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.

(1) P. R. Stapp, *J. Org. Chem.*, **34**, 479 (1969).
(2) F. S. H. Head, *J. Chem. Soc.*, 2972 (1963).
(3) Y. K. Yur'ev, N. K. Sodoraya, and M. A. Gal'barshtam, *Zh. Obschch. Khim.*, **32**, 259 (1962); *Chem. Abstr.*, **57**, 16535*h* (1962).
(4) S. R. Buc, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 101.

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]

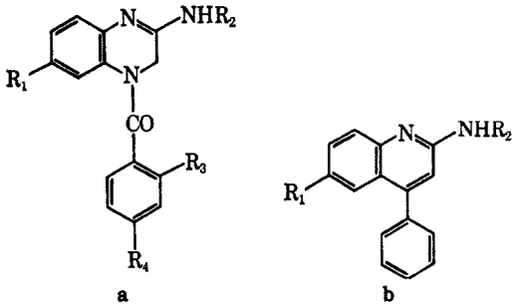
Yields were found to vary depending upon the amine chosen. In the case of primary amines, the yields were high (approximately 80–85% after purification) while for ammonia and secondary amines, the yields were lower.

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

(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).
(4) G. F. Field and L. H. Sternbach, unpublished results.

TABLE I

SUBSTITUTED 4-BENZOYL-2-AMINOQUINOXALINES AND 4-PHENYLQUINOLINES



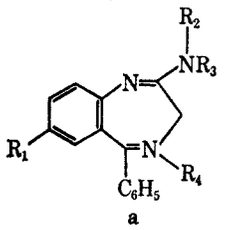
a b

Compd	R_1	R_2	R_3	R_4	Yield, %	Crystd from[a]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
4a[b]	H	CH_3	H	H	71	A	209–219 dec	$C_{16}H_{15}N_3O$	72.45	5.70	72.24	5.45
5a	H	CH_3	Cl	H	76	B/C	184–187	$C_{16}H_{14}ClN_3O$	64.11	4.71	64.26	4.67
6a	H	C_4H_9	Cl	H	33[c]	A/D	225–229	$C_{19}H_{20}ClN_3O \cdot HCl$	60.32	5.60	60.63	5.74
7a	H	CH_3	H	CH_3	79	E/C	186–190	$C_{17}H_{17}N_3O$	73.09	6.13	72.99	6.13
8a	H	CH_3	H	NO_2	85	F	184–187	$C_{16}H_{14}N_4O_3$	61.93	4.55	62.11	4.69
9a[b]	Cl	CH_3	H	H	63	A	225–233 dec	$C_{16}H_{14}ClN_3O$	64.11	4.71	63.92	4.97
10b[b]	NO_2	CH_3			6	A/D	211–215	$C_{16}H_{13}N_3O_2$	68.80	4.69	68.93	4.53

[a] A = ethanol, B = chloroform, C = hexane, D = ether, E = tetrahydrofuran, F = isopropyl alcohol. [b] The starting materials for these compounds are reported in one of the following references: S. Motylewski, *Ber.*, **41**, 800 (1908); S. C. Bell and S. J. Childress, *J. Org. Chem.*, **29**, 506 (1964), and R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964). [c] Isolated as the hydrochloride.

TABLE II

SUBSTITUTED 3H-1,4-BENZODIAZEPINES



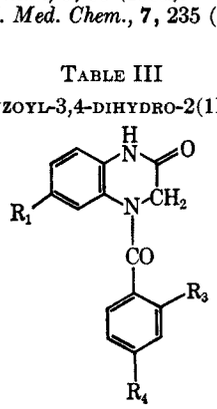
a

Compd[a]	R_1	R_2	R_3	R_4	Yield, %	Crystd from[b]	Mp, °C	Ref[c]	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
11	NO_2	H	CH_3		19	A	225–228		$C_{16}H_{14}N_4O_2$	65.29	4.80	65.26	4.85
12	Cl	H	CH_3		89	B/C	243–248	*d*					
13	Cl	H	CH_3	O	83	A	238–242	*e*					
14	Cl	CH_3	CH_3	O	29	D	205–209	*f*					
15	Cl	H	$CH(CH_3)_2$	O	7.4	D	248–250		$C_{18}H_{18}ClN_3O$	65.95	5.53	66.28	5.69
16	Cl	$-(CH_2)_4-$		O	12	E/C	164–170		$C_{19}H_{18}ClN_3O$	67.88	5.70	67.71	5.54
17	Cl	H	H		16	A	278–283	*e*					

[a] 1,4-Benzodiazepinones used as starting materials are reported by L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963), and L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). [b] A = methanol, B = tetrahydrofuran, C = hexane, D = ethanol, E = dichloromethane, F = ether. [c] References are given for known compounds. [d] S. C. Bell, G. Gochman, and S. J. Childress, *J. Med. Chem.*, **5**, 63 (1962). [e] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961). [f] S. Faber, H. M. Wuest, and R. I. Meltzer, *J. Med. Chem.*, **7**, 235 (1964).

TABLE III

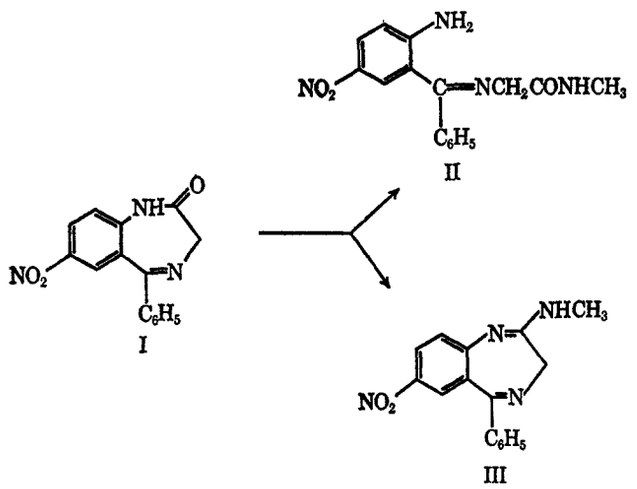
SUBSTITUTED 4-BENZOYL-3,4-DIHYDRO-2(1H)-QUINOXALINONES



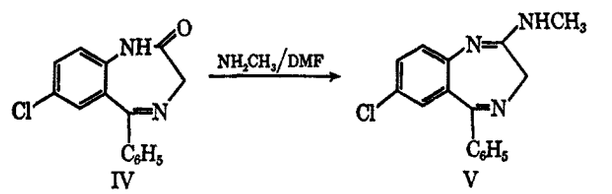
Compd	R_1	R_3	R_4	Yield %	Crystd from[a]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	H	Cl	H	56	B/C	226–229	$C_{15}H_{11}ClN_2O_2$	62.84	3.87	62.95	3.95
2	H	H	CH_3	51	D/F	261–265	$C_{16}H_{14}N_2O_2$	72.16	5.30	72.30	5.44
3	H	H	NO_2	65	D/F	275–278	$C_{15}H_{11}N_3O_4$	60.60	3.73	60.73	3.90

[a] A = ethanol, B = tetrahydrofuran, C = hexane, D = dimethylformamide, E = ether, F = water.

compound II formed by a transamidation reaction (Scheme I).[5]



Amidines could also be prepared directly from some benzodiazepin-2-ones in the absence of the Lewis acid catalyst but in lower yield. Thus a solution of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IV) in dimethylformamide could be converted into 7-chloro-2-methylamino-5-phenyl-1,4-benzodiazepine (V) by treatment with methylamine under pressure. These reactions without the use of titanium



tetrachloride were restricted to compounds which were not substituted in the 7 position with a nitro group. In the case of the 7-nitro compounds the only products isolated (up to 90%) were the open amides of type II.[5]

Experimental Section

Melting points were determined microscopically on a hot stage and are corrected. Where the expected products were known compounds, mixture melting points were determined with authentic samples and infrared spectra were compared in order to confirm the expected structural changes.

Substituted Benzoyl-3,4-dihydroquinoxalin-2-(1H)-ones (Compounds 1–3, Table III).—A suspension of 7.4 g (5 mmol) of crude 3,4-dihydroquinoxalin-2(1H)-one[6] in 100 ml of ether was treated with 5 mmol of the appropriate benzoyl chloride. The mixture was stirred at room temperature for 40 min while 50 ml of 1 *N* sodium hydroxide solution was added in portions large enough to maintain the aqueous phase slightly alkaline. The solids were collected, washed with ether and water, and then dried to give the desired product.

Amidines from Amides (Compounds 4a–9a, 10b, 11–17, Tables I and II).—A solution of 0.0184 mol of the amide in 125 ml of dry tetrahydrofuran was added to a solution of 15 g of the amine in 100 ml of dry tetrahyrofuran. The mixture was contained in a three-necked round-bottomed flask fitted with a stirrer, dropping funnel and Dry Ice condenser. The flask was externally cooled in an ice bath. A tetrahydrofuran–titanium tetrachloride complex prepared by adding 1.8 g (0.01 mol) of titanium tetrachloride to 60 ml of tetrahydrofuran was added slowly (20 min) to the reaction mixture. The resulting mixture was continually stirred and allowed to reach room temperature. After 4 hr or when thin layer chromatography indicated that the reaction was complete, the reaction mixture was treated with 10 ml of water and then filtered. The filtrates were evaporated to dryness, and the residue was dissolved in 500 ml of dichloromethane. The organic solution was washed with 20 ml of dilute ammonium hydroxide, two 100-ml portions of saturated brine solution, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was recrystallized from a mixture of the appropriate solvent to give the amidine.

2-[(2-Amino-5-nitrophenyl)phenylmethylenimino]-N-methylacetamide (II) and 2-Methylamino-7-nitro-5-phenyl-3H-1,4-benzodiazepine (III).—A solution of 5 g (0.0178 mol) of 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one in 150 ml of dry tetrahydrofuran was added to a solution of 10 g of methylamine in 100 ml of dry tetrahydrofuran. The resulting solution was cooled and treated with a solution of 2.4 g (0.017 mol) of titanium tetrachloride in 50 ml of dry benzene. The mixture was allowed to warm to room temperature and stirred overnight. Approximately 10 ml of water was added to decompose excess titanium tetrachloride and the solution was filtered. Solvent was removed and the residue was treated with 50 ml of ethanol. The open amide, compound II,[5] was removed by filtration [4.1 g (74%), mp 190–192°] and the mother liquors were concentrated to yield the other product. Recrystallization from methanol gave 1.0 g (19%) of pure III as prisms.

Registry No.—**1**, 18756-07-5; **2**, 18756-08-6; **3**, 18756-09-7; **4a**, 18756-10-0; **5a**, 18756-11-1; **6a**, 18756-12-2; **7a**, 18756-13-3; **8a**, 18756-14-4; **9a**, 17953-25-2; **10b**, 18756-16-6; **11**, 13677-83-3; **15**, 18756-18-8; **16**, 3712-28-5.

Acknowledgment.—We are indebted to Dr. F. Scheidl and his staff for the microanalyses and to Mr. S. Traiman for the determination of infrared spectra.

(5) We have previously shown [R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967)] that compounds of type I react with amines to give only the transamidation products.

(6) W. H. Perkin and G. C. Riley, *J. Chem. Soc.*, **123**, 2403 (1923).

Acid-Catalyzed Reaction of Isocyanide with a Schiff Base. New and Facile Syntheses of Imidazolidines

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Recently we reported the reaction of alkyl isocyanides with carbonyl compounds in the presence of a Lewis acid catalyst at −78°, in which 1:2 and 2:3 cyclic cooligomers were formed by the opening of the carbon–oxygen double bond and the α,α addition of the isocyanide carbon.[1,2]

The present communication describes the cationic reaction of alkyl isocyanide with the carbon–nitrogen double bond. In the presence of a Lewis acid catalyst, alkyl isocyanide reacts with benzaldehyde N-alkylimine (a Schiff base of aliphatic amine) to produce a derivative of imidazolidine, namely the 1:2 cyclic cooligomer.

Table I illustrates the preparations of some 2,5-diphenylimidazolidines. The structures of the products were clearly established by elemental analysis, molecular weight determination and ir and nmr spectra. As catalyst, an equimolar amount of $AlCl_3$ was required. The 1:1 complexization of $AlCl_3$ with the imidazolidine product probably deactivated a stoichio-

(1) T. Saegusa, N. Taka-ishi, and H. Fujii, *Polymer Lett.*, **5**, 779 (1967).

(2) T. Saegusa, N. Taka-ishi, and H. Fujii, *Tetrahedron*, **24**, 3795 (1968).