A Convenient Procedure for Bromomethylation of Aromatic Compounds. Selective Mono-, Bis-, or Trisbromomethylation

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Bromomethyl-substituted benzene derivatives are often superior to the corresponding chloromethyl compounds in organic transformations. Unfortunately, the preparation of bromomethylated aromatics is not as well documented as that of chloromethylated aromatics, which are prepared by direct, electrophilic aromatic substitution.[1-4] Bromomethyl-substituted benzenes can be obtained by side-chain bromination of aromatic $-CH_3$ groups with Br_2 or NBS. However, this method may give rise to the formation of $-CHBr_2$ groups, particularly in the preparation of aromatics with more than one $-CH_2Br$ group.[5,6] As we needed such aromatic compounds, we had a closer look at the direct introduction of a $-CH_2Br$ group. Direct bromomethylation of aromatic compounds can be achieved with[1-4,7] (i) bromomethyl alkyl ethers in the presence of zinc or tin halides or (ii) a mixture of formaldehyde (or its polymers) and hydrogen bromide in the presence of a Lewis acid catalyst. Method i has the disadvantage that bromomethyl methyl ethers are highly toxic.[8,9] Method ii has the disadvantage that the addition of gaseous formaldehyde and/or hydrogen bromide is inconvenient in large-scale preparations or, that in the case of aqueous solutions of these reagents, the reaction proceeds relatively slowly.[10]

We found that bromomethylation could be effected very conveniently by adding a (commercially available) 30 wt % solution of HBr in acetic acid to a mixture of acetic acid, paraformaldehyde, and an aromatic compound. This procedure eliminates the use of gaseous and toxic reagents.[11] We are aware that this bromomethylating agent has been described before in the literature,[12] but as far as we know its selectivity (vide infra) with respect to the number of $-CH_2Br$ groups to be introduced has not been noticed and utilized before. Very good results are obtained with activated aromatic compounds, such as various methylbenzenes. Another attractive feature of this bromomethylation agent is that it allows precise control over the number of $-CH_2Br$ groups to be introduced by simply adjusting the reaction temperature. For example, when a mixture of 1 molar equiv of mesitylene and 3 molar equiv of HBr (in acetic acid) and paraformaldehyde was heated for 2 h at 50 °C, only mono(bromomethyl)mesitylene was formed. When the temperature was raised to 80 °C bis(bromomethyl)mesitylene was formed quantitatively after 6 h. Finally, after 8 additional h at 95 °C, tris(bromomethyl)mesitylene was obtained in quantitative yield.[13] Surprisingly, as chloromethylation is generally accompanied by these side reactions, no diarylmethanes were formed. Thus, the reaction products were isolated in excellent purity simply by cooling the reaction mixture and/or by addition of water, upon which the crystalline products were filtered off.

Table I shows that yields of this bromomethylation method are virtually quantitative and that the reaction is highly selective with respect to the number of $-CH_2Br$ groups to be introduced. This high selectivity indicates that the reactivity of the active bromomethylating species formed under the reaction conditions is distinctly different from the species formed with other bromomethylating agents[14] as the deactivating effect of one $-CH_2Br$ group is already sufficient to inhibit the introduction of a second group. Further, we found that benzene could be bromomethylated only once, even after prolonged reaction times, whereas with the NaBr, H_2SO_4, and H_2CO system 1,4-bis(bromomethyl)benzene was obtained in good yield.[14] Finally, it appeared impossible to introduce a $-CH_2Br$ group into chlorobenzene, a compound generally regarded as the lower limit in chloromethylation.[7]

Table I also shows that it is possible to introduce $-CH_2Br$ groups in any geometrical position relative to each other when the proper starting methyl benzene is selected.

Another advantage of our bromomethylating procedure is that it is easily amenable to large-scale preparations.

Although we have not investigated the full scope of the bromomethylating agent described here, we feel that its high selectivity and relative mildness will make it a useful addition to the organic chemist's tool kit.

Experimental Section

Hydrogen bromide dissolved in acetic acid was obtained as a 30–32 wt % solution from Aldrich or Fluka. Paraformaldehyde

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(1) Fuson, R. C.; McKeever, C. H. *Org. React.* **1942**, *1*, 63.

(2) Olah, G. A.; Tolgyesi, W. S. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York; 1964; Vol. II, p 659.

(3) Roedig, A. In *Houben-Weyl Methoden der organischen Chemie*; Georg Thieme Verlag: Stuttgart, 1960; Band 5.4, p 484.

(4) The unpopularity of bromomethylation may very well be due to a translation error: Darzens, one of the early investigators on bromomethylation, wrote (in French) that bromomethylation gives much better yields than chloromethylation (see: Darzens, G. *Compt. Rend.* **1939**, *208*, 818.). This was translated incorrectly by Fuson and McKeever (ref 1) as "Darzens states that the yields (in bromomethylation) are lower than in chloromethylation". This statement was copied in the only other English language review on halomethylation by Olah et al. (ref 2).

(5) For example, the side-chain bromination of mesitylene with NBS gives tris(bromomethyl)benzene in only 23% yield; see Vögtle, F.; Zuber, M.; Lichtenthaler, R. G. *Ber.* **1973**, *106*, 717.

(6) However, side-chain bromination can be selective: (a) Box, V. G.; Yiannikouros, G. F. *Heterocycles* **1990**, *31*, 1261. (b) Futamura, S.; Zong, Z.-M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 345.

(7) Taylor, R. In *Electrophilic Aromatic Substitution*; John Wiley & Sons: Chichester, 1990; p 219.

(8) Warshawsky, A.; Deshe, A.; Gutman, R. *Br. Polym. J.* **1984**, *16*, 234 and references cited therein.

(9) The less volatile *n*-octyl bromomethyl ether, sold by Aldrich, has the disadvantage that the *n*-octanol formed in the reaction is sometimes difficult to remove from the final product.

(10) Mitchell, R. H.; Iyer, V. S. *Synlett* **1989**, 55 and references cited therein.

(11) In situ formation of highly toxic bis(bromomethyl) ether (see ref 8) under the reaction conditions was disproved by a GC/MS analysis, which showed the total absence of this compound.

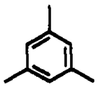
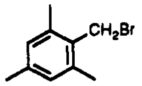
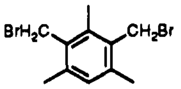
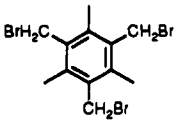
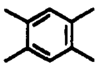
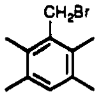
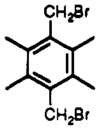
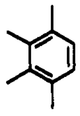
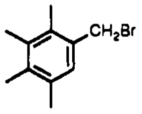
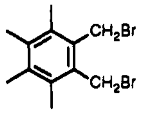
(12) See, for example: Gates, M. *J. Org. Chem.* **1982**, *47*, 578. Jenkner, H.; Buettgens, W. (Chem. Fabrik Kalk GabH) Ger. Offen 2,302,319, 25 July 1974.

(13) The only other reported synthesis of tris(bromomethyl)mesitylene involves the treatment of mesitylene with gaseous hydrogen bromide and paraformaldehyde in liquid SO_2: Fr. Patent 2,216,920 06 Sept 1974 to E. I. Du Pont de Nemours & Co.

(14) More reactive bromomethylating species are formed in the combination of bromomethyl alkyl ethers and Lewis acids or the combination of NaBr, H_2SO_4, and H_2CO; see: Kubiczek, G.; Neugebauer, L. *Monatsh.* **1950**, *81*, 917. Alves, A. A.; da Rocha, R. V. P. *Ann. Ass. Bras. Quim.* **1967**, *26*(3–4), 15. A less reactive bromomethylating species is formed in aqueous systems as described in ref 10.

0022-3263/93/1958-1262$04.00/0

Table I. Results Obtained for the Bromomethylation of Various Benzene Derivatives

substrate	product	time (h), temp (°C)	yield (%)
		2, 50	94
		8, 80	95
		12, 95	91-100
		2, 50	98
		8, 120	95
		3, 80	95
		8, 100	97

(Baker; for histology), methylbenzenes (Aldrich or Fluka), and acetic acid (Aldrich, 99.7%; ACS reagent) were used as received.

The structure and purity of all bromomethylated compounds were established by ^1H and ^{13}C NMR spectra ($CDCl_3$, 300 and 75 MHz, respectively) as well as elemental analysis (C, H, Br) and melting points. All shifts are reported in ppm relative to TMS. In the assignment of the NMR spectra the C atom of the aromatic nucleus to which the CH_2Br group is attached is C-1; the other aromatic C-atoms are numbered clockwise. Melting points are uncorrected.

Warning. Although the formation of bis(bromomethyl) ether is avoided, the toxicity and corrosiveness of the reagents and the lachrymatory properties of the bromomethylated products require the use of an efficient hood and protective gloves.

General Procedure. 1-(Bromomethyl)-2,4,6-trimethylbenzene (= Mono(bromomethyl)mesitylene). The preparation of mono(bromomethyl)mesitylene will serve as an example. The reaction conditions for the other compounds are listed below and in Table I. To a mixture of mesitylene (12.0 g; 0.10 mol), paraformaldehyde (3.08 g; 0.10 mol), and 50 mL of glacial acetic acid was added 20 mL of a 31 wt% HBr/acetic acid solution rapidly. The mixture was kept for 2 h at 40–50 °C and then poured into 100 mL of water. The product was filtered off on a G3 glass frit and dried in vacuum. The yield was 20.0 g (94%) of mono(bromomethyl)mesitylene as a white powder: mp 49 °C (lit.[10] mp 46–7 °C); solidifies at 51 °C (lit.[15] 51 °C); ^1H NMR δ 6.87 (s, 2 H, phenyl), 4.57 (s, 2 H, $-CH_2Br$), 2.39 (s, 6 H, 2,6-CH_3), 2.27 (s, 3 H, 4-CH_3); ^{13}C NMR δ 138.22 (C-4), 137.27 (C-2, 6), 130.99 (C-1), 129.17 (C-3, 5), 29.55 (CH_2Br), 20.96 (4-CH_3), 19.04 (2,6-CH_3). Anal. Calcd for $C_{10}H_{13}Br$: C, 56.36; H, 6.15; Br, 37.49. Found: C, 56.16; H, 6.04; Br, 37.70.

1,3-Bis(bromomethyl)-2,4,6-trimethylbenzene (= Bis(bromomethyl)mesitylene). Prepared according to the general procedure except that 6.15 g (0.20 mol) of paraformaldehyde and 40 mL of a 31% HBr/acetic acid solution were used. Yield 29.1 g (95%) of bis(bromomethyl)mesitylene as a white solid: mp 133 °C (lit.[10] mp 133–4 °C); ^1H NMR δ 6.90 (s, 1 H, phenyl), 4.57 (s, 4 H, $-CH_2Br$), 2.44 (s, 3 H, 2-CH_3), 2.38 (s, 6 H, 4,6-CH_3); ^{13}C NMR δ 138.00 (C-2), 137.13 (C-4, 6), 132.55 (C-1, 3), 130.66 (C-5), 29.71 (CH_2Br), 19.43 (2-CH_3), 14.63 (4,6-CH_3). Anal. Calcd for $C_{11}H_{14}Br_2$: C, 43.17; H, 4.61; Br, 52.22. Found: C, 43.32; H, 4.72; Br, 52.04.

1,3,5-Tris(bromomethyl)-2,4,6-trimethylbenzene (= Tris(bromomethyl)mesitylene). Prepared according to the general procedure except that 10.0 g (0.33 mol) of paraformaldehyde and 70 mL of 31% HBr/acetic acid solution were used. Yield 36.3 g (91%) of tris(bromomethyl)benzene as a white solid (when the mother liquor is used as a solvent in a subsequent run the yield increases to almost 100%): mp 186 °C (lit.[13] mp 183–6 °C); ^1H NMR δ 4.57 (s, 6 H, $-CH_2Br$), 2.46 (s, 9 H, $-CH_3$); ^{13}C NMR δ 137.92 (C-2, 4, 6), 133.27 (C-1, 3, 5), 29.95 (CH_2Br), 15.44 (CH_3). Anal. Calcd for $C_{12}H_{15}Br_3$: C, 36.13; H, 3.79; Br, 60.08. Found: C, 36.29; H, 3.84; Br, 59.91.

1-(Bromomethyl)-2,3,5,6-tetramethylbenzene (= Mono(bromomethyl)durene). Prepared according to the general procedure except that 13.42 g (0.1 mol) of durene were first dissolved in 50 mL of hot glacial acetic acid before paraformaldehyde (3.08 g, 0.10 mol) and 20 mL of a 31% HBr/acetic acid solution were added. Yield 22.6 g (98%) of a white solid, which was a strong lachrymator: mp 84 °C; ^1H NMR δ 6.97 (s, 1 H, phenyl), 4.65 (s, 2 H, $-CH_2Br$), 2.31, 2.26 (2 s, 12 H, CH_3); ^{13}C NMR δ 134.10 (C-1), 133.79 (C-3, 5), 133.38 (C-2, 6), 132.27 (C-4), 30.80 (CH_2Br), 20.30 (3,5-CH_3), 14.09 (2,6-CH_3). Anal. Calcd for $C_{11}H_{15}Br$: C, 58.17; H, 6.66; Br, 35.18. Found: C, 58.30; H, 6.70; Br, 35.01.

1,2-Bis(bromomethyl)-3,4,5,6-tetramethylbenzene (= Bis(bromomethyl)durene). Prepared according to the general procedure except that 6.15 g (0.20 mol) of paraformaldehyde and 40 mL of a 31% HBr/acetic acid solution were used. Yield 30.3 g (95%) as a white solid: mp 212 °C (lit.[13] mp 215–6 °C); ^1H NMR δ 4.60 (s, 4 H, CH_2Br), 2.33 (s, 12 H, CH_3); ^{13}C NMR δ 134.60 (C-1, 4), 134.05 (C-2, 3, 5, 6), 30.93 (CH_2Br), 15.88 (CH_3). Anal. Calcd for $C_{12}H_{16}Br_2$: C, 45.03; H, 5.04; Br, 49.93. Found: C, 45.20; H, 5.15; Br, 49.70.

1-(Bromomethyl)-2,3,4,5-tetramethylbenzene (= Mono(bromomethyl)prehnitene). Prepared according to the general procedure except that 13.42 g (0.1 mol) of prehnitene was used. As the product failed to crystallize, the reaction mixture was poured into water, after which the organic layer was separated and dissolved in an equal volume of $CHCl_3$ and extracted twice with water. The organic layer was dried over $MgSO_4$ and concentrated on a rotary evaporator, upon which the product was obtained as a slightly yellow, strongly lachrymatory solid: yield 21.5 g (95%); mp 45 °C; ^1H NMR δ 7.10 (s, 1 H, phenyl), 4.63 (s, 2 H, CH_2Br), 2.41, 2.37, 2.33, 2.13 (4 s, 12 H, CH_3); ^{13}C NMR δ 136.11, 136.00 (C-3, 4), 133.82, 133.1, (C-2, 5), 132.56 (C-1), 128.96 (C-6), 34.13 (CH_2Br), 20.47 (2-CH_3), 16.19 (3,5-CH_3), 15.42 (4-CH_3). Anal. Calcd for $C_{11}H_{15}Br$: C, 58.17; H, 6.66; Br, 35.18. Found: C, 58.07; H, 6.61; Br, 35.36.

1,2-Bis(bromomethyl)-3,4,5,6-tetramethylbenzene (= Bis(bromomethyl)prehnitene). Prepared according to the general procedure, except that 13.42 g (0.1 mol) of prehnitene, 6.15 g (0.20 mol) of paraformaldehyde, and 40 mL of a 31% HBr/acetic acid solution were used. Yield 31.0 g (97%) of a white solid: mp 162 °C (lit.[13] mp 162–3 °C); ^1H NMR δ 4.72 (s, 4 H, CH_2Br), 2.35, 2.24 (2 s, 12 H, CH_3); ^{13}C NMR δ 137.00 (C-1, 2), 134.17 (C-3, 6), 132.12 (C-4, 5), 29.52 (CH_2Br), 17.07, 15.92 (CH_3). Anal. Calcd for $C_{12}H_{16}Br_2$: C, 45.03; H, 5.04; Br, 49.93. Found: C, 45.22; H, 5.11; Br, 50.11.

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(15) Vavon, G.; Bolle, J.; Calin, J. *Bull. Soc. Chim. Fr.* **1939**, *6*, 1025.