Substituted Benzotrichloride Synthesis by Phase Transfer-Catalyzed Chlorination

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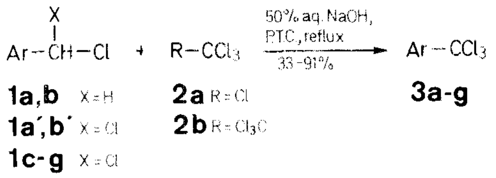
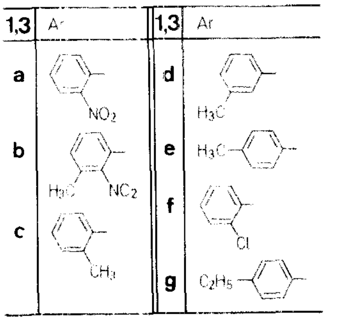
A new method for converting benzyl and benzal chlorides to benzotrichlorides is reported. In contrast to prior art, the process involves contacting the substrates with strong alkali in a two-phase system containing phase transfer catalyst using organic soluble perchloralkanes acting upon base-generated carbanions. The method is particularly useful for preparing benzotrichlorides substituted by either alkyl or nitro groups.

Free radical chlorination of methylarenes is a general method for producing the corresponding benzotrichlorides. This exemplary method fails, however, in two divergent categories. In the first, powerful electron-withdrawing substituents such as nitro impede such halogenations. Several remedies have recently focused on this problem. In one[1], nitrobenzyl chlorides as substrates are chlorinated using mixtures of hypochlorites, optionally employing a phase transfer catalyst. Another modification[2] uniquely employs chlorine oxide to advantage, while a third[3] converts selected nitrobenzoic acids to the corresponding benzotrichlorides using certain phosphorus halides at high temperatures. All three of these methods fail to give *o*-nitrobenzotrichlorides.

Constituting a second circumstance limiting methylarene halogenation is selective preparation of alkyl(methyl)benzotrichlorides. Thus, free radical multiple chlorination of xylenes leads to unavoidable substitution at both methyl groups in these activated substrates. This difficulty has been confronted recently[4] by converting the monochlorinated xylene to the corresponding methyl benzyl sulfide; the latter serves to confine multiple chlorination to this moiety, and combined with subsequent sulfur cleavage, methylated benzotrichlorides are produced.

In addressing simultaneously the two limiting categories discussed above, our studies focused on use of organic soluble chlorinating agents such as carbon tetrachloride (**2a**) and hexachloroethane (**2b**)[5-8] as sources of positive chlorine acting on benzyl and benzal chlorides under strong base and phase transfer conditions. Benzal halides were found to be particularly advantageous since these materials are simply obtained in high yields from a variety of benzaldehydes[9]. In addition, these dihalides facilitate chlorination by increasing the latter's ease of carbanion formation, while decreasing chlorine and base usage for formation of **3**. From our experiments the only benzyl halides sufficiently acidic to undergo carbanion chlorination under these conditions possessed a nitro substituent.





The use of carbon tetrachloride (**2a**) can be wasteful of base, since stoichiometry requires 3 moles per chlorine atom introduced. This is aggravated by the finding that speedy reaction and high yields depend on continued high concentrations of base. This led to two modifications of experimental procedure: (1) A water azeotrope trap was inserted to continuously collect water formed during the reaction; (2) Hexachloroethane (**2b**) as chlorinating agent not only served to reduce base requirements and minimize water formation but could be optionally regenerated in a separate step by chlorination of the resulting olefin. However, if the procedures described here are confined only to laboratory preparations, where caustic outlays and payloads are not critical, use of carbon tetrachloride is preferred due to minimum workup problems. A variety of quaternary ammonium salts were found that could serve as phase transfer catalyst. The best were *n*-dodecyltrimethylammonium halide salts charged at 2–5% by weight of **1**. Quaternary benzyl ammonium salts proved unsatisfactory.

$$\underset{\mathbf{1}}{Ar{-}CHCl_2} + \underset{\mathbf{2a}}{CCl_4} + 3\ NaOH \longrightarrow \underset{\mathbf{3}}{Ar{-}CCl_3} + 3\ NaCl + 2\ H_2O + CO$$

$$\underset{\mathbf{1}}{Ar{-}CHCl_2} + \underset{\mathbf{2b}}{Cl_3C{-}CCl_3} + NaOH \longrightarrow \underset{\mathbf{3}}{Ar{-}CCl_3} + NaCl + H_2O + Cl_2C{=}CCl_2$$

Table. Substituted Benzotrichlorides **3a**–**g** prepared

Substrate	Product	Yield [%]^a	m.p. [°C] or n_D^{20} of distillate	Molecular Formula^b or Lit. Data	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
1a	**3a**	70^c	25–26.5°	$C_7H_4Cl_3NO_2$ (240.5)^d	7.6 (m, 4H_{arom})	–
1b'^{e}	**3b**	84	61–62°	$C_8H_6Cl_3NO_2$ (254.5)^f	2.3 (s, 3H, CH_3)	17.6 (CH_3); 93.1 (CCl_3)
1c	**3c**	33^g	–	–	–	–
1d	**3d**	87	1.5540	1.5545^4	2.25 (s, 3H, CH_3)	21.4 (CH_3); 97.9 (CCl_3)
1e	**3e**	71	45–47°	46°^{4}	2.25 (s, 3H, CH_3)	21.0 (CH_3); 97.8 (CCl_3)
1f	**3f**	91	27–28°	29–30°^{11}	–	95.6 (CCl_3)
1g	**3g**	89	1.5484	$C_9H_9Cl_3$ (223.5)^h	1.2 (t, 2H, CH_3); 2.7 (q, 2H, CH_2)	15.2 (CH_3); 28.4 (CH_2); 97.9 (CCl_3)

[a] Yield of isolated product based on **1** charged unless otherwise indicated.

[b] Microanalyses performed by Atlantic Microlab. Inc., Atlanta, Georgia 30346, U.S.A.

[c] Yield estimated by G.L.C.

[d] Appropriate physical data are not reported in the original literature[1]. Calc. C 34.96 H 1.68 N 5.83; found 35.02 1.71 5.79

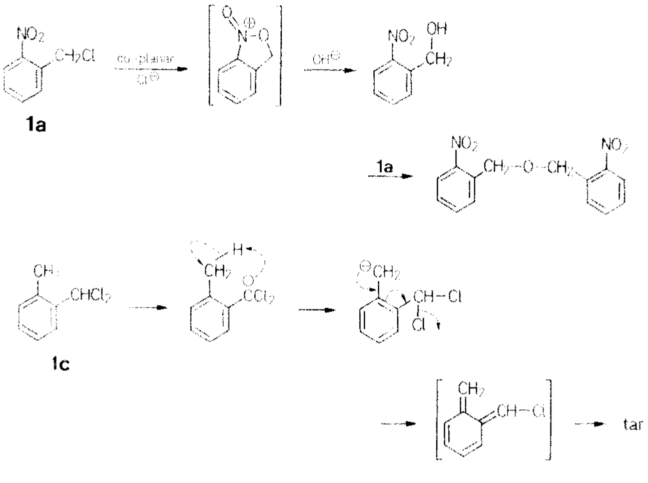
[e] $C_8H_7Cl_2NO_2$ (220.1) calc. C 43.66 H 3.21 Cl 32.22 N 6.37; found 43.62 3.25 32.15 6.63

[f] Calc. C 37.75 H 2.38 Cl 41.79 N 5.50; found 37.79 2.38 41.76 5.48

[g] Yield estimated by G.L.C.; product indentified by G.L.C./M.S.

[h] Calc. C 48.36 H 4.06 Cl 47.58; found 48.51 4.10 47.37

The new methodology as described above appears suitable for a variety of aromatic substrates, although with the exception of **3f**, products **3** chosen for the Table are confined to the two divergent categories discussed in the introductory paragraphs. Two examples in the Table represent adverse chlorination. In one, *o*-nitrobenzyl chloride gave a fair amount of the dibenzyl ether, while in the other, *o*-methylbenzal chloride gave tars along with reduced product yield. Both can be postulated to occur via *ortho* substituent interaction. These phenomena are not encountered with two other *o*-substituted examples in the Table; presumably substrates **1b** possess a sufficiently non-planar *o*-nitro substituent that obviates neighboring group participation, while the *o*-chlorine in **1f** is inert to such interaction.



Melting points were determined on a Laboratory Devices Mel-temp apparatus and are uncorrected. ^{1}H-N.M.R. spectra were obtained on a Varian EM-360L, while ^{13}C-N.M.R. were recorded on a Bruker WM-360. Mass spectra were measured on a Varian CH-7 mass spectrometer. Microanalyses were performed by Atlantic Microlab Inc.

3-Methyl-2-nitrobenzotrichloride (3b); Typical Procedures:

Either 3-methyl-2-nitrobenzyl chloride (**1b**) or 3-methyl-2-nitrobenzal chloride (**1b'**) could separately be converted to **3b** in comparable yield. The following procedures illustrate the method using: (Method A) both of these substrates as a mixture and (Method B) pure 3-methyl-2-nitrobenzal chloride as starting material.

Method A: In a 4-necked, 1-l, round bottom flask fitted with reflux condenser, mechanical stirrer, dropping funnel and thermometer are charged 3-methyl-2-nitrobenzal chloride (**1b'**; 9.6 g; prepared from 3-methyl-2-nitrobenzaldehyde by methods described in Ref.[9]; new compound, m.p. 62–63°C) and 3-methyl-2-nitrobenzyl chloride (**1b**; 9.6 g), *n*-dodecyltrimethylammonium chloride, (0.6 g), dichloromethane (160 ml), carbon tetrachloride (100 ml), 50% (wt/wt) caustic (250 ml) and *t*-butyl alcohol (10 g). The mixture is refluxed 3.5 h, then worked up by cooling, adding ice/water and some additional dichloromethane with stirring until the flask is nearly full. The contents are transferred to a separatory funnel and the bottom organic layer separated from the top aqueous layer and a small middle rag phase. After solvent removal, the residue weighs 24.1 g; this was distilled to give product which solidifies on standing; yield: 18.8 g, Recrystallization from cold methanol gives an analytical sample; yield: 16.0 g (> 99% assay by G.L.C. area %).

Method B: 3-Methyl-2-nitrobenzal chloride (**1b'**: 22.0 g, 0.1 mol) is dissolved in dichloromethane (150 ml) and carbon tetrachloride (80 ml). To this solution are added 50% aqueous sodium hydroxide (150 ml), *t*-butyl alcohol (5 g), and *n*-dodecyltrimethylammonium chloride (0.5 g). The stirred mixture is heated at reflux and small aliquots are worked up (per description in Method A), and give the following results: (time in h, ratio **3**:**2** by G.L.C. area %) 1.0, 75:25; 2.0, 87:12; 2.67, 95:5; 3.25, 94:4 (high boiler detected). After 3.25 h, the mixture is cooled and diluted with addition of both ice/water and dichloromethane. After further workup the crude residue weighs 25.3 g, which is subjected to kugelrohr distillation (150–160°C/0.1 torr) to give the product; yield: 22.0 g; possessing a 97% assay.

4-Ethylbenzotrichloride (3g); Typical Procedure for 3c–g:

In a 4-necked, 500-ml round bottom flask equipped with a reflux condenser, thermometer, mechanical stirrer, and heating mantle are added 4-ethylbenzal chloride (**1 g**; 22.7 g, 0.12 mol), carbon tetrachloride (**2a**; 100 g), 50% aqueous sodium hydroxide (150 ml) and *n*-dodecyltrimethylammonium chloride (1.0 g). The mixture is heated to reflux with stirring. An aliquot is taken after 1 h and G.L.C. indicates that the reaction is complete. Ice and water are added to nearly fill the flask, then the contents are transferred to a separatory funnel. After separation, the aqueous layer is washed with fresh carbon tetrachloride (2 × 50 ml), while the combined organic layers are washed with 1% sulfuric acid (100 ml). After solvent removal from the organic phase, the residue is subjected to kugelrohr distillation (90–100 °C/0.15 torr) to give **3g** having a 96.7 % assay by G.L.C., area %; yield: 23.8 g.

3-Methylbenzotrichloride (3d); Typical Procedure using Water Azeotrope:

To a 500-ml, round bottom, 4-necked flask equipped with mechanical stirrer, thermometer, reflux condenser with recycle type water trap[10], and heating mantle are added 3-methylbenzal chloride, (**1d**; 26.3 g, 0.15 mol), carbon tetrachloride (**2a**; 92.4 g, 0.6 mol), 50 % caustic (72 g, 0.9 mol), and *n*-dodecyltrimethylammonium chloride (0.5 g). The trap is filled with carbon tetrachloride and the reaction mixture is heated with stirring to reflux. The reaction is monitored by G.L.C. of withdrawn aliquots. The reaction proceeds smoothly with the reaction mixture becoming more emulsified as reaction nears completion. After 4 h, G. L. C. indicates conversion at 99.7 %. Water removal is fairly constant throughout the reaction, slowing only toward the end; total water removal is 30 ml. The reaction mixture is cooled to 25 °C and the liquid contents removed by suction using a coarse fritted gas dispersion tube as a filter. The remaining solid is washed by adding carbon tetrachloride (2 x 50 ml) and continuing the filtration. Water (~ 100 ml) is added to the crude filtrate and the layers are separated. The organic layer is vacuum treated to remove solvent and the residue distilled by kugelrohr to give **3d** yield: 29.7 g; having G. L. C. assay of 98.5 %.

3-Methylbenzotrichloride (3d); Typical Procedure using Hexachloroethane (2b):

To a 500 ml, round bottom, 4-necked flask equipped with thermometer, mechanical stirrer, reflux condenser, water azeotrope trap[10], and heating mantle are added 3-methylbenzal chloride (**1d**; 36.2 g, 0.207 mol), hexachloroethane (**2b**; 53.9 g, 0.228 mol), 50 % caustic (66.3 g, 0.828 mol), *n*-dodecyltrimethylammonium chloride (0.7 g), and tetrachloroethylene (207 g) as solvent. The mixture is stirred and heated to reflux under sufficient vacuum to produce reflux at 87–92 °C. After 1 h, water (20.3 ml) has been removed. At this time a withdrawn aliquot indicates 93 % conversion by G.L.C. The mixture is refluxed an additional hour and more water (10.5 ml) is removed from the reaction. At this point, G.L.C. indicates 99.6 % conversion of **1d**. After cooling to room temperature, water (150 ml) is added and hydrogen chloride gas passed through to give an acidic aqueous layer. The organic layer is separated, solvent removed under vacuum on a rotary evaporator, the residue distilled in a kugelrohr (80–90 °C/0.6 torr) to give product assaying at 97.2 %; yield: 36.7 g.

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