

An Efficient Method for the Preparation of Benzylic Bromides

Peinian Liu,^a Yingchun Chen,^b Jingen Deng,^{*b} Yongqiang Tu^a

^a Department of Chemistry & National Laboratory of Organic Chemistry, Lanzhou University, Lanzhou 730000, China

^b Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, the Chinese Academy of Sciences, Chengdu 610041, China

Fax +86(28)5223978; E-mail: jgdeng@cioc.ac.cn

Received 19 April 2001; revised 6 August 2001

Abstract: Substituted benzylic compounds are brominated with an excess of *N*-bromosuccinimide (NBS) in CCl₄ to the corresponding polybrominated mixtures which are then debrominated with diethyl phosphite and *N,N*-diisopropylethylamine to afford the desired monobromides in satisfactory yields and high purity.

Key words: debromination, benzylic bromides, diethyl phosphite, *N,N*-diisopropylethylamine

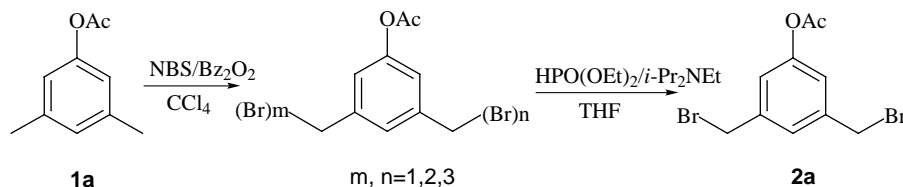
The benzylic bromides, especially the poly(monobromomethyl)arenes are very useful intermediates in organic synthesis. They are used widely in the synthesis of the dendrimers,¹ caged compounds,² cappedophanes and cuppedophanes,³ etc. Generally, the preparation of such compounds is carried out by converting benzylic alcohols to benzylic bromides, however, the alcohols are commonly very expensive or have to be synthesized following a cumbersome route.^{1,3-5} Although the benzylic bromination with *N*-bromosuccinimide (NBS)⁶ is an important method and the reaction gives 67% yield of benzyl bromide from toluene, it is not satisfactory for three reasons. First, in multiple brominations, e.g., of xylenes or mesitylene, yields are reduced significantly because of the inevitable dibromination or even polybromination. Secondly, the byproducts, polybromides and monobromides have the same R_f values in TLC, which causes the purification very difficult. Finally, the electron-withdrawing substituents and heteroatoms make the yields worse. For example, 2,6-lutidine was brominated in only 2% yield to 2,6-bis(bromomethyl)pyridine in CCl₄.^{7,8}

Many reports have demonstrated that diethyl phosphite–triethylamine system is a good choice for debromination of α,α -dibromomethyl arylketones, *gem*-dibromoalkenes and *gem*-dibromocyclopropanes⁹⁻¹² to the corresponding monobromo compounds in good yields. In the present

work we report a convenient two-step procedure for the preparation of benzylic bromides from methyl benzenes which are brominated first with an excess of NBS in CCl₄ and then debrominated selectively to the monobromides with diethyl phosphite and *N,N*-diisopropylethylamine (*i*-Pr₂NEt) in satisfactory yields and high purity.

Initially, compound **1a** was reacted with 2 equivalents of NBS¹³ in CCl₄ at reflux temperature in the presence of a catalytic amount of benzoyl peroxide, but the subsequent debromination of the mixture of the bromides with diethyl phosphite and triethylamine gave the corresponding quaternary ammonium halide. The debromination of dibromo product in the reaction mixture to the monobromide **2a** could be successfully achieved by treating with 2 equivalents diethyl phosphite and a non-nucleophilic base, such as *i*-Pr₂NEt in THF at room temperature in 75% yield (Table 1). Under these reaction conditions, polymethylated benzenes **1b–d**, 2,6-lutidine (**1e**) and 4-methylbenzotrile (**1f**) were also brominated with 2 equivalents of NBS and then debrominated with diethyl phosphite and *i*-Pr₂NEt to give the monobromides **2b–f** in satisfactory yields and high purity (Scheme, Tables 1 and 2). Further debromination of the monobromide was not observed by TLC or ¹H NMR analysis, except for **2e**.

In contrast to the reaction with the substrates carrying an electron-withdrawing group (**1a,b**), the debromination of polybrominated *m*-xylene could not be carried out completely with 4 equivalents of reagents even in 5 days with portionwise addition of the reagents. When the reaction temperature was increased to 60 °C, the conversion of polybromide to monobromide took place completely in 40 hours, but the yield (7%) fell greatly. Finally, we increased the quantities of reagents to 8 equivalents and the reaction progressed smoothly at room temperature. For mesitylene (**1d**), 4 equivalents of reagents were needed



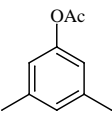
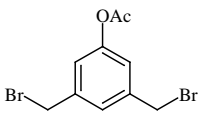
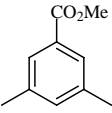
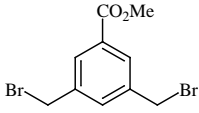
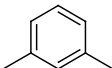
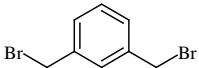
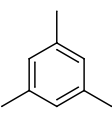
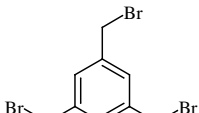
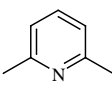
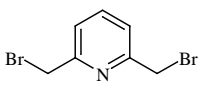
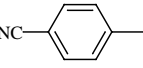
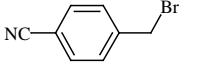
Scheme

Synthesis 2001, No. 14, 26–10 2001. Article Identifier: 1437-210X,E;2001,0,14,2078,2080,ftx,en;F03401SS.pdf.

© Georg Thieme Verlag Stuttgart · New York

ISSN 0039-7881

Table 1 Preparation of Benzylic Bromides **2a–f**^a

Entry	Substrate	Time (h)	HPO(OEt) ₂ / <i>i</i> -Pr ₂ NEt (equiv)	Product ^b	Yield (%)	
					found	reported
1		24	2:2		75	–
2	1a 	24	2:2		79	28 ¹⁴
3	1b 	72	8:8		54	31 ¹⁵
4	1c 	29	4:4		52	23 ¹⁶
5 ^c	1d 	5	4:4		76	2 ⁷
6	1e 	15	4:4		82	38 ¹⁵
	1f			2f		

^a All reactions were carried out in THF at 25 °C under argon with 3 mmol of the substrate.

^b All compounds prepared showed physical and spectral data in accordance with their expected structures (see Table 2).

^c The debromination of this substrate could be monitored by TLC.

for complete debromination. However, the debromination of polybromides of *o*- and *p*-dimethylarenes was unsuccessful. For example, *o*-xylene and 3,4-dimethylphenyl acetate gave complicated mixtures and an undetectable gum was obtained from the debromination of *p*-xylene and 1,2,4,5-tetramethylbenzene, respectively.

Although the polybromides of 2,6-lutidine (**1e**) were completely debrominated with 2 equivalents of reagents at 60 °C, higher yield (76% vs. 50%) was obtained when 4 equivalents of reagents were used (Table 1). Because the polybromides are separable on TLC (silica gel), **1e** was subjected to further investigations to study the influence of reaction conditions. The results showed that the inorganic base K₂CO₃ also accelerated the debromination reaction, but the debromination could not be carried out when pyridine, 2,6-lutidine, 2,4,6-trimethylpyridine, *N*-methylmorpholine or proton sponge was used as the base with diethyl phosphite. Moreover, pyridine and *N*-methyl-

morpholine formed the corresponding quaternary ammonium halides with the monobromides. Tetrahydrofuran was found to be the best solvent for the debromination as compared to dichloromethane and no product was detected in DMSO as solvent. The debromination could also be carried out neat without solvent.

In conclusion, we have developed a practical and efficient method to prepare monobromomethyl and *meta* bis- or tris-bromomethyl benzenes, having various substituents or heteroatom, in satisfactory yields and high purity. This method overcomes the shortcomings of classical benzylic bromination with NBS.¹⁵

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. ¹H NMR spectra were measured using Bruker 300 MHz and 400 MHz spectrometers. IR spectra were recorded on a Nicolet Mx-1 spectrometer. Mass spectra were recorded on a VG7070E, GC/MS/DS instrument. Elemental analyses were carried out on a Carlo Erba-1160 instrument. All

Table 2 Melting Points and Spectral Data of Benzylic Bromides **2a–f**

Product	Mp (°C)	¹ H NMR (CDCl ₃) δ, J (Hz)	MS (70 eV, EI) M/z (%)	IR (KBr) cm ⁻¹
2a ^a	84–85	2.26 (s, 3 H), 4.40 (s, 4 H), 7.04 (d, 2 H, J = 1.6), 7.23 (t, 1 H, J = 1.6)	322 (M + 2, 5), 280 (37), 241 (16), 199 (56), 120 (32), 91 (29), 43 (100)	1764 (C=O), 1614, 1589, 1451, 1369, 1296, 1203, 1141, 1022, 982, 913, 693
2b	95–97	3.93 (s, 3 H), 4.49 (s, 4 H), 7.61 (br s, 1 H), 7.99 (d, 2 H, J = 1.6)	322 (M + 2, 6), 291 (8), 241 (100), 162 (43), 103 (24)	1728 (C=O), 1604, 1436, 1318, 1231, 1108, 996, 902, 771, 698, 600
2c	75–77	4.50 (s, 4 H), 7.32 (m, 3 H), 7.44 (m, 1 H)	264 (M + 2, 10), 185 (89), 104 (100)	1485, 1439, 1263, 1209, 1163, 897, 798, 698, 583, 532
2d	94–95 ^b	4.45 (s, 6 H), 7.35 (s, 3 H)	355 (M + 1, 17), 275 (100), 233 (10), 196 (54), 115 (54), 91 (28)	1824, 1800, 1610, 1460, 1440, 1218, 1171, 1128, 986, 900, 862, 708
2e	87–88 ^c	4.55 (s, 4 H), 7.39 (d, 2 H, J = 7.8), 7.72 (t, 1 H, J = 7.8)	265 (M + 2, 16), 184 (100), 105 (35), 78 (20)	1595, 1578, 1460, 1220, 1210, 1169, 1090, 1000, 962, 872, 820, 749
2f	116–118	4.49 (s, 2 H), 7.53 (m, 2 H), 7.66 (dd, 2 H, J = 2.1, 6.6)	197 (M + 2, 4), 116 (100), 89 (18)	2225 (C≡N), 1605, 1504, 1411, 1289, 1230, 1097, 847, 743, 604

^a Anal. Calcd for C₁₀H₁₀Br₂O₂: C, 37.31; H, 3.11; Br, 49.64. Found: C, 37.53; H, 3.23; Br, 50.00.

^b Lit.¹⁶ mp 94 °C.

^c Lit.⁴ mp 85–89 °C.

substrates and reagents were obtained commercially except **1a** and **1b**, which were prepared by standard procedures. THF was distilled from sodium/benzophenone. CCl₄ was distilled and NBS was recrystallized before use.

Benzylic Bromides **2a–f**; General Procedure

NBS (10.8 g, 60 mmol) was added in three equal portions during 9 h to a solution of **1** (10 mmol) in refluxing CCl₄ (60 mL), each addition being followed by a few milligrams of benzoyl peroxide. The mixture was cooled and filtered to remove the succinimide. The filtrate was washed with aq NaHCO₃ solution (30 mL) and brine (30 mL). After drying (Na₂SO₄), the solvent was evaporated under reduced pressure and the residue was dissolved in anhyd THF (20 mL). To the resulting solution were added diethyl phosphite (15.4 mL, 120 mmol) and *i*-Pr₂NEt (20.8 mL, 120 mmol) at 0 °C under Ar with stirring. The mixture was gradually warmed to r.t. and stirred for 29 h (the reaction was monitored by ¹H NMR). The mixture was poured into ice/water and extracted with Et₂O (3 × 40 mL). The organic layer was washed with 1 M HCl (except for **2e**) and brine, dried (Na₂SO₄), filtered and evaporated to give the crude product. The pure product was obtained by silica gel column chromatography with petroleum ether (bp 60–90 °C) as eluent (Tables 1 and 2).

Acknowledgement

We are grateful to the National Science Fund for Distinguished Young Scholars of China (No. 20025205).

References

- (1) (a) Chessa, G.; Scrivanti, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 307. (b) Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, F.; Jiang, Y.-Z.; Chai, M. C. K.; Chan, A. S. C. *Chem. Commun* **2001**, 1488.
- (2) Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862.
- (3) Vinod, T. K.; Hart, H. *J. Org. Chem.* **1991**, *56*, 5630.
- (4) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392.
- (5) Cochrane, W. P.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. (C)* **1968**, 630.
- (6) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Liebigs Ann. Chem.* **1942**, *551*, 80.
- (7) Barnes, R. A.; Fale, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 3830.
- (8) The yields were somewhat improved by selective choice of solvents and addition of Lewis acid, see: (a) Offermann, W.; Vögtle, F. *Synthesis* **1977**, 272. (b) Xue, G.-P.; He, Y.-B.; Wu, C.-T. *Chinese Chem. Lett.* **1994**, *5*, 23. (c) *Chem. Abstr.* **1994**, *121*, 9378.
- (9) Diwu, Z.; Beachdel, C.; Klaubert, D. H. *Tetrahedron Lett.* **1998**, *39*, 4987.
- (10) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745.
- (11) (a) Hirao, T.; Masunaga, T.; Hayashi, K.; Ohshiro, Y. *Nippon Kagaku Kaishi* **1987**, 1277. (b) *Chem. Abstr.* **1988**, *108*, 94084.
- (12) Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1881.
- (13) Two equivalents of NBS were necessary for the complete bromination of the methyl groups; see also Ref.^{3,14,15}
- (14) Löwik, D. W. P. M.; Weingarten, M. D.; Broekema, M.; Brouwer, A. J.; Still, W. C.; Liskamp, R. M. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1846.
- (15) Offermann, W.; Vögtle, F. *J. Org. Chem.* **1979**, *44*, 710; and references cited therein.
- (16) Vögtle, F.; Zuber, M.; Lichtenthaler, R. G. *Chem. Ber.* **1973**, *106*, 712.