N-Monochlorination and N-Monobromination of Carbamates and Carboxamides by Sodium Hypochlorite and Hypobromite [1a]

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Our studies on the chromous chloride promoted addition of *N*-chlorocarbamates to olefins[2] led us to devise a convenient method for the preparation of *N*-monochlorocarbamates in high yield, free from the *N*,*N*-dichloro derivatives. This method was also applied to the preparation of *N*-monochlorocarboxamides and of *N*-monobromocarbamates and -carboxamides needed for the chromous chloride pro- moted addition studies[2c] and some photochemical work.[3] The recent publication of Swern and coworkers[4] on the preparation of ethyl and methyl *N*-chlorocarbamates prompted us to report our results.

The method consists of the formation of the sodium salt of the monohalo derivative followed by careful neutralization. The salt is prepared by treating a slight excess (0.5- 2%) of the amide with sodium hypochlorite or hypobro- mite5 (5-6% solution) at ca. 0° (eq 1).

$$ZCONH_2 + NaOX \longrightarrow ZCONXNa + H_2O \quad (1)$$

$$ZCONXNa + H_3O^+ \longrightarrow ZCONHX + H_2O + Na^+ \quad (2)$$

After the addition of methylene chloride, dilute (1-2 *N*) sulfuric acid is added slowly until the sodium salt (eq 2) and the excess sodium hydroxyde are neutralized (an excess of acid must be avoid- ed). The solvent is removed at reduced pressure at 20-25°. The results are recorded in Table I.

N-**Chlorocarbamates**. The yields of the N-monochloro- carbamates 1-6[7] are excellent (86-98%) with the purity of the crude reaction products being satisfactory for use in reactions without further purification. The method is thus very efficient.

N-**Chlorocarboxamides**. The N-monochlorocarboxam- ides 8-16 were obtained in good yield, the purity of the crude reaction products being satisfactory for use in reactions. The method was not successful with the sterically hindered 2,2-dimethylpropionamide nor was it convenient for the preparation of the water-soluble *N*-chloroformamide (7). Beckwith and Goodrich[8] have prepared *N*-monochlorocarboxamides in good yield by the bromine-catalyzed reaction of primary carboxamides with *tert*-butyl hypo- chlorite.

N-**Bromocarbamates**. We have studied the bromination of ethyl, 2,2,2-trichloroethyl, and benzyl carbamates (**17**, **18**, and **19**) and, to our knowledge, this is the first reported preparation of N-bromocarbamates. It appears that the disproportionation of the *N*- bromocarbamates **17** and **18** (eq 3) does occur to a significant extent ($K_{eq.} \approx 0.08$ and 0.1, respectively, at ca. 37°).

$$2ROCONHBr \rightleftharpoons ROCONH_2 + ROCONBr_2 \quad (3)$$

Indeed, although both the io- dometric and neutralization analyses of the crude *N*-bromocarbamates **17** and **18** indicated a purity of l00%, their ir and nmr spectra showed the presence of nonbrominated carbamate. A careful examination of the integration for the various protons of the nmr spectra indicated clearly the presence of a third product, most probably the *N*,*N*- dibromocarbamate, the aliphatic protons of which had the same chemical shift as those of the *N*- monobromocarbamate, the molar ratio being approximately equal to that of the non- brominated carbamate (see Experimental Section for details).

The crude benzyl *N*-bromocarbamate (**19**) was found to decompose rapidly under reduced pressure, as evidenced by continuous evolution of gas within the oily product, the loss of active bromine, and reduction in weight of material (the yield and active bromine content reported in **Table I** refer to a crude product kept under reduced pressure for 10 min after evaporation to dryness). The crude *N*-bromocarbamates **17**, **18**, and **19** could be stored in the refrigerator for several days without any loss of active bromine.

Table I
Preparation of *N*-Haloamides

N-Halo amide	(No.)	Yield,[a] %	Purity, % of theory: Iodometric	Purity, % of theory: Neutralization	% starting amide[b]	Mp, °C: Crude	Mp, °C: Purified[c]	Mp, °C: Lit.	Registry no.
$CH_3CH_2OCONHCl$	(1)	98	99	100		17–19		9[d]	51-79-6
$CH_3CH_2CH_2OCONHCl$	(2)	86	98			Oil			
$CH_3OCH_2CH_2OCONHCl$	(3)	93	96			Oil			
$ClCH_2CH_2OCONHCl$	(4)	91	96	98		53–55	56.5–57.5	42[e]	
$Cl_3CCH_2OCONHCl$	(5)	92	98	99		61–63	63–63.5		
$C_6H_5CH_2OCONHCl$	(6)	98	98	99		27–29			621-84-1
$HCONHCl$	(7)	50	86			Oil			75-12-7
$CH_3CONHCl$	(8)	70[f]	100				109–110	110[g]	60-35-5
$CH_3CH_2CONHCl$	(9)	78	94	95		Oil			79-05-0
$ClCH_2CH_2CONHCl$	(10)	88	96			69–74	74–74.5		5875-24-1
$BrCH_2CONHCl$	(11)	80	101			67–68	68.5–69		683-57-8
$ClCH_2CONHCl$	(12)	83	98	100		66–68	68–69.5		79-07-2
$FCH_2CONHCl$	(13)	79	101			98.5–100	100.5–101		640-19-7
$Cl_2CHCONHCl$	(14)	81	101			70–71	70–71		683-72-7
$Cl_3CCONHCl$	(15)	85	99			120–122	122–123		594-65-0
$F_3CCONHCl$	(16)	63	99			Oil[h]			354-38-1
$CH_3CH_2OCONHBr$	(17)	85	100	101	~10	Oil			
$Cl_3CCH_2OCONHBr$	(18)	92	100	101	~13	Oil			
$C_6H_5CH_2OCONHBr$	(19)	79	83		~15	Oil			
$CH_3CH_2CONHBr$	(20)	87	100	100		74–75	76–77		
$CH_3CH_2CH_2CH_2CONHBr$	(21)	80	94	96		Oil			626-97-1
$ClCH_2CH_2CONHBr$	(22)	89	97			87–88	89–90		
$BrCH_2CONHBr$	(23)	78	99	100		103–104.5			
$ClCH_2CONHBr$	(24)	79	98	98	~4	74–76	77–78	75[i]	
$FCH_2CONHBr$	(25)	65	99		~6	82–83	83.5–84		
$Cl_2CHCONHBr$	(26)	57	83		~18	73–77	94.5–95.5	96[i]	
$Cl_3CCONHBr$	(27)	45	77			95–97[j]		125[i]	
$F_3CCONHBr$	(28)	19	52					62[i]	

[a] Of active halogen compound before purification, based on the amide. [b] Starting amide present in the crude product as determined by nmr. [c] By recrystallization from methylene chloride or methylene chloride–hexane mixtures (iodometric purity >99%). [d] D. Saika and D. Swern, *J. Org. Chem.*, **33**, 4548 (1968). [e] P. Chabrier, *C. R. Acad. Sci.*, **214**, 353 (1942). [f] Of recrystallized product. [g] K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 986 (1927). [h] Crystalline in the refrigerator. [i] Reference 10. [j] The active bromine content was not significantly increased by recrystallization: 82%, mp 96–98°.

***N*-Bromocarboxamides**. Kergomard[6] has prepared *N*- bromoacetamide by adding a sodium hypobromite solution[5] to a solution of acetamide in acetic acid. *N*-Bromo- benzamides have been prepared by using bromine in aqueous alkaline solution with subsequent rapid acidification using acetic acid[9] Our procedure gave better yields for the preparation of N-bromopropionamide (**20**) and *N*-bromopentanamide (**21**) and we have used it successfully also to prepare the N-bromocarboxamides 22-25. The method is not convenient for the N-bromination of the dichloro-, trichloro-, and trifluoroacetamides (26, 27, and 28), the yield and the purity of the crude product decreasing in the order 26 > 27 > 28. Park, et al[10] has used bromine and silver oxide in anhydrous trifluoroacetic acid to prepare *N*- bromo-α-haloacetamides in good yield and Beebe and Wolfe[11] have obtained *N*- bromotrifluoroacetamide (**26**) in high yield using acetyl hypobromite.

In comparison to the N-bromocarbamates, the N-bromo- carboxamides have much less tendency to undergo dispro- portionation into the carboxamide and the *N*,*N*-dibromo derivative. In the ir and nmr spectra of the pure (>99%) samples of the *N*-bromo-α-haloacetamides **23**-**26**, there is a small but detectable amount (2-4%) of nonbrominated carboxamide.[12]

Experimental Section [14]

Melting points were determined on a Buchi apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectro- photometer, Model 257. Nmr spectra were determined on a Varian A-60 spectrometer using TMS as internal standard. The sodium hypochlorite solution was obtained from Anachemia Chemicals Ltd.[15] and contained between 5.0 and 5.7% active chlorine (0.67- 0.77 mmol/ml) and excess sodium hydroxide (-0.15 mmol/ml). The carbamates and carboxamides, unless specified otherwise, were obtained from Aldrich Chemical Co.

Iodometric Analyses. The samples (about 1 mmol accurately weighed) were dissolved in 50 ml of a 50350 mixture of methanol and water. An excess of potassium iodide dissolved in water (5 ml) was added followed by sulfuric acid (1 ml of a 4 N solution). The solution was then titrated with 0.1 N sodium thiosulfate.

Neutralization Analyses. The samples (about 1 mmol accu- rately weighed) were dissolved in a 10:40 mixture of methanol and water. The solution was cooled in an ice bath and titrated with 0.1 N NaOH using a pH meter.

Preparation of *n*-Propyl, 2-Methoxyethyl, 2-Chloroethyl, and 2,2,2-Trichloroethyl Carbamate (29,30, 31, and 32). These compounds were prepared from the corresponding alcohols accord- ing to the procedure described by Loev and Korrnendy:[16] **29**, 65% yield (crude), mp 49-52° (lit.[17] mp 52.5°); 30, 55% yield (crude), mp 44-46° (lit.ls mp 46.8°); 31,33% yield (crude), mp 71-73° (lit.[18] mp 77O); 32, 40% yield (recrystallized), mp 63-64°, ir ($CHCl_3$) 3540,3430,2940,1750,1585,1385,1325,1115, and 1050 cm^{-1}, nmr ($CDCl_3$) δ 4.70 (s,2 H), 5.62 (broad s, 2 H).
Anal. Calcd for $C_3H_4Cl_3N0_2$: Cl,56.25. Found C1,54.88.

2,2,2-Trichloroacetamide (31) was prepared by treating the acid chloride with concentrated NH40H: 76% yield; mp 141-142.5° (lit.[20] mp 137°).

Typical Procedure for the Monochlorination of Carba- mates and Carboxamides. Preparation of Ethyl *N*-Chlorocar- bamate (1). To 35.6 g (400 mmol) of ethyl carbamate in a 2-1. coni- cal flask cooled in an ice bath was added 545 ml of yellow NaOCl solution (0.73 mmol/ml, 398 mmol). The mixture was stirred until it became colorless (15 min). Methylene chloride (300 ml) was added. Then 241 ml (482 mequiv) of 2 *N* Na_2S0_4 was added dropwise with vigorous stirring. The addition took 2 hr. The organic phase was decanted and the aqueous layer was extracted with methylene chloride (4 X 100 ml). The combined extracts were dried (Na_2S0_4) and the solvent was removed on the rotatory evap- orator at ca. 25° to yield 49.0 g of 1 as a pale yellow oil which crys- tallized upon cooling (see Table I): ir (CCl_4) 3400, 3300 (broad), 1770, 1730, 1700, 1380, 1330, 1310, 1200, and 1060 cm^{-l}; nmr ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 4.28 (q, *J* = 7 Hz, 2 H), and 6.63 (broad s, 1 H).

The other *N*-chloroamides listed in Table I were prepared in the same way but on a smaller scale (from 10 to 100 mmol), the excess of amide varying from 1 to 2%. With amides very insoluble in water, a larger reaction time was needed (up to 30 min) with a few milliliters of methylene chloride being added to speed up the reaction. When working on a 10-40-mmol scale, acidifications were carried out with 1 *N* H_2SO_4. Because of the higher solubility of *N*- chlorocarboxamides in water, four to ten extractions with methylene chloride were performed. The ir spectra (CCl_4) of the *N*-chlorocarbamates 2-6 are quite similar to that of ethyl N-chlorocarbamate (1) and they all show a band in the following regions: 3400 (free NH), 3200-3180 (broad, associated NH), 1770 (C=O), 1740- 1730 (C-0), 1710-1700 (C-O), 1410-1380, 1350-1330, 1200 (ester), and 1080-1000 cm^{-l} (ester).

Typical Procedure for the Monobromination of Carbamates and Carboxamides. Preparation of Ethyl *N*-Bromocarbamate (17). To 4.43 g (43 mmol) of NaBr was added 53.4 ml of NaOCl solution (0.75 mmol/ml, 40 mmol). The mixture was stirred for 15 min at room temperature. The deep yellow hypobromite so- lution was cooled in an ice bath and 3.60 g (40.4 mmol) of ethyl carbamate was added. The reaction mixture was stirred until it be- came pale yellow (almost colorless). Methylene chloride (50 ml) was added followed by the dropwise addition of 41 ml (47 mequiv) of 1.15 *N* H_2SO_4 with vigorous stirring. The addition took 1.5 hr. The reddish organic phase was decanted and the aqueous layer was extracted with methylene chloride (3 X 15 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed on the rotatory evaporator to yield 5.71 g of 17 as a yellow oil (see Table I): ir (CCl_4) 3400, 3200 (broad), 1720 (broad, strong), 1415, 1375, 1330, 1220, 1190 (shoulder), and 1065 cm^{-l}, and weak bands at 3500 and 1590 cm^{-l} due to the presence of ethyl carbamate; nmr (CCl_4) 6 1.28 (t, *J* = 7 Hz, carbamate CH_3) and 1.33 (t, *J* = 7 Hz, N-bromo- and N,N-dibromocarbamate CH_2), 4.17 (q, *J* = 7 Hz, carbamate CH_2) and 4.28 (q, J = 7 Hz, N-bromo- and N,N-dibro- mocarbamate CHz), 5.41 (broad s, carbamate NHz), and 6.55 (broad s, N-bromocarbamate NH) with the following relative inte- grations-7.7 (the two overlapping triplets), 5.0 (the two overlapping quadruplets), 1.0, and 1.6.

The other N-bromoamides listed in Table I were prepared in ex- actly the same way except that for water-insoluble amides, longer reaction time was needed (up to 30 min) for the reaction with NaOBr. The ir and nmr absorptions of the crude N-bromocarba-mates 18 and 19 are given below.

Crude **18**: ir ($CHCl_3$) 3400, 3200 (broad), 1745 (broad, strong), 1390, 1325, 1230, 1185, 1110, and 1045, and weak bands at 3530 and 1585 cm-l (nonbrominated carbamate); nmr (cc14) 6 4.75 (s,

carbamate CH_2), 4.81 (s, N-bromo- and *N*,*N*-dibromocarbamate CH_2), 5.60 (broad s, carbamate NH_2), 6.40 (broad s, *N*-bromocarbamate NH) with a relative integration of 1.9:8.7:1.0:4.6.

Crude **19**: ir (cc14) 3400, 3240 (broad), 1720 (broad, strong), 1395, 1325, 1210, 1180 (shoulder), and 1050, and weaker bands at 3500 and 1590 cm^{-1} (nonbrominated Carbamate); nmr (CCl4) 6 5.05 (8, carbamate CH_2), 5.85 (s, N-bromocarbamate CH_2), 5.35 (broad s, carbamate NH_2), 6.48 (broad s, *N*-bromocarbamate NH), 7.30 and 7.33 (s, aromatic H of the carbamate and the *N*-bromo derivative) with a relative integration of 1.0:2.3:1.1:1.2:7.7.

Registry No.-1, 16844-21-6; 2, 52175-97-0; 3, 52175-98-1; 4, 30830-84-3; 5,30830-85-4; 6,30830-47-8; 7,52175-99-2; 8,598-49-2; 9, 36448-95-0; 10, 52176-00-8; 11, 35070-76-9; 12, 35070-77-0; 13, 35077-08-8; 14, 35077-09-9; 15, 35077-10-2; 16, 52176-01-9; 17, 52176-02-0; 18, 52176-03-1; 19, 52176-04-2; 20, 3699-17-0; 21, 3699-20-5; 22, 52176-05-3; 23, 52176-06-4; 24, 35077-11-3; 25, 36015-63-1; 26, 52259-82-2; 27, 35077-12-4; 28, 359-45-5; 29, 627- 12-3; 30, 1616-88-2; 31, 2114-18-3; 32, 107-69-7; sodium hypochlo- rite, 7681-52-9; sodium hypobromite, 13824-96-9.

Supplementary Material Available. Characteristic ir absorp- tions (position of the NH and C==0 bands) of the *N*-chlorocarboxamides 9-16 and of the *N*-bromocarboxamides 20-26, and the nmr absorptions of these N-haloamides and of the *N*-chlorocarbamates 2-6 will appear in Table II (ir) and Table III (nrnr) following these pages in the microfilm edition of this volume of the journal. Photo-copies of the supplementary material from this paper only or mi- crofiche (105 X 148 mm, 24X reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, refer- ring to code number JOC-74-3136.

References and Notes

(I) (a) Supported by a grant tom the National Research Councli of Canada; (b) Arts Council of Canada Predoctoral Fellow, 1969-1971; (c) NRCC Postdoctoral Fellow, 1968-1970; (d) France-Quebec Predoctoral Fel- low, 1970-1972.
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