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Chloromethylation with Chloromethyl Methyl Ether and 60%-Fuming Sulfuric Acid. A Simple Synthesis of Some Nitropolymethylbenzyl Chlorides and Dihalopolymethylbenzyl Chlorides[1]

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A common method to introduce chloromethyl group directly into aromatic nucleus is to treat an aromatic compound with formaldehyde and hydrogen chloride in the presence of a Lewis acid catalyst like zinc chloride.[2] However, nitropolymethylbenzenes and dibromopolymethylbenzenes were found to remain mostly unchanged in the attempted chloromethylation according to the ordinary procedure. The presence of the three or four activating methyl groups was not sufficient to counterbalance the deactivating effect of a nitro or two halogen atoms. The reported procedures[3] for the chloromethylation of deactivated aromatic systems generally requires a quite long reaction time to obtain a moderate yield. The use of stronger catalyst led to the extensive resinification of the substrate as well as the partial migration of bromine atom.

An excellent result of chloromethylation was obtained by dissolving these deactivated aromatic compounds in an excess of chloromethyl methyl ether and adding dropwise with shaking 60%-fuming sulfuric acid. The active reaction immediately took place. After standing for some minutes, the dark brown mixture was diluted with water to precipitate the desired benzyl chloride in good yield. Neither charring nor polymerization was observed under these conditions. The use of a large excess of chloromethyl methyl ether (bp 55—60°C) prevents the temperature of the system from rising too much and thus the reaction from going too far to form polymeric products. This modification also suppresses the formation of undesirable diarylmethane derivatives, which are often a major product in the chloromethylation of deactivated aromatic compounds under drastic conditions.[4]

With increasing amounts of fuming sulfuric acid and extended reaction time, or with the use of smaller amounts of chloromethyl methyl ether, the reaction proceeded very vigorously and the second chloromethylation giving bis(chloromethyl)benzenes as well as the condensation leading to polymeric substances became a prominent process. Owing to poor solubility and high melting point, bischloromethylated products readily separated as a crystalline mass from the hot reaction mixture.

In contrast to the case of lower alkyl homologs, the action of nitrating agent upon tri- or tetramethylbenzyl chlorides usually gives a complicated mixture of side-chain substituted products.[5] Thus, the present method provides the most simple direct route for the highly alkylated nitrobenzyl chlorides in high state of purity. Nine benzyl chlorides and four bis(chloromethyl)benzenes were prepared from nitro and dihalo derivatives of some polymethylbenzenes, and their physical properties are summarized in Table 1.

Experimental

Melting points were determined with a hot stage and are uncorrected. IR spectra were recorded on Nujol mulls with a Jasco DS-402G spectrophotometer and only prominent peaks are given. NMR spectra were determined in carbon tetrachloride solutions (TMS as internal standard) at 60 MHz with a JEOL JNM-3H 60 spectrometer. A commercial chloromethyl methyl ether of ordinary grade was used without purification.

2,5-Dibromo-3,6-dimethylbenzyl Chloride. 2,5-Dibromo-*p*-xylene (10 g) was dissolved in chloromethyl methyl ether (20 g) and 60%-fuming sulfuric acid (*ca.* 8—9 g) was added carefully with stirring. The dark hot mixture was stood for some minutes and then diluted with water. The oily precipitate soon solidified, which was collected by filtration, washed, and dissolved into a mixture of methylene chloride and ligroin. The solution was dried over anhydrous calcium chloride, and removal

1) The Reaction of Polysubstituted Aromatics. Part XIX; Part XVIII; H. Suzuki, *Nippon Kagaku Zasshi*, **91**, 484 (1970).

2) R. C. Fuson and C. H. McKeever, "Organic Reactions," Vol. 1, John Wiley & Sons. Inc., New York (1942), p. 63.

3) a) L. Wals and W. Th. Nauta, *Rec. Trav. Chim. Pays-Bas*, **87**, 65 (1968);b) V. M. Berezovskii, V. A. Kurdyukova and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **21**, 1163,1269 (1951).

4) T. Matsukawa, T. Matsuno and K. Shirakawa, *Yakugaku Zasshi*, **63**, 1 (1943).

5) *Cf.* H. Suzuki and K. Nakamura, This Bulletin, **43**, 477 (1970), line 51 on the right column.

Table 1. Physical properties of some polysubstituted benzyl chlorides and fully substituted bis(chloromethyl)benzenes

Compound	Mp or bp*1 (°C)	NMR spectra (τ) ArH	CH_2	CH_3	IR spectra (cm^{-1})*2	Elementary analysis Calcd	Found	Yield (%)
Benzyl Chlorides								
5,6-Dibromo-2,3-dimethyl-	118—120	2.55	5.11	7.58(1)*3 7.68(1)	723, 748, 873 934, 1019, 1174 1200, 1259	C: 34.60% H: 2.90	34.62% 3.17	72
2,6-Dibromo-3,5-dimethyl-*4	123—125 (162—163/ 8 mmHg)	2.81	4.89	7.46(2)	749, 871, 903 948, 984, 1033 1045, 1258, 1303	C: 34.60% H: 2.90	34.51% 2.92	58
2,5-Dibromo-3,6-dimethyl-	94—96 (154—156/ 6 mmHg)	2.50	5.09	7.33(1) 7.50(1)	746, 872, 920 953, 1015, 1114 1168, 1261	C: 34.60% H: 2.90	34.62% 2.97	63
3,5-Dichloro-2,4,6-trimethyl-	104—106		5.35	7.44(2) 7.52(1)	718, 796, 886 1012, 1175, 1255	C: 50.55% H: 4.67	50.63% 4.82	—
5,6-Dichloro-2,3,4-trimethyl-	95—97		5.22	7.56(1) 7.60(1) 7.72(1)	686, 908, 942 1208, 1260	C: 50.55% H: 4.67	50.47% 4.87	72
3-Nitro-2,4,6-trimethyl-	61—62	3.02	5.39	7.53(1) 7.66(1) 7.72(1)	686, 793, 839 873, 1034, 1186 1256, 1519, 1610	C: 56.20% H: 5.66	55.91% 5.70	75
6-Nitro-2,3,4,5-tetramethyl-	123—125		5.51	7.53(1) 7.63(2) 7.76(1)	688, 727, 828 846, 1074, 1255 1300, 1524	C: 58.02% H: 6.15	57.79% 6.15	73
5-Nitro-2,3,4,6-tetramethyl-	119—120		5.27	7.47(1) 7.58(2) 7.67(1)	706, 835, 853 1228, 1261, 1523	C: 58.02% H: 6.15	58.25% 6.26	58
4-Nitro-2,3,5,6-tetramethyl-	112—113		5.35	7.57(2) 7.79(2)	711, 842, 1023 1225, 1258, 1270 1298, 1532	C: 58.02% H: 6.15	57.93% 6.22	66
*Bis(chloromethyl)benzenes*5								
5,6-Dibromo-2,3-dimethyl-1,4-	217—219		5.04	7.52(2)	731, 887, 909 943, 1155, 1202 1258	C: 33.28% H: 2.79	33.15% 2.85	74
3,5-Dibromo-2,6-dimethyl-1,4-	208—210		4.89 5.28	7.39(2)	732, 809, 879 998, 1165, 1255	C: 33.28% H: 2.79	33.01% 2.77	51
2,5-Dibromo-3,6-dimethyl-1,4-	213—215		5.06	7.33(2)	710, 730, 838 928, 1010, 1128 1189, 1262	C: 33.28% H: 2.79	32.71% 2.83	66
5-Nitro-2,4,6-trimethyl-1,3-	168—169		5.05	7.66(3)	699, 726, 828 856, 1027, 1255 1253, 1266	C: 50.39% H: 5.00	50.54% 4.85	88

*1 Bp in parentheses.
*2 Principal peaks in the regions, 650—1350 and 1500—2000 cm^{-1}.
*3 Numerals in parentheses refer to the number of methyl groups.
*4 The appearance of a methylene proton peak at lower field and of a ring proton peak at higher field than those of the two isomers favors this orientation over the alternative one, 2,6-dimethyl-3,5-dibromobenzyl chloride.
*5 NMR spectra were determined in deuteriochloroform solutions.

of the solvent, followed by fractional distillation under reduced pressure gave the unchanged starting material (2.9 g) at 110—112°C/7 mmHg and the chloride (5.3 g, 63%) at 154—156°C/6 mmHg. Crystallization of the latter fraction from light petroleum gave white fine needles, mp 94—96°C (lit,[3a] 96—97°C).

When a warm solution of dibromo-*p*-xylene (5 g) in chloromethyl methyl ether (5 g) was treated with 60%-fuming sulfuric acid (*ca.* 4—5 g), the reaction proceeded with vigorous evolution of heat and the mixture soon turned into a black crystalline mass. The product was washed with water, dissolved into a mixture of methylene chloride and ligroin, and freed from the colored polymeric substances through chromatography on a short alumina column. Removal of the solvent, followed by recrystallization of the product (4.5 g, 66%) from chloroform gave **1,4-bis(chloromethyl)-2,5-dibromo-3,6-dimethylbenzene** as colorless fine needles, mp 213—215°C. It sublimes on heating.

5,6-Dichloro-2,3,4-trimethylbenzyl Chloride. 4,5-Dichloro-1,2,3-trimethylbenzene (1 g) was dissolved in chloromethyl methyl ether (3 g) and 60%-fuming sulfuric acid (*ca.* 3 g) was carefully added with shaking. The mixture became dark brown and the active reaction immediately started. After the end of the reaction, the mixture was diluted with water and the precipitate

was collected by filtration, washed, and chromatographed on a short alumina column using a mixture of light petroleum and methylene chloride as eluant. Evaporation of the solvent from the eluate gave colorless prisms (0.9 g, 72%), mp 95—97°C.

3-Nitro-2,4,6-trimethylbenzyl Chloride. Nitromesitylene (3 g) was dissolved in chloromethyl methyl ether (3 g), to which was added dropwise and with frequent shaking 60%-fuming sulfuric acid (*ca.* 2—3 g). After the cease of the active reaction, the mixture was quenched with water. Working up as above, followed by crystallization from light petroleum gave colorless prisms, mp 61—62°C. Yield, 2.9 g (75%).

When a further amount (*ca.* 2—3 g) of fuming sulfuric acid was added to the above mixture, a vigorous exothermal reaction followed and the content soon solidified to a dark crystalline mass, which was washed with water, taken up into hot benzene, and decolorized through chromatography on a short alumina column. Evaporation of the solvent from the eluate gave **2,4-bis(chloromethyl)-6-nitro-1,3,5-trimethylbenzene** (4.2 g, 88%) as colorless prisms, mp 168—169°C.