COMMUNICATIONS

Synthetic Methods and Reactions. X[1]. 1-Chloro-4-chloro(bromo)methoxybutane and 1,4-Bis-[chloro(bromo)methoxy]butane: New Convenient Halomethylating Agents

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Since the discovery of the chloromethylation reaction by Grassi-Cristaldi and Maselli[2], a variety of formaldehyde derivatives such as aqueous formalin solutions, paraformaldehyde, or trioxane were found to be capable of producing chloromethylated derivatives in the presence of hydrogen chloride and a suitable catalyst[3]. Similarly chloromethyl ethers, particularly bis-chloromethyl and chloromethyl methyl ethers which are effective chloromethylating agents in non-aqueous solutions, gained wide-spread use[3]. However, recent realization of the carcinogenic properties of these volatile chloromethyl ethers puts serious restrictions on their use.

We wish to report to have now found in 1-chloro-4-chloro(bromo)methoxybutane and 1,4-bis[chloro(bromo)methoxy]butane, respectively, extremely effective new chloro(bromo)methylating agents of wide utility. At the same time the substantially decreased volatility of these reagents decrease the danger associated with the use of more volatile chloromethyl ethers.

Results of the tin(IV) chloride-catalyzed chloromethylation of benzene and methylbenzenes as well as the zinc bromide-catalyzed bromomethylation of the same arenes are summarized in the Table (yields of isolated halomethylarenes are given).

Both 1,4-bis[halomethoxy]butanes and 1-chloro-4-halomethoxybutanes in their Friedel-Crafts type reactions show selectivities characteristic of a strongly electrophilic reagent. Competitive tin(IV) chloride-catalyzed chloromethylation of toluene and benzene with 1,4-bis[chloromethoxy]butane, for example, gives a rate ratio $k_T:k_B = 22$ with an isomer distribution of 43% *ortho*, 5% *meta*, and 52% *para* chloromethyltoluene. Both substrate and positional selectivity can be effected by the reaction conditions (such as catalyst and its concentration) which change the nature of the haloalkylating agent.

Preparations and some typical examples of halomethylation reactions with these reagents are given below.

1,4-Bis[halomethoxy]butane:
A mixture of paraformaldehyde (120 g) and 1,4-butandiol (180 g) cooled in a cold water bath was saturated with anhydrous hydrogen halide for 6 h. On being allowed to stand, the mixture separated into 2 layers. The lower layer, after separation, was dried with magnesium sulfate and distilled under vacuum to give the product.

1,4-Bis[chloromethoxy]butane; yield: 200 g (54%); b.p. 110°/9 torr.

$C_6H_{12}Cl_2O_2$	calc.	C 38.50	H 6.41	Cl 37.96
(187)	found	38.39	6.43	38.10

1,4-Bis[bromomethoxy]butane; yield: 300 g (54%); b.p. 140–143°/12 torr.

$C_6H_{12}Br_2O_2$	calc.	C 26.08	H 4.34	Br 57.97
(276)	found	26.89	4.28	58.10

1-Chloro-4-halomethoxybutane:
4-Halo-1-butanol (0.5 mol) was mixed with paraformaldehyde (20 g). Into the well-stirred mixture at 20–30°, dry hydrogen halide was introduced (with occasional ice bath cooling to regulate the temperature) until a clear solution was obtained. Subsequent work up involved treatment with saturated sodium chloride solution, separation of the organic layer, drying over anhydrous magnesium sulfate, and vacuum distillation to give the product.

1-Chloro-4-chloromethoxybutane; yield: 47%; b.p. 70°/5 torr

$C_5H_{10}Cl_2O$	calc.	C 38.21	H 6.36	Cl 45.22
(157)	found	38.36	6.30	45.40

1-Chloro-4-bromomethoxybutane; yield: 49%; b.p. 94°/5 torr.

$C_5H_{10}BrClO$	calc.	C 29.74	H 4.96	Cl 17.61	Br 39.70
(201.5)	found	29.80	5.03	17.78	40.02

Halomethylation of Arenes; General Procedure:
An arene (0.5 mol) was allowed to react with 1,4-bis[halomethoxy]-butane or 1-chloro-4-halomethoxybutane (0.1 mol) in the presence of zinc bromide or tin(IV) chloride (0.1 mol), generally at 60–65° for 3 h. The reaction mixture was then allowed to cool, quenched with water, washed, dried, and worked up in the usual manner. Halomethylarenes were analyzed by G.L.C. as well as N.M.R. and I.R. spectroscopy, also by comparing with authentic samples of the corresponding pure halomethylarenes.

1-Chloro-4-halomethoxybutanes and 1,4-bis[halomethoxy]-butanes in their Friedel-Crafts halomethylation reactions act, due to strong oxygen participation in the developing carbocationic substituting agents, as incipient halomethyltetrahydrofuranonium ions, i. e. reactive Meerwein type oxonium ions. Tetrahydrofuran formed as by-product of the reaction complexes the Lewis acid catalyst and greatly diminishes formation of diarylmethane by-products.

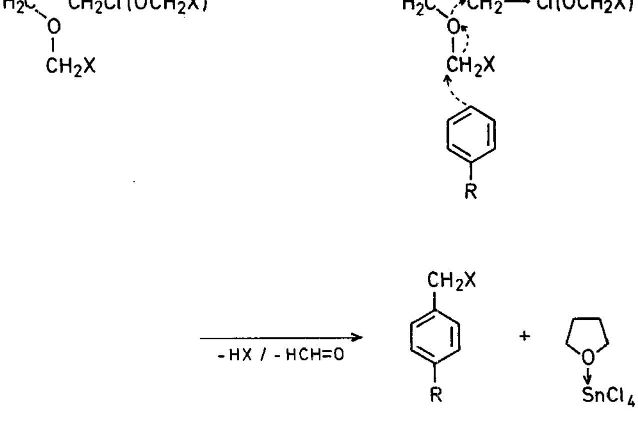
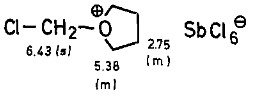


Table. Halomethylation of Benzene and Methylbenzenes

Arene	Yield (%) of Chloromethylarene using:		Yield (%) of Bromomethylarene using:	
	1,4-Bis[chloromethoxy]butane	1-Chloro-4-chloromethoxybutane	1,4-Bis[bromomethoxy]butane	1-Chloro-4-bromomethoxybutane
Benzene	43	50	66	63
Toluene	53	44	85	78
p-Xylene	41	41	58	58
m-Xylene	51	55	95	96
Mesitylene	60	70	75	70

The existence of the corresponding chloromethyltetrahydrofuranonium ion was proven by preparing this novel oxonium ion from its respective precursors under stable ion conditions in sulfur dioxide solutions with antimony(V) chloride at −50°. The ^{1}H-N.M.R. signals are as shown below.



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[2] G. Grassi-Cristaldi, M. Maselli, *Gazz. Chim. Ital.* **20**, 477 (1898).

[3] For a review see: G. A. Olah, W. S. Tolgyesi in "*Friedel-Crafts and Related Reactions*" G. A. Olah, Ed., Vol. II, Wiley Interscience Publishers, New York, 1964, pp. 659–784.