Formation of *N*-Substituted Trichloroacetamides from Amines and Hexachloroacetone

By **Clive Bew**, (Mrs.) **Virginia Otero de Joshi**, **Jim Gray**, **Perry T. Kaye**, and **G. Denis Meakins**,* Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY

Procedures are described for converting primary amines into their well-crystalline trichloroacetyl-derivatives by treatment with hexachloroacetone under mild conditions. Although secondary aromatic *N*-methylamines are unaffected by hexachloroacetone, saturated heterocyclic amines react vigorously.

A mechanistic study using 2-amino-4-t-butylthiazole showed that the reaction is first order in hexachloroacetone, second order in amine, and base-catalysed; there is no appreciable kinetic isotope (H/D) effect nor accumulation of intermediates during the reaction. A sequence which accommodates these results is suggested.

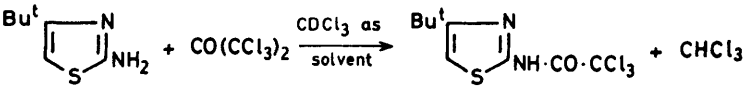
N-SUBSTITUTED trichloroacetamides can be prepared by treating primary and secondary amines with trichloroacetyl chloride [1] and primary amines with ethyl trichloroacetate,[2] and, in low yield, by rearrangement of alkyl acetimidates.[3] Some *N*-trichloroacetylphenylamines have also been obtained from the amines using aqueous hexachloroacetone;[4] this ketone (in dimethyl sulphoxide) has been used for the trichloroacetylation of dipeptides.[5] The present work stemmed from the observation that 4-methyl- and 5-ethyl-2-trichloroacetamidothiazole, originally prepared using trichloroacetyl chloride,[6] are formed readily from the 2-aminothiazoles and hexachloroacetone. A mechanistic investigation was carried out (largely with 4-t-butyl-2-aminothiazole) to establish the main features of the reaction between primary amines and hexachloroacetone. This led to the development of general procedures which were then applied to series of 2-aminothiazoles, and aliphatic, heterocyclic, and aromatic amines.

Table 1 summarises the mechanistic study. In the reaction shown the trichloroacetyl derivative is formed cleanly; deuteriochloroform was used as solvent so that the disappearance of the amine and the appearance of both the trichloroacetyl derivative and chloroform could be followed by ^{1}H n.m.r. spectrometry. Kinetic runs, in which the ratios of the reactants were varied (within the

TABLE 1

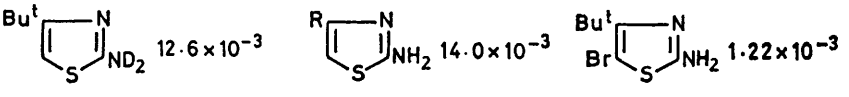
Mechanism of the amine–hexachloroacetone reaction

The amines are numbered as in Table 2. Values of k (kg^2 mol^{-2} s^{-1}) are at 306 K.

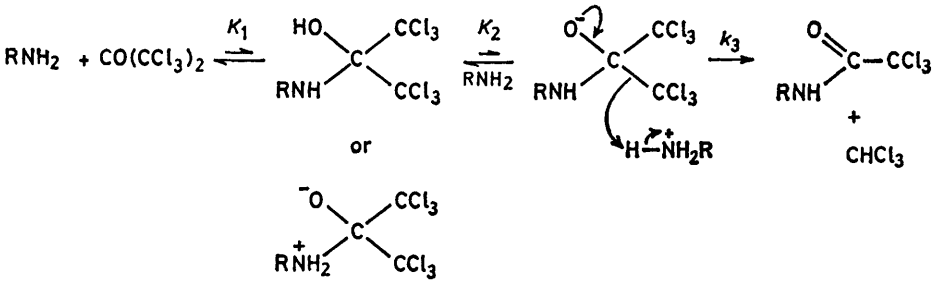


(3)

(i) Rate = k[amine]^2[CO(CCl$_3$)$_2$] $k = 12.8 \times 10^{-3}$ $E_a = 41 \pm 5$ kJ mol^{-1}.
(ii) Catalysis by base. (iii) No appreciable accumulation of intermediates.
(iv) k Values:



(5) R = 1-adamantyl (9)



Rate = $K_1K_2k_3$[RNH$_2$]^2[CO(CCl$_3$)$_2$]

range 0.12—0.48 molal for each reactant), established that the reaction is first order in hexachloroacetone but second order in amine. Rate constants at four temperatures and hence the energy of activation were determined. Evidence for base catalysis was found in the marked acceleration caused by adding the non-nucleophilic base 1,8-bisdimethylaminonaphthalene ('proton sponge'); however, since examination of the *N,N*-dideuterio-amine showed that there is no significant kinetic isotope effect the base catalysis is unlikely to operate in a rate-determining or rate-limiting step. By examining the i.r. C=O bands of hexachloroacetone and the product it was shown that there is a direct relationship between the utilisation of the ketone and the formation of the trichloroacetamide: thus there is no appreciable build-up of intermediates during the reaction. The reaction of 4-(1-adamantyl)-2-aminothiazole was also third-order, and the rate constant with this amine is similar to that of the 4-t-butyl analogue. Examination of the 5-bromo-4-t-butyl-2-aminothiazole was less complete, but established that electron withdrawal in the substrate markedly reduces the rate of reaction.

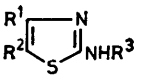
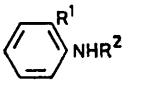
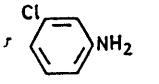
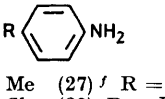
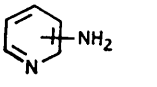
In the sequence shown in Table 1, which appears to be the simplest to satisfy the foregoing results, two fast, reversible steps are followed by the irreversible rate-limiting step involving loss of the trichloromethyl group (possibly with concomitant protonation by the conjugate acid of the amine). 'Proton sponge' will act by replacing the primary amine, a weaker base, in the second stage and greatly increasing the value of K_2, while the 5-bromo-substituent will reduce the nucleophilicity of the amine and hence the value of K_1.

The results obtained with series of amines are collected in Table 2. In the simplest procedure (A) a solution of the amine and a slight excess of hexachloroacetone in chloroform is heated, or kept at 20 °C for a longer time. Procedure (B), which is preferable for very reactive amines, involves adding the ketone to a solution of the amine in carbon tetrachloride at −10 °C, keeping the solution at 20 °C, and hydrolysing the excess of hexachloroacetone during the work-up. Procedure (C), in which 'proton sponge' is used to catalyse the reaction, is rapid but expensive. The trichloroacetamides produced are crystalline and may be useful for characterising liquid amines. All but three of the primary amines studied reacted satisfactorily under one or more of the procedures. The exceptions are phenylamines containing electron-withdrawing substituents; of the chlorophenylamines only the *ortho*-isomer failed to react, but with the strongly deactivating nitro-group reaction is inhibited even in the *para*-compound. While the two secondary *N*-methylamines (4) and (21) could not be converted into their trichloroacetyl derivatives using hexachloroacetone, the secondary heterocyclic amines (17)—(19) reacted vigorously. The difference between the groups probably arises from the influence of amine structure on the first step (*i.e.* the feature represented as K_1 in the primary amine sequence of Table 1). In the *N*-methylamines, but not in the saturated heterocyclic

TABLE 2

The reaction $>NH + CO(CCl_3)_2 \longrightarrow >N{\cdot}CO{\cdot}CCl_3$

The references are to amines which have previously been converted into their trichloroacetyl derivatives; Table 7 shows the characterisation of new trichloroacetamides. The procedures are described in the Experimental section. Yields refer to purified products.

Amines [a]				Procedure(s) and yield(s) (%)		
						
	R^1	R^2	R^3			
(1) [b]	Me	H	H	A, 77		
(2)	Pr	H	H	A, 71		
(3)	Bu^t	H	H	A, 78		
(4)	Bu^t	H	Me	A, 0	B, 0	C, 0
(5)	1-adamantyl	H	H	A, 79		
(6)	H	Me	H	A, 71		
(7) [b]	H	Et	H	A, 73	B, 71	
(8)	Me	Et	H	A, 81		
(9)	Bu^t	Br	H	A, 25		C, 69
(10)	Bu^t	CO_2Et	H			C, 73
(11)	CO_2Et	Et	H	A, 74	B, 72	
$R\text{-}NH_2$						
(12) [c] R = Pr^i (13) [c] R = Bu^t (14) [c] R = $PhCH_2$				A + B, 70—75		
(15) [c] R = Et (16) [c] R = Pr				B, 70—80		
(17)  (18) 						
(19) 						
						
	R^1	R^2				
(20) [d]	H	H		A, 75	B, 74	
(21) [e]	H	Me		A, 0	B, 0	
(22)	Me	H		A, 76		
(23)	Cl	H		A, 0	B, 0	
(24)	Br	H			B, 0	
(25) [f] 				A, 68		
						
(26) [f] R = Me (27) [f] R = OMe (28) [g] R = Cl (29) R = Br (30) [e] R = NO_2				A + B, 69—78 A, 0		
						
(31) *o*-NH_2 (32) *m*-NH_2 (33) *p*-NH_2				A, 70—76		

[a] Apart from compounds (9) (Experimental section), and (10) and (11) (A. Barton, S. P. Breukelman, P. T. Kaye, G. D. Meakins, and D. J. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 1982, 159) all the amines are well known. [b] Ref. 6. [c] Ref. 3. [e] F. A. Berti and L. Marioziti, *Arch. Pharm.*, 1952, **285**, 372. [d] Ref. 1. [f] Ref. 4. [g] H. Erlenmeyer, L. Hensfeld, and B. Prijs, *Helv. Chim. Acta*, 1955, **38**, 1291.

substrates, a transition state involving electrophilic attack will cause greater repulsion between the groups already attached to the nitrogen atom. The successful preparations of the trichloroacetyl derivatives of the 2-aminothiazole (4) and [1] of the phenylamines (21) and (30) using trichloroacetyl chloride confirm the higher reactivity of this reagent as compared with hexachloroacetone.

EXPERIMENTAL

Work Summarised in Table 1.—$CDCl_3$ was used as solvent. ^1H N.m.r. spectra were obtained with a Brüker 90 MHz spectrometer. Probe temperatures were checked against a calibrated thermometer and are judged to be accurate to ±1 K. I.r. spectra were obtained with a Perkin-Elmer 521 instrument. Kinetic data, full details of which are recorded elsewhere, were processed by the standard methods set out in ref. 8. For ^1H n.m.r. work a solution consisting of weighed amounts of the amine and $CDCl_3$ was added to an n.m.r. tube containing a weighed amount of hexachloroacetone. The tube was shaken and transferred quickly into the spectrometer's probe, which had been set at the required temperature. The integrals of signals from the amine, the trichloroacetyl derivative [*e.g.* the Bu^t signals of amine (3) and its derivative at τ 8.77 and 8.67, respectively], and $CHCl_3$ were examined at known time intervals.

TABLE 3

Molal concentrations used in the reactions of the amine (3) with hexachloroacetone

Run	1	2	3	4	5	6
Amine (3)	0.129	0.120	0.228	9.477	0.119	0.122
Hexachloroacetone	0.128	0.119	0.130	0.120	0.282	0.476

TABLE 4

Orders of reaction

Order in hexachloroacetone:

Time (min)	Runs 1 and 5	Runs 1 and 6	Runs 2 and 5	Runs 2 and 6
20	0.96	0.96	0.96	0.96
40	0.97	1.06	0.87	0.97
60	1.03	0.89	0.99	0.85

Order in amine (3):

Time (min)	Runs 1 and 3	Runs 1 and 4	Runs 2 and 3	Runs 2 and 4
20	2.21	2.02	1.92	1.89
30	2.17	2.01	1.94	1.92
60	2.03		1.85	

Six runs were carried out at 306 K on the amine (3) using solutions of the molal concentrations shown in Table 3. Results from pairs of experiments at three selected times were used to evaluate the order of the reaction with respect to the reactants (Table 4). Rate constants were calculated at selected times for each run. For example, run 1 gave the values shown in Table 5.

A solution of the amine (3) (0.75 g) in MeOD (8 ml) was stirred in a sealed flask for 1.5 h at 20 °C, and then evaporated (oil pump). Repetition of the MeOD treatment and evaporation gave 4-t-butyl-2-(dideuterioamino)thiazole, m.p. 99—101 °C, *m/z* 158 (M^+, 33%) and 142 (100), estimated by ^1H n.m.r. to contain a total of less than 10% of the di- and mono-protioamines. This amine was used in place of 4-t-butylthiazole (3) in runs 1 and 3 described previously for the protio-amine. The concentrations of the dideuterio-amine and the trichloracetyl derivative were followed. The amounts of $CHCl_3$ formed were less than 10% (on a molar basis) of those of the trichloroacetyl derivatives. These experiments and corresponding ones with the amines (5) and (9) gave the *k* values shown in Table 1.

TABLE 5

Rate constants at selected times

Time (min)	3.5	6	10	16	34	48
$k/10^{-3}$ kg^2 mol^{-2} s^{-1}	12.8	12.7	12.4	12.2	12.9	12.9

Repetitions of run 1 with amine (3) at different temperatures gave the *k* values shown in Table 6.

TABLE 6

Rate constants at selected temperatures

Temp. (K)	306	313	320	328
$k/10^3$ kg^2 mol^{-2} s^{-1}	12.8	19.8	26.4	380

A solution containing the amine (3) (0.058 molal), hexachloroacetone (0.056 molal), and ' proton sponge ' (0.113 molal) was prepared from components previously cooled, and then mixed, at 268 K. The solution was examined at a probe temperature of 273 K. The first spectrum, obtained after 2 min, indicated that the reaction was complete.

Equal volumes of 0.1M-solutions of the amine (3) and hexachloroacetone were mixed at 303 K, and the i.r. spectrum of the resulting solution was examined at 303 K. The intensities of the C=O bands due to hexachloroacetone (1 782 and 1 753 cm^{-1}) and the trichloroacetyl derivative (1 725 cm^{-1}) were measured at intervals and compared with the extinction coefficients of the bands (obtained by examining the components separately). After 45, 60, and 90 min (when substantial quantities of hexachloroacetone were still present), the amounts of hexachloroacetone consumed and trichloroacetyl derivative produced were equal within the accuracy of the i.r. measurements (±8%).

2-Amino-5-bromo-4-t-butylthiazole (9).—Br_2 (0.33 ml) was added during 5 min to a stirred solution of 2-amino-4-t-butylthiazole [9] (3) (1 g) in dioxan (5 ml) at 20 °C. The precipitate, 5-bromo-4-t-butylthiazol-2-ylammonium bromide, was collected, washed with Et_2O, and dissolved in H_2O (10 ml) and Et_2O (25 ml). After the addition of saturated aq. $NaHCO_3$ the Et_2O layer was worked up to give *2-amino-5-bromo-4-t-butylthiazole* (0.95 g), m.p. 93—94 °C (from $CHCl_3$–light petroleum) (Found: C, 35.9; H, 4.7; Br, 33.7; N, 11.7. $C_7H_{11}BrN_2S$ requires C, 35.8; H, 4.7; Br, 34.0; N, 11.9%), τ 8.60 (9 H, s, Bu^t).

4-t-Butyl-2-(N-methyltrichloroacetamido)thiazole.—CCl_3COCl (0.35 ml) was added during 10 min to a stirred solution of 4-t-butyl-2-methylaminothiazole [9] (4) (0.5 g) and Et_3N (0.42 ml) in dry Et_2O (5 ml) at 5 °C. The resulting slurry was diluted with Et_2O (10 ml) and stirred at 20 °C for 12 h. H_2O (25 ml) was added, and the Et_2O layer was worked up to give the *amide* (0.71 g) (Table 7).

Preparation of N-*Substituted Trichloroacetamides*.—Three procedures are described in the following sections. Procedure (*A*) is the simplest, and the one used most widely. Procedure (*B*) is longer, but is preferable for very reactive amines, and, since the excess of hexachloroacetone is destroyed, for amines giving products which are to be distilled. Most of the trichloroacetamides have m.p.s > 50 °C; these were purified by crystallisation from MeOH or MeOH–H_2O, or by sublimation at 0.1 mmHg. The few

TABLE 7

Characterisation of new trichloroacetamides

Amine	Product	M.p. (°C)	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(2)	4-Propyl-2-trichloroacetamidothiazole	106—107	33.6	3.0	9.5	$C_8H_9Cl_3N_2OS$	33.4	3.15	9.7
(3)	4-t-Butyl-2-trichloroacetamidothiazole	135—136	36.0	3.6	9.2	$C_9H_{11}Cl_3N_2OS$	35.8	3.7	9.3
(4)	4-t-Butyl-2-(*N*-methyltrichloroacetamido)thiazole	79—81	37.3	4.1	9.0	$C_{10}H_{13}Cl_3N_2OS$	38.05	4.15	8.9
(5)	4-(1-Adamantyl)-2-trichloroacetamidothiazole	197—198	47.75	4.9	7.2	$C_{15}H_{17}Cl_3N_2OS$	47.4	4.5	7.4
(6)	5-Methyl-2-trichloroacetamidothiazole	227—228	27.6	2.2	10.7	$C_6H_5Cl_3N_2OS$	27.8	1.9	10.6
(8)	5-Ethyl-4-methyl-2-trichloroacetamidothiazole	218—219	33.5	3.15	9.7	$C_8H_9Cl_3N_2OS$	33.4	3.15	9.7
(9)	4-t-Butyl-5-bromo-2-trichloroacetamidothiazole	93—95	28.7	2.8	7.6	$C_9H_{10}BrCl_3NOS$	28.4	2.65	7.4
(10)	Ethyl 4-t-butyl-2-trichloroacetamidothiazole-5-carboxylate	*ca.* 270 †	38.55	4.2	7.7	$C_{12}H_{15}Cl_3N_2O_3S$	38.6	4.05	7.5
(11)	Ethyl 5-ethyl-2-trichloroacetamidothiazole-4-carboxylate	111—113	34.6	3.0	8.4	$C_{10}H_{11}Cl_3N_2O_3S$	34.75	3.2	8.1
(17)	*N*-Trichloroacetylpyrrolidine	29—30	33.5	3.7	6.5	$C_6H_8Cl_3NO$	33.3	3.7	6.5
(18)	*N*-Trichloroacetylpiperidine	35—37	36.6	4.3	6.3	$C_7H_{10}Cl_3NO$	36.5	4.4	6.1
(19)	*N*-Trichloroacetylmorpholine	81—82	31.1	3.7	6.0	$C_6H_8Cl_3NO_2$	31.0	3.5	6.0
(22)	2-Methyl-*N*-trichloroacetylphenylamine	93—94	42.7	3.25	6.0	$C_9H_8Cl_3NO_2$	42.8	3.2	5.55
(29)	4-Bromo-*N*-trichloroacetylphenylamine	128—130	30.3	1.4	4.5	$C_8H_5BrCl_3NO$	30.3	1.6	4.4
(31)	2-Trichloroacetamidopyridine	100—102	35.2	2.1	11.6	$C_7H_5Cl_3N_2O$	35.1	2.1	11.7
(32)	3-Trichloroacetamidopyridine	152—154	35.1	2.0	11.8	$C_7H_5Cl_3N_2O$	35.1	2.1	11.7
(33)	4-Trichloroacetamidopyridine	144—146	35.3	2.0	11.9	$C_7H_5Cl_3N_2O$	35.1	2.1	11.7

† Decomp.

with m.p.s <50 °C were purified by distillation at *ca.* 0.5 mmHg. Procedure (*C*) was investigated with only a few amines.

(*A*) Hexachloroacetone (b.p. 198—201 °C at 760 mmHg; 5 g, 0.019 mol) was added during 10 min to a stirred solution of the amine (0.016 mol) in $CHCl_3$ (15 ml) at 20 °C. The solution was either boiled under reflux for 3 h and then cooled, or kept at 20 °C for 3 d. Most of the products were obtained at this stage as crystalline precipitates, which were collected and purified. In those cases where little or no insoluble material was present the solutions were concentrated at 100 °C and 20 mmHg and the residues were purified.

(*B*) Hexachloroacetone (5 g) was added during 20 min to a stirred solution of the amine (0.016 mol) in CCl_4 (20 ml) at -10 °C, and the solution was kept at 20 °C for 2 d. Saturated aq. $NaHCO_3$ (25 ml) was added, and the mixture was stirred at 20 °C for 12 h. Extraction with Et_2O gave the product.

(*C*) A solution of 1,8-bisdimethylaminonaphthalene (0.86 g, 0.004 mol) in $CHCl_3$ (10 ml) was added to a stirred solution of the substituted 2-aminothiazole (0.002 mol) and hexachloroacetone (0.53 g, 0.002 mol) in $CHCl_3$ (10 ml) at 20 °C. After 1 h the solution was washed with 3M-HCl (2 × 25 ml) and worked up to give the product.

[1/1446 *Received*, 16*th September*, 1981]

REFERENCES

1 L. Spiegel and P. Spiegel, *Ber.*, 1907, **40**, 1730.
2 M. M. Joullie and A. R. Day, *J. Am. Chem. Soc.*, 1954, **76**, 2990.
3 F. Cramer and N. Hennrich, *Chem. Ber.*, 1961, **94**, 976.
4 V. P. Rudavskii and I. G. Khaskin, *Ukr. Khim. Zh.*, 1967, **33**, 391.
5 C. A. Panetta and T. G. Casanova, *J. Org. Chem.*, 1970, **35**, 2423.
6 T. N. Birkinshaw, S. A. Harkin, P. T. Kaye, G. D. Meakins, and A. K. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1982, preceding paper.
7 P. T. Kaye, D.Phil. Thesis, Oxford, 1979.
8 J. F. Bunnet, ' Investigation of Rates and Mechanisms of Reactions. Part I,' ed. E. S. Lewis, Wiley, New York, 1974.
9 J. B. Dickey, E. B. Towne, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 499.