5-Dimethyl-4-benzyloxy-benzoic acid (4a)

m.p. 146°; ^{1}H-NMR ($CDCl_3$) : δ 2.3 (s, 6H, $2CH_3$); 4.85 (s, 2H, $O-CH_2$); 7.4 - 7.45 (m, 2H, aromatic); 7.8 (s, 5H, aromatic); IR ($CHCl_3$) : 1680, 1610, 1200 & 1100 cm^{-1}; mass : m/e 256 (M^+).

3-5-Dimethyl-4-hydroxy-benzoic acid (4b)

m.p. 217°; ^{1}H-NMR ($CDCl_3$ + DMSO-D_6) : δ 2.25 (s, 6H, $2CH_3$); 8.1 (s, 1H, OH); 7.65 (s, 2H, aromatic); IR (KBr) : 3425, 1670, 1600, 1325 & 1190 cm^{-1}; mass : m/e 166 (M^+).

3-5-Dimethyl-4-benzyloxy-phenyl acetic acid (5a)

m.p. 83°; ^{1}H-NMR ($CDCl_3$) : δ 2.3 (s, 6H, $2CH_3$); 4.8 (s, 2H, OCH_2); 3.55 (s, 2H, CH_2); 6.95 (s, 2H, aromatic); 7.3 - 7.5 (m, 5H, aromatic); IR ($CHCl_3$) : 1700, 1300 & 1150 cm^{-1}; mass : m/e 270 (M^+).

3-5-Dimethyl-4-hydroxy-phenyl acetic acid (5b)

m.p. 144.3°; ^{1}H-NMR ($CDCl_3$) : δ 2.2 (s, 6H, $2CH_3$); 3.45 (s, (2H, CH_2); 5.2 (s, 1H, OH); 6.9 (s, 2H, aromatic). IR (KBr) : 3400, 1700, 1470, 1290 & 1200 cm^{-1}, mass : m/e 180 (M^+).

3-5-Dimethyl-4-benzyloxy-acetophenone (6a)

Liquid; ^{1}H-NMR ($CDCl_3$) : δ 2.31 (s, 6H, $2CH_3$); 2.56 (s, 3H, $COCH_3$); 4.83 (s, 2H, OCH_2); 7.43 (s, 5H, aromatic); 7.68 (s, 2H, aromatic); IR ($CHCl_3$) : 1650, 1580, 1360, 1300 & 1160 cm^{-1}; mass : m/e 254 (M^+).

3-5-Dimethyl-4-hydroxy-acetophenone (6b)

m.p. 162.0°; ^{1}H-NMR ($CDCl_3$) : δ 2.31 (s, 6H, $2CH_3$); 2.56 (s, 3H, $1CH_3$); 5.12 (s, 1H, OH); 7.62 (s, 2H, aromatic). IR ($CHCl_3$) : 3320, 1640, 1580, 1350 & 1300 cm^{-1}; mass : m/e 164 (M^+).

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(Received in the UK 05 May 1994)