An Improved Synthesis of Bis(chloromethoxy)methane

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In connection with studies of a low-temperature modification of the Prins reaction,[1] it was noted that paraformaldehyde reacted with hydrogen chloride, in the presence of an olefin catalyst, to give a 55% yield of bis(chloromethoxy)methane (I). This compound has been observed as a by-product in the synthesis of bis(chloromethyl) ether (II)[2] and the best yields of I which have been reported were obtained from the reaction of paraformaldehyde with thionyl chloride (0–40%) or formalin with gaseous hydrogen chloride (28%).[3] Thus the new synthesis offers a convenient route to this highly reactive compound (I).

Suitable olefin catalysts for the reaction, which do not condense with paraformaldehyde and hydrogen chloride under these conditions, include ethylene, allyl chloride and sulfolene. For example, the addition of only 2 mol % of allyl chloride to a suspension of paraformaldehyde in methylene chloride at −65° gives I and II in a molar ratio of 5.5:1 when hydrogen chloride is passed into the mixture. On the other hand, omission of the olefin catalyst reverses the ratio of products to 1:22. The function of the olefin in controlling the product distribution is catalytic in nature since the unchanged olefin can be recovered from the reaction.

Experimental Section

All melting and boiling points are uncorrected. Glpc analyses were performed using an F & M Model 720 gas chromatograph equipped with a 10-ft 20% Dow-Corning-200 silicone oil on Chromosorb P column operated isothermally at 125°.

Preparation of Bis(chloromethoxy)methane.—Only the most convenient preparatory procedure is given. Other experiments demonstrated the equivalence of ethylene and sulfolene as catalysts. A 1-l. three-necked flask, equipped with a stirrer, low-temperature thermometer, gas dispersion tube, and an exit bubbler, was charged with 200 g (184 g, 6.13 mol) of 92% paraformaldehyde, 11.1 g (0.14 mol) of allyl chloride, and 300 ml of methylene chloride. The flask was cooled in a Dry Ice–acetone bath and hydrogen chloride was passed in through the dispersion tube for 2.5 hr at which time HCl uptake ceased. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature overnight. The organic layer was separated, dried over calcium chloride, and the solvent was removed through a short column. The residue was fractionated under reduced pressure to give 35.8 g (10%) of bis(chloromethyl) ether,[4] bp 44–50° (100 mm), and 162.8 g (55%) of bis(chloromethoxy)methane: bp 56–58° (15 mm); $n^{20}D$ 1.4515 [lit.[2] bp 58–61° (16 mm), $n^{20}D$ 1.4511].

Anal. Calcd for $C_3H_6Cl_2O_2$: C, 24.8; H, 4.1; Cl, 48.9; mw 145. Found: C, 24.8; H, 4.1; Cl, 48.5; mw 144.

Further characterization of bis(chloromethoxy)methane was carried out by preparation of a bisisothiouronium salt. Addition of 65 mmol of bis(chloromethoxy)methane to a warm solution of 130 mmol of thiourea in 200 ml of absolute ethanol gave 16.1 g (83%) of colorless crystals, mp 92–94° dec (from absolute ethanol).

Anal. Calcd for $C_5H_{14}Cl_2N_4O_2S_2$: C, 20.2; H, 4.7; N, 18.9. Found: C, 20.0; H, 5.1; N, 19.2.

The bispyridinium salt was prepared by addition of bis(chloromethoxy)methane to 2 equiv of pyridine in dry ether. After recrystallization from ethyl acetate–absolute ethanol, there was obtained a 56% yield of fluffy, hygroscopic needles, mp 168–170° dec (bath preheated to 140°).

Anal. Calcd for $C_{13}H_{16}Cl_2N_2O_2$: C, 51.4; H, 5.3; N, 9.2. Found: C, 51.7; H, 5.4; N, 9.2.

Registry No.—Bis(chloromethoxy)methane, 15112-21-7; bis(chloromethoxy)methane (bisisothiouronium salt), 18749-94-5; bis(chloromethoxy)methane (bispyridinium salt), 18741-98-5.

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A Synthesis of Amidines from Cyclic Amides

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In a recent article, Weintraub, Oles, and Kalish[1] reported a general synthesis of amidines from amides *via* the isolated intermediate imidate fluoroborates. We would like to report on a general one-step method for the preparation of cyclic amidines from amides in which a solution of the amide and amine in tetrahydrofuran is treated at ice-bath temperature with a tetrahydrofuran–titanium tetrachloride complex. The reaction is in most cases rapid, and work-up affords the desired amidines in good yield. Under these conditions, we found that cyclic amides could be converted into amidines with ammonia, with primary as well as secondary amines.[2]

The reaction appears to be quite general for secondary heterocyclic amides and examples are given for a substituted carbostyril, and for some substituted quinoxalones and 1,4-benzodiazepinones (Tables I and II).

The 4-benzoyl derivatives of the quinoxalones were chosen for amidation since they were readily available, having been prepared in conjunction with other work.[3] It was surprising to note that the benzoyl amides were not converted into benzamidines under these conditions and we have also found that the amidation of 7-chloro-1,3-dihydro-2H-1,4-benzodiazepine-2,5-4(H)-dione with methylamine afforded only the corresponding 2-methylamino-1,4-benzodiazepin-5-one derivative.[4]

Yields were found to vary depending upon the amine chosen. In the case of primary amines, the yields were high (approximately 80–85% after purification) while for ammonia and secondary amines, the yields were lower.

In the case of 7-nitro-substituted 1,4-benzodiazepin-2-one I and methylamine, amidine III was formed in low yield and the major reaction product was the open

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(1) L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968).

(2) W. A. White and H. Weingarten [*ibid.*, **32**, 213 (1967)] have used titanium tetrachloride complexes to form enamines from secondary amines and aldehydes or ketones.

(3) G. F. Field and L. H. Sternbach, *ibid.*, **33**, 4438 (1968).

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