1,3-Acyl Migration in Carbonic Acid Derivatives—Synthesis of *S*-Polyhalogenoalkyl *N*-Acyl-*N*-aryl(alkyl)thiocarbamates

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Aryl(alkyl)iminochloromethyl polyhalogenoalkyl sulphides react with carboxylic acids to give *S*-polyhalogenoalkyl *N*-acyl-*N*-aryl(alkyl)thiocarbamates, which have not been synthesized by other routes. By analogy with known 1,3 rearrangements, the reaction appears to involve a nucleophilic substitution followed by a new type of 1,3-acyl migration. Similarly, with sodium azide 1-methyl- and 1-phenyl-5-trichloromethylthiotetrazoles are also obtained.

In view of the known antifungal activity of *S*-polyhalogenoalkylthioimides [1] and the herbicidal action of *NN*-dialkylthiocarbamates,[2] we wished to prepare *NN*-disubstituted *S*-polyhalogenoalkylthiocarbamates for biological tests. So far, only *N*-monoalkyl-substituted compounds of this type are known and these show some activity against fungi, insects, and bacteria.[3]

However, no obvious route to the desired products was available since the required intermediates, polyhalogenoalkylthiols, are neither stable nor known.[4]

In addition, many attempts to alkylate the *N*-monosubstituted *S*-trichloromethyl thiocarbamates failed, which resulted in decomposition of the intermediate anion to alkyl isocyanates with release of the 'good leaving group' $SCCl_3$.[5]

Thus, a different route, *via* a 1,3 rearrangement was investigated. Among the 1,3 (from O to N) thermal rearrangements, the Chapman rearrangement of imidates is the most well known example; [6] both aryl and alkyl groups are known to migrate in this and in a few other structurally related rearrangements of imidocarbonates, thioimidocarbonates, and isoureas.[7] Acyl groups are also known to migrate in other types of 1,3 thermal rearrangements, the most investigated being the isoimide–imide rearrangement studied by Curtin and Miller.[8]

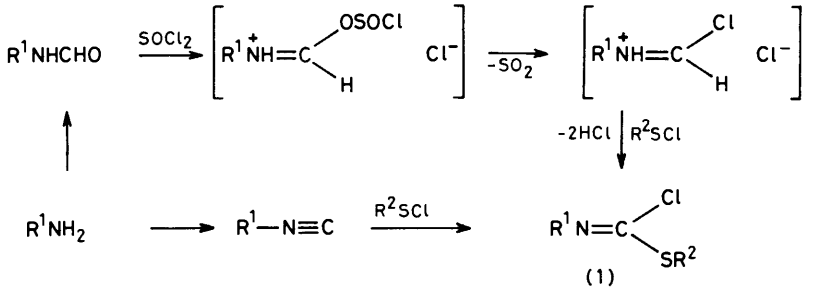
While our attempts to obtain alkyl migration in polyhalogenoalkyl iminomethyl sulphides failed (see below), we were successful in carrying out the corresponding acyl migration, which led to the new *S*-polyhalogenoalkyl *N*-acyl-*N*-aryl(alkyl)thiocarbamates. To our knowledge, no other reports of acyl migration in iminocarbonic acid derivatives are in the literature.

RESULTS AND DISCUSSION

Aryliminochloromethyl sulphides (1) can easily be prepared by addition of sulphenyl chlorides to isonitriles or, more generally, to the intermediate products, prepared *in situ* from the corresponding formamides in the presence of thionyl chloride (Scheme 1).[9]

Various polyhalogenated sulphenyl chlorides, of which perchloromethylthiol is the most readily available, are known and easily handled intermediates,[10] suitable precursors to compounds (1) with R^2 = polyhalogenated alkyl. As for the imidoyl chlorides, the chlorine atom in compounds (1) was easily displaced by nucleophiles, such as alcohols and amines, but the resulting products were usually found to be unstable; only a few amines, as the nucleophiles, gave *S*-polyhalogenoalkyl isothioureas that could be isolated.[5]

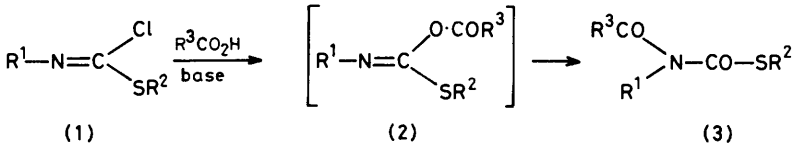
To the contrary, when the substrates (1) were treated with a carboxylic acid, the new compounds (3) were obtained as stable products (Scheme 2). Two main methods were used to carry out this reaction.



SCHEME 1 R^1 is aryl or alkyl; R^2 is polyhalogenoalkyl

Method A.—A benzene (or light petroleum) solution of the substrate (1) and an aqueous solution of the alkaline carboxylate were refluxed, under vigorous stirring, for 3 h in the presence of a small amount of a phase-transfer catalyst (p.t.c.). This method was finally adopted for compounds in which R^1 was a phenyl, substituted phenyl, or cyclohexyl group.

Method B.—A benzene solution of compound (1) and the carboxylic acid were refluxed for 3 h in the presence of triethylamine. This appeared to be the best method when R^1 was methyl. The yields, which have not been optimized, were in the range of 20—70%, as shown in Table 1. Physical and analytical data for the compounds (3a)—(3v) are shown in Table 2.



(1) (2) (3)

SCHEME 2

The most suitable conditions for different R groups needs comment; the choice is the result of a compromise between the need to avoid hydrolysis by water and to provide a successful attack by the carboxylate nucleophile. Under the conditions of method A, the substrates (1) (R^1 = Me) were found to be completely transformed into the corresponding *N*-methylthiocarbamates. This was not totally unexpected in view of the known hydrolysis of the $SCCl_3$ derivative [equation (1)].[3]

$$MeN{=}C(Cl)SCCl_3 + H_2O \longrightarrow MeNHC(O)SCCl_3 + HCl \quad (1)$$

Consequently, method B proved the most suitable for the *N*-methyl substrates. An alternative method which showed the importance of avoiding water, was found by treating compound (1) (R^1 = Me, R^2 = CCl_3), dissolved in benzene, with solid sodium benzoate, which remained mainly out of phase, in the presence of a phase-transfer catalyst. These modified conditions of method A also successfully gave the homologous product with R^1 = Bu^n [compound (3e)].

With respect to the substrates derived from alkylamines, the *N*-aryl intermediates are less susceptible to nucleophilic attack and were recovered almost unchanged under the conditions of method B.

Attempts were also made to carry out the reaction in polar solvents, such as dimethylformamide, dimethyl sulphoxide, ethanol, and acetone, with sodium benzoate (at least partially dissolved) as the nucleophile. Under these conditions compounds (1) (R^1 = aryl) disappeared quickly when heated, but no rearranged products (3) were isolated.

Consequently, p.t.c. was the method of choice when starting from the *N*-aryl substrates. Hydrolysis under method A was minor, as shown by the low amounts of *N*-aryl-thiocarbamates formed, and the hydrolysis of the final rearranged products (3) (R^1 = aryl) could be contained by carrying out the reaction for <3 h.

Besides providing the nucleophile with suitable strength for chlorine displacement, p.t.c. conditions are probably also successful inasmuch as they subtract the chlorine ion, as soon as it is displaced, from the organic phase. Thus, this ion cannot compete for the acyl displacement [path (*a*)] with the nitrogen atom [path (*b*)], involved in the rearrangement shown in the Figure.

When compound (1) (R^1 = Ph, R^2 = CCl_3) was treated

TABLE 1

$R^1N{=}CClSR^2 + R^3CO_2H \longrightarrow R^3CON(R^1)COSR^2 + HCl$
(1) (3)

Compounds (3)	R^1	R^2	R^3	Method	Yield (%)
a	Me	CCl_3	CH_2Cl	B	49
b	Me	CCl_3	Ph	B,A [a]	35
c	Me	CCl_3	C_6H_4Me-*o*	B	40
d	Me	CCl_3	C_6H_4OPh-*m*	B	24 [b]
e	Bu^n	CCl_3	Ph	A [a]	45
f	Cyclohexyl	CCl_3	Ph	A	26 [c]
g	Ph	CCl_3	CH_2Cl	A	52 [b]
h	Ph	CCl_3	CH_2OMe	A	27 [b]
i	Ph	CCl_3	CCl_3	A	32
j	Ph	CCl_3	CH_2Ph	A	25 [b]
k	Ph	CCl_3	CH_2OPh	A	21
l	Ph	CCl_3	$CH_2OC_6H_4Cl$-*p*	A	39
m	Ph	CCl_3	Ph	A	58
n	Ph	$CHCl_2$	Ph	A	39
o	Ph	$CFCl_2$	Ph	A	40
p	Ph	CCl_2CHCl_2	Ph	A	61
q	Ph	CCl_3	C_6H_4Me-*o*	A	26 [b]
r	Ph	CCl_3	2-furyl	A	70
s	C_6H_4Me-*o*	CCl_3	Ph	A	34 [b]
t	C_6H_4Me-*o*	CCl_3	C_6H_4Cl-*p*	A	57
u	C_6H_4OMe-*p*	CCl_3	Ph	A	20 [c]
v	$C_6H_3Me_2$-*o*,*o*	CCl_3	Ph	A	26 [c]

[a] Method A modified (see Experimental section). [b] Compound purified by column chromatography. [c] From the amine *via* isonitrile; yield is calculated on the amine.

with benzoic acid in the presence of triethylamine (method B), the very small extent of reaction observed was found to give mainly *N*-phenylthiocarbamate and benzoic anhydride, clearly derived from benzoyl chloride, conceivably formed through displacement (*a*) in the Figure.

made with the known isoimide–imide rearrangement,[8] as far as the migrating group is concerned, and with some Chapman-like rearrangements (only quoted as unpublished results in ref. 7) as far as the nature of the substrates (carbonic acid derivatives) is concerned.

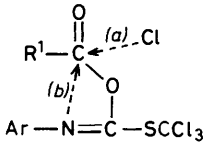
If our assumption is correct, the rearrangement step

TABLE 2

Physical and analytical data for compounds (3a)—(3v)

Compd.		Found (%)						Requires (%)				
(3)	M.p. (°C)	C	H	Cl	N	S	Formula	C	H	Cl	N	S
a	125—126	20.65	1.8	49.35	4.95	11.55	$C_5H_5Cl_4NO_2S$	21.08	1.77	49.77	4.91	11.25
b	126—127	38.65	2.6	33.6	4.5	10.0	$C_{10}H_8Cl_3NO_2S$	38.43	2.58	34.02	4.48	10.26
c	107—108	40.25	3.1	32.05	4.2	9.55	$C_{11}H_{10}Cl_3NO_2S$	40.45	3.09	32.56	4.29	9.82
d	oil	47.85	2.95	26.75	3.5	7.75	$C_{16}H_{12}Cl_3NO_2S$	47.49	2.99	26.28	3.46	7.92
e	oil	43.8	3.9	29.55	3.9	9.0	$C_{13}H_{14}Cl_3NO_2S$	44.03	3.98	29.99	3.95	9.04
f	77—78	47.05	4.2	27.6	3.6	8.25	$C_{15}H_{16}Cl_3NO_2S$	47.33	4.24	27.94	3.68	8.42
g	129—130	34.9	2.1	40.35	4.0	9.05	$C_{10}H_7Cl_4NO_2S$	34.61	2.03	40.86	4.03	9.24
h	114—115	38.25	2.85	30.85	4.15	9.15	$C_{11}H_{10}Cl_3NO_2S$	38.56	2.94	31.04	4.09	9.36
i	126—127	29.05	1.25	50.75	3.3	7.95	$C_{10}H_5Cl_6NO_2S$	28.88	1.21	51.14	3.37	7.71
j	105—106	49.2	3.15	26.9	3.5	8.4	$C_{16}H_{12}Cl_3NO_2S$	49.45	3.11	27.36	3.60	8.24
k	123—124	47.75	2.7	25.9	3.55	8.05	$C_{16}H_{12}Cl_3NO_3S$	47.49	2.74	26.28	3.46	7.92
l	125—126	43.55	2.6	31.95	3.25	7.45	$C_{16}H_{11}Cl_4NO_3S$	43.77	2.53	32.29	3.19	7.30
m	102—103	48.75	2.6	28.9	3.75	8.45	$C_{15}H_{10}Cl_3NO_2S$	48.09	2.69	28.39	3.74	8.56
n	110—111	53.3	3.35	20.7	4.2	9.75	$C_{15}H_{11}Cl_2NO_2S$	53.59	3.30	21.09	4.16	9.54
o	85—86	50.5	2.8	19.55	3.85	8.95	$C_{15}H_{10}Cl_2FNO_2S$	50.87	2.85	20.02	3.95	9.05
p	116—117	45.35	2.6	33.3	3.35	7.5	$C_{16}H_{11}Cl_4NO_2S$	45.42	2.62	33.51	3.31	7.58
q	92—93	49.15	3.05	26.9	3.65	8.35	$C_{16}H_{12}Cl_3NO_2S$	49.45	3.11	27.36	3.60	8.24
r	133—134	45.55	2.3	28.85	3.75	8.95	$C_{13}H_8Cl_3NO_2S$	45.29	2.21	29.17	3.84	8.80
s	oil	49.05	3.2	26.8	3.5	8.05	$C_{16}H_{12}Cl_3NO_2S$	49.45	3.11	27.36	3.60	8.24
t	96—97	45.95	2.55	32.9	3.35	7.5	$C_{16}H_{11}Cl_4NO_2S$	45.64	2.63	33.67	3.32	7.61
u	133—134	47.85	2.7	25.8	3.4	8.05	$C_{16}H_{12}Cl_3NO_3S$	47.49	2.74	26.28	3.46	7.92
v	130—130.5	50.35	3.45	25.95	3.5	7.8	$C_{17}H_{14}Cl_3NO_2S$	50.71	3.50	26.41	3.48	7.96

From the practical point of view, the p.t.c. conditions of method A resemble the role played by silver ions during isoimide synthesis from imidoyl chlorides, when



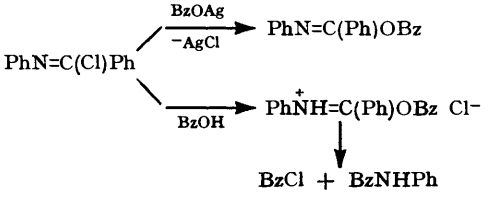
FIGURE

silver carboxylate is preferentially used with respect to the free acid to prevent decomposition to acyl chloride and amides (Scheme 3).[11]

The mechanism of the reaction presented herein was not studied in detail and, so far, no attempt has been made to isolate the supposed intermediates (2). The assumption of the sequence (1) ⟶ (2) ⟶ (3) is based only on the obvious nucleophilic displacement of chlorine

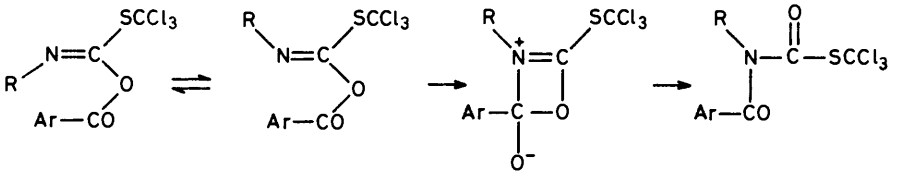
requires a fast pre-equilibrium between the possible *anti* and *syn* forms of the intermediates (2), only the latter being suitable for the supposed four-membered cyclic transition state (Scheme 4).[7,8]

Support for the mechanism analogous with imidoyl chlorides also comes from the reaction observed when N_3^-



SCHEME 3

was used as the nucleophile. The azido-group is known to react with imidoyl chlorides to give the corresponding tetrazoles by a N to N rearrangement following the

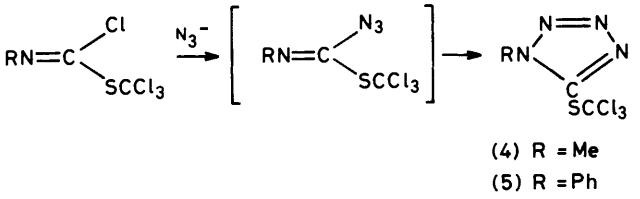


SCHEME 4

by the carboxylate ion, followed by what we believe, by analogy, to be a novel type of rearrangement, which involves a 1,3-acyl migration from oxygen to nitrogen in the assumed intermediates (2). Comparisons can be

chlorine displacement.[11] When this reaction was tried with our substrates, we obtained 1-methyl and 1-phenyl-5-trichloromethylthiotetrazoles [compounds (4) and (5)] (Scheme 5).

The new compounds show noticeable biological activity, in particular as fungicides against, *e.g.*, *Botrytis cinerea* and *Plasmopara viticola*, as already claimed in a patent.[12]



(4) R = Me
(5) R = Ph

SCHEME 5

EXPERIMENTAL

M.p.s were determined on a Büchi apparatus and are uncorrected. I.r. spectra were recorded for Nujol mulls on a Perkin-Elmer instrument Model 21. ^{1}H N.m.r. spectra were recorded on a Varian EM-390 spectrometer in ^{2}H chloroform solutions with Me_4Si as internal standard. Mass spectra were recorded on a Perkin-Elmer 270 instrument (direct inlet).

1,1,2,2-Tetrachloroethylsulphenyl chloride, required for preparation of *S*-(1,1,2,2-tetrachloroethyl) *N*-benzoyl-*N*-phenylthiocarbamate (3p), was obtained from trichloroethylene as described in reference 13. The other reagents were commercial products.

Example of Method A: Compound (3m).—Chloro(phenylimino)methyl trichloromethyl sulphide (1) (R^1 = Ph and R^2 = CCl_3) (2.90 g, 0.01 mol) in benzene (10 ml), sodium benzoate (2.90 g, 0.02 mol) in water (4 ml), and tricaprylmethylammonium chloride (Aliquat 336, 0.15 g, 0.4 mmol) were vigorously stirred under reflux for 3 h. The mixture was cooled to room temperature; diethyl ether (10 ml) and water (10 ml) were added to enable easy phase separation.

The organic phase was washed with water (10 ml), dried (Na_2SO_4), and evaporated under reduced pressure. Addition of hexane (10 ml) to the crude residue and cooling to −15 °C separated a white solid, *S*-trichloromethyl *N*-benzoyl-*N*-phenylthiocarbamate (3m) (2.2 g, 58%), m.p. 98—100 °C (after recrystallization from 95% ethanol, m.p. 102—103 °C); $\nu_{max.}$ (Nujol) 1 680 (COS), 1 660 (CO), 1 255, 1 130, and 1 080 cm^{-1}; δ ($CDCl_3$) 7.15—7.50 (m, Ar).

All the compounds (3f)—(3v), synthesized by method A, were similarly prepared. Light petroleum (b.p. 60—80 °C) may be used as well as benzene as solvent for the starting compounds (1). As phase-transfer catalyst, benzyltriethylammonium chloride (BTEAC) or hexadecyltrimethylammonium bromide (CTMAB) have also been used, with comparable results. When the addition of hexane separated a thick oil, this was purified by flash chromatography [14] (eluant, hexane–ethyl acetate, 4 : 1). All the compounds gave spectroscopic characteristics similar to those of compound (3m).

S-Trichloromethyl *N*-benzoyl-*N*-butylthiocarbamate (3e) was obtained by the following modification of method A. Solid sodium benzoate was used (out of phase), without water; all the other operating conditions were as described above. The yield was 45%. When this modified method A was applied to the synthesis of *S*-trichloromethyl *N*-benzoyl-*N*-methylthiocarbamate (3b) it gave a yield (20%) lower than that obtained with method B (35%).

Example of Method B: Compound (3b).—Triethylamine (1.0 g, 0.01 mol) in benzene (5 ml) was stirred, as drops at room temperature, into a mixture of chloro(methylimino)-methyl trichloromethyl sulphide (1) (R^1 = Me and R^2 = CCl_3) (2.27 g, 0.01 mol) and benzoic acid (1.22 g, 0.01 mol) in benzene (40 ml).

The mixture was refluxed for 3 h. Filtration from the precipitated triethylamine hydrochloride and evaporation of the solvent under reduced pressure gave a crude oil.

Addition of hexane (10 ml) and cooling at −15 °C separated a white solid [compound (3b)] (1.1 g, 35%), m.p. 121—123 °C (after recrystallization from hexane, m.p. 124—125 °C); $\nu_{max.}$ (Nujol) 1 675, 1 650, 1 220, 1 050, and 830 cm^{-1}; δ($CDCl_3$) 3.32 (3 H, s, Me) and 7.50—7.65 (5 H, m, Ar); *m/e* 194 (*M*-CCl_3), 162 (*M*-$SCCl_3$), 117 (CCl_3), and 105 (Bz).

S-Trichloromethyl *N*-methyl-*N*-(3-phenoxybenzoyl)thiocarbamate (3d) was purified by flash chromatography [14] (eluant, hexane–ethyl acetate, 4 : 1).

Compound (3v).—The required isonitrile was obtained *via* the method of Weber *et al.*,[15] slightly modified. 2,6-Dimethylaniline (12.1 g, 0.1 mol) and chloroform (10 ml, 0.12 mol) in toluene (100 ml), together with sodium hydroxide (16 g, 0.4 mol) in water (16 ml) and benzyltriethylammonium chloride (BTEAC, 0.4 g, 1.8 mmol) were vigorously stirred at 50 °C for 2 h. The mixture was cooled to room temperature and the organic phase separated off and washed with water (2 × 50 ml). To this solution perchloromethylmercaptan (18.6 g, 0.1 mol) was added at room temperature and the whole was stood overnight. Sodium benzoate (28.8 g, 0.2 mol) in water (40 ml) and tricaprylmethylammonium chloride (Aliquat 336, 1.5 g, 3.8 mmol) were added and the mixture was vigorously stirred under reflux for 3 h. The mixture was cooled, the organic phase was separated off, washed with aqueous 5% sodium hydrogencarbonate (2 × 50 ml) and water (2 × 50 ml), filtered through silica gel, dried (Na_2SO_4), and evaporated under reduced pressure to give a crude oil (25 g). Addition of hexane (40 ml) and cooling at −15 °C separated a pale yellow solid (10.3 g, 26% calculated on the starting amine), m.p. 110—115 °C. Recrystallization from 95% ethanol gave a white solid [*S*-trichloromethyl *N*-benzoyl-*N*-(2,6-dimethylphenyl)thiocarbamate (3v)], m.p. 130—130.5 °C; $\nu_{max.}$ (Nujol) 1 690 (COS), 1 662 (CO), 1 265, 1 230, 1 140, 1 110, and 835 cm^{-1}; δ($CDCl_3$) 2.25 (6 H, s, Me) and 7.05—7.65 (9 H, m, Ar).

S-Trichloromethyl *N*-benzoyl-*N*-cyclohexylthiocarbamate (3f) and *S*-trichloromethyl *N*-benzoyl-N-(4-methoxyphenyl)thiocarbamate (3u) were synthesized in a similar manner. Their spectroscopic characteristics confirm the assigned structure.

1-*Methyl*-5-*trichloromethylthiotetrazole* (4).—Chloro(methylimino)methyl trichloromethyl sulphide (1) (R^1 = Me and R^2 = CCl_3) (1.1 g, 5.0 mmol) in absolute ethanol (5 ml) was dropped into a mixture of sodium azide (0.65 g, 10 mmol) and absolute ethanol (35 ml), at room temperature, with stirring.

The mixture was heated at 60 °C for 10 min. The solid was filtered off and the solution set aside to cool.

A solid separated [compound (4)] (0.6 g, 51%), m.p. 142—143 °C (Found: C, 15.9; H, 1.25; Cl, 46.0; N, 24.3; S, 13.55. $C_3H_3Cl_3N_4S$ requires C, 15.45; H, 1.3; Cl, 45.55; N, 24.0; S, 13.75%); $\nu_{max.}$ (Nujol) 1 185, 800, 765, 725, and 695 cm^{-1}; *m/e* 232 (M^+), 197 (*M* − Cl), 149 ($SCCl_3$), and 117 (CCl_3).

1-*Phenyl*-5-*trichloromethylthiotetrazole* (5).—Compound (5)

was obtained in a similar way in 45% yield, m.p. 96—97 °C; $\nu_{max.}$ 1 500, 808, 765, 755, and 680 cm^{-1}.

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