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# A NEW SYNTHETIC PROCEDURE FOR THE CONVENIENT PREPARATION OF THIOCARBAMOYL CHLORIDES AND THE NOVEL BIS-THIOCARBAMOYL CHLORIDES

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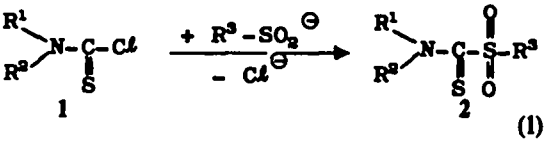
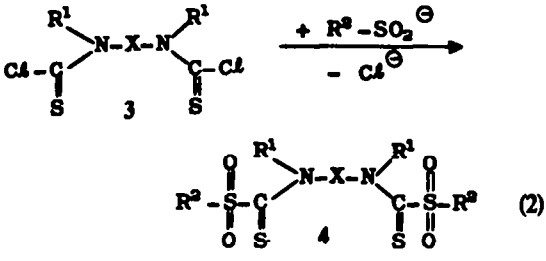
**Abstract**—Treatment of N-silylamines with excess thiophosgene affords thiocarbamoyl chlorides in good yields and excellent purity. This method was also suitable for preparing the first bis-thiocarbamoyl chlorides from N,N'-bis(trimethylsilyl)-diamines. Bis-thiocarbamoyl chlorides are useful synthetic intermediates.

A previous report from this laboratory[1] summarized early work with C-sulfonylthioformamides 2 which are available from the corresponding thiocarbamoyl chlorides 1 according to eqn (1).



(1)

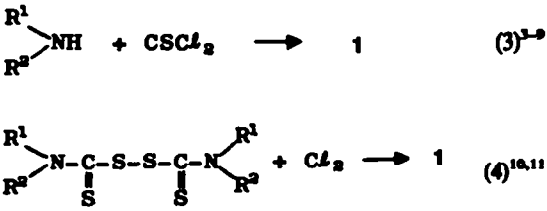
Recently we took a renewed interest in 2 when routine anticancer screening at the U.S. National Cancer Institute revealed distinct cytostatic properties of certain 2.[2] Speculations on a "bioacylating" principle paralleling the well-known "bioalkylating" mode of action of certain cytostatics[2] suggested that it might be worthwhile to synthesize and test the bis compounds 4.



(2)

An obvious approach to 4, i.e. reaction (2), required the bis-thiocarbamoyl chlorides 3 which, as far as we could ascertain in a careful literature search, do not appear to have been reported yet.

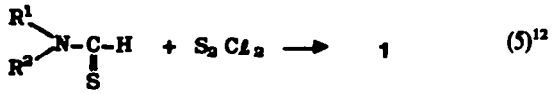
To the best of our knowledge the following six methods are on record as providing monofunctional thiocarbamoyl chlorides:



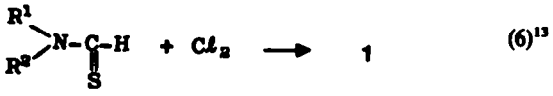
(3)[3-9]



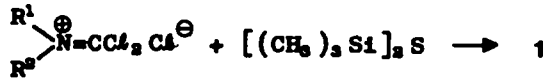
(4)[10,11]



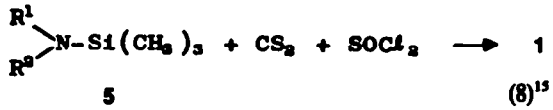
(5)[12]



(6)[13]



(7)[14]



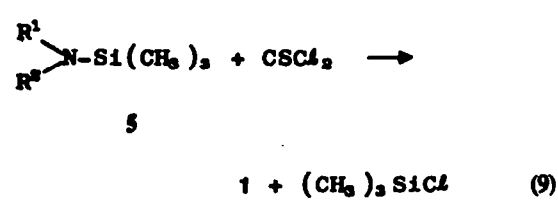
(8)[15]

As far as these methods' suitability for the synthesis of 3 is concerned, (3) appears impractical because of the likely formation of thioureas, (4) because of the insolubility of the necessarily polymeric or macrocyclic starting material, and (7) because the starting material has to be prepared from a thiocarbamoyl chloride.[16]

Reactions (5) and (6) require the prior preparation of the corresponding bis-thioformamides which adds several steps to the overall synthetic sequence. Nevertheless, (5) was tried with HCSN $(CH_3)$ $CH_2CH_2N$ $(CH_3)$ CHS, but in our hands did not yield any 3 ($R^1$=$CH_3$, X=$CH_2CH_2$).

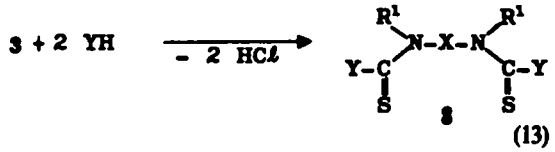
Reaction (8) which from the outset looked most promising as an access to 3, likewise failed to yield 3 ($R^1$=$CH_3$, X=$CH_2CH_2$) when tried by us.

We thus felt a need to devise a new method for the synthesis of 1 which would also be suitable for the preparation of 3. Reaction (9) turned out to constitute such a method.



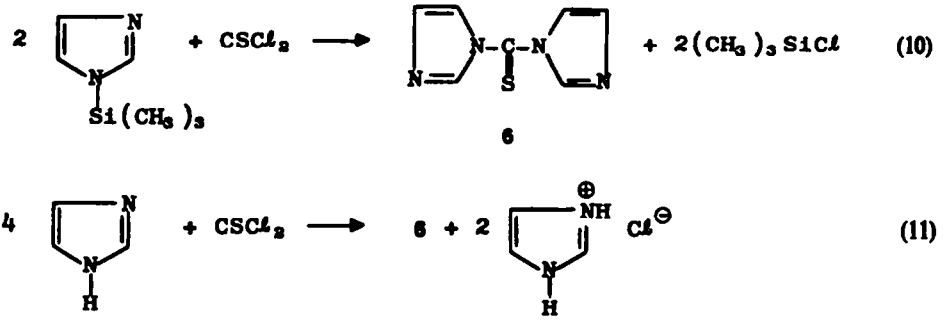
(9)

The salient features of (9) are the absence of acids and bases and the ease with which the volatile trimethylchlorosilane and the excess thiophosgene can be removed. Thus, the formation of insoluble intermediates (such as hydrochlorides) and/or troublesome by-products (such as sulfur) is avoided and already the crude precipitated 3 is of remarkable purity, sufficient for most synthetic purposes. In the related reaction (10) it has already been shown[17] that the thiocarbonyl compound 6 is obtained in a purer and thus more stable state than in (11), where contamination with imidazole hydrochloride cannot be avoided.



(13)

Compound 3 ($R^1$=X=$CH_2CH_2$) is remarkable for its extremely low solubility in all solvents tried and its infusibility. 3 ($R^1$=$CH_3$, X=$CH_2CH_2$) exhibits a temperature-dependent $^1$H NMR spectrum (shown in Fig. 1) corresponding to a mixture of E,E-, E,Z-, and Z,Z-



(10)



(11)

conformers, analogous to the situation in the corresponding bisthioformamides.[19]

In the $^1$H NMR spectrum of 8 ($R^1$=X=$CH_2CH_2$, Y=$N(CH_2CH_2)_2O$) all protons are accidentally equivalent.

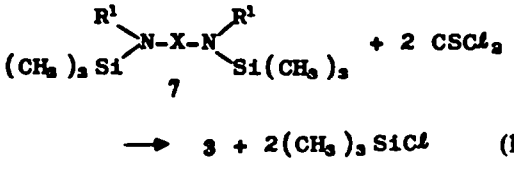
The yields in our examples for (9) are not optimized. While the reaction temperature does not appear to be critical for (9) and (12) in general, formation of unidentified high-melting products was a problem in (9), ($R^1$=$CH_3$, $R^2$=$C_6H_5$) unless extremely low temperatures were employed (Table 1).

Table 1. Temperature dependence of (9), ($R^1$=$CH_3$, $R^2$=$C_6H_5$)

| Bath temperature (°C) | M.p. of crude product (°C) |
|---|---|
| 0[a] | 105–108 |
| −80[a] | 60–62 |
| −130[b] | 38–39 |

[a] Solvent = ether. [b] Solvent = pentane.

Reaction (9) could readily be applied to bissilylamines 7 as shown in eqn (12).



(12)

In both cases 5 or 7, respectively, is slowly added to excess thiophosgene. The silylamines 5 and 7 are readily available by silylation of the appropriate amines and a large number of 5 and 7 are reported in the literature.[18]

The novel compounds 3 were characterized in the usual manner, including derivatization with amines and thiols according to (13).

## EXPERIMENTAL

The 60 MHz $^1$H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. The mass spectra were obtained with a CEC 21-104 mass spectrometer with direct inlet and an ionizing potential of 70 eV. All known products were identified by m.p., IR, MS and NMR. All preparations of 1 and 3 were carried out with freshly distilled thiophosgene.

*N,N-Tetramethylenethiocarbamoyl chloride*, 1 ($R^1$=$R^2$=$CH_2CH_2CH_2CH_2$). A stirred soln of 2.8 g (0.024 mole) thiophosgene in dry ether (100 ml) was kept at −78°. With a syringe 2.0 g (0.014 mole) N-(trimethylsilyl)-pyrrolidine[20] was slowly injected through a rubber septum. After the addition the mixture was

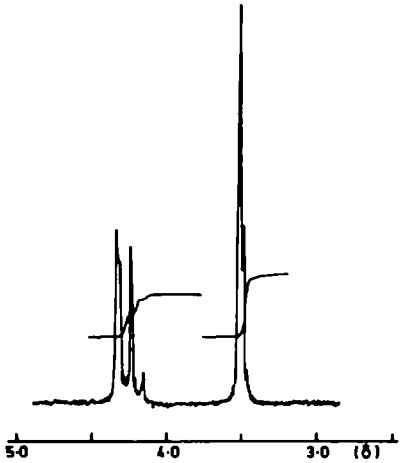



Fig. 1. The $^1$H NMR spectrum of 3 ($R^1$=$CH_3$, X=$CH_2CH_2$).

allowed to come to room temp. The ether was evaporated and the crude product recrystallized from ether, yield: 1.3 g (62%), m.p. 96°, lit.[6,15] m.p. 96°.

*N-Methyl-N-phenylthiocarbamoyl chloride*, 1 ($R^1$=$CH_3$, $R^2$=$C_6H_5$). A stirred soln of 2.1 g (0.018 mole) thiophosgene in dry pentane (50 ml) was kept at −128° (pentane/liquid $N_2$ bath). With a syringe 2.2 g (0.012 mole) N - methyl - N - (trimethylsilyl) - aniline[21] was slowly injected through a rubber septum. After the addition the mixture was allowed to come to room temp. The ppt was filtered off and recrystallized from chloroform/petroleum ether, yield: 1.7 g (76%), m.p. 37–38°, lit.[5,13] m.p. 36–38°.

*1,4-Bis-(chlorothioformyl)-piperazine*, 3 ($R^1$=X=$CH_2CH_2$). A stirred soln of 22 g (0.19 mole) thiophosgene in dry tetrachloromethane (500 ml) was kept at −23°. With a syringe 6.7 g (0.029 mole) 1,4-bis-(trimethylsilyl)-piperazine[22] was slowly injected through a rubber septum. After the addition the mixture was allowed to come to room temp and the ppt filtered off. The crude product was too insoluble for recrystallization and analyzed as such, yield: 7.0 g (99%), the material decomposes slowly above 228°. IR: $\nu_{CS}$ 1485 $cm^{-1}$ (KBr). MS: *m/e* 242 (M), 207 (M–Cl), 171 (M–2Cl). Found: C 29.31, H 3.86, Cl 30.11, N 11.94, S 25.98. $C_6H_8Cl_2N_2S_2$ requires: C 29.63, H 3.32, Cl 29.16, N 11.52, S 26.38%.

*N,N' - Bis - (chlorothioformyl) - N,N' - dimethyl - ethylenediamine*, 3 ($R^1$=$CH_3$, X=$CH_2CH_2$). A stirred soln of 6.0 g (0.052 mole) thiophosgene in dry benzene (75 ml) was kept at 8°. With a syringe 5.0 g (0.023 mole) N,N' - bis - (trimethylsilyl) - N,N' - dimethyl - ethylenediamine[23] was injected slowly through a rubber septum. The crude product, obtained by evaporation of the benzene *in vacuo*, was recrystallized from acetone, yield: 5.3 g (94%), m.p. 142–143°. IR: $\nu_{CS}$ 1505 $cm^{-1}$ (KBr). MS: *m/e* 244 (M), 209 (M–Cl), 177 (M–2Cl), 136 (M–$C_2H_3ClNS$), 122 (M–$C_3H_5ClNS$). NMR: see Fig. 1. Found: Cl 28.72, S 25.63. $C_6H_{10}Cl_2N_2S_2$ requires: Cl 28.92, S 26.15%.

*1,4 - Bis - (1 - morpholinothiocarbonyl) - piperazine*, 8 ($R^1$=X=$CH_2CH_2$, Y=$N(CH_2CH_2)_2O$). To excess morpholine 3 ($R^1$=X=$CH_2CH_2$) was added in small portions with stirring. When the addition was complete, the mixture was clarified by gentle heating, filtered warm, and poured into water. The crude product precipitated in quantitative yield. After recrystallization from acetonitrile the m.p. was 209–210°. IR: $\nu_{CS}$ 1450 $cm^{-1}$ (KBr). MS: *m/e* 344 (M), 258 (M–$C_4H_8NO$), 173 (M–$C_8H_{15}N_2O_2$), 130 ($O(CH_2CH_2)_2NCS$). NMR: $\delta$ 3.70 (s). Found: N 16.24, S 18.66. $C_{14}H_{24}N_4O_2S_2$ requires: N 16.27, S 18.61%.

*N,N' - Bis - (1 - morpholinothiocarbonyl) - N,N' - dimethyl - ethylenediamine*, 8 ($R^1$=$CH_3$, X=$CH_2CH_2$, Y=$N(CH_2CH_2)_2O$). This compound was prepared like the preceding one, Crude yield: 100%, m.p. 163–164° (from abs EtOH). IR: $\nu_{CS}$ 1492$cm^{-1}$ (KBr). MS: *m/e* 346 (M), 186 (M–$C_6H_{11}N_2OS$), 130 ($O(CH_2CH_2)_2NCS$). NMR: $\delta$ 3.17 (s, 6H), 3.30–3.55 (m, 8H), 3.62–3.85 (m, 8H), 4.07 (s, 4H). Found: N 16.15, S 18.53. $C_{14}H_{26}N_4O_2S_2$ requires: N 16.17, S 18.50%.

*Dibenzyl 1,4-piperazinedicarbodithioate*, 8 ($R^1$=X=$CH_2CH_2$, Y=$SCH_2C_6H_5$). A soln of sodium phenylmethanethiolate was prepared by dissolving 0.20 g (0.0083 mole) Na and 1.03 g (0.0083 mole) phenylmethanethiol in abs EtOH. 3 ($R^1$=X=$CH_2CH_2$), 1.00 g (0.0041 mole), was added and the mixture refluxed for 1.5 hr. The mixture was poured into water and the ppt recrystallized from 2-propanol to yield 1.15 g (67%) of the bis-dithioester, m.p. 122–123°, lit.[24–26], m.p. 124–125°.

*N,N' - Bis - (benzylthiothiocarbonyl) - N,N' - dimethyl - ethylenediamine*, 8 ($R^1$=$CH_3$, X=$CH_2CH_2$, Y=$SCH_2C_6H_5$). This synthesis was carried out like the preceding one except that the crude product was collected by filtration of the ethanolic soln, yield: 81%, m.p. 150–151° (from acetonitrile). IR: $\nu_{CS}$ 1475 $cm^{-1}$ (KBr). MS: *m/e* 420 (M), 329 (M–$C_7H_7$), 253 (M–$C_8H_7S_2$), 123 ($C_7H_7S$), 91 ($C_7H_7$). NMR: $\delta$ 3.36 (s, 6H), 4.35 (s, 4H), 4.53 (s, 4H), 7.18–7.50 (m, 10H). Found: N 6.63, S 30.59. $C_{28}H_{24}N_2S_4$ requires: N 6.66, S 30.48%.

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