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Heterocyclics from Malonyl Chlorides

II. Syntheses with Thiocyanates*

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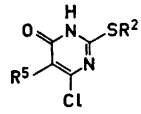
Thiocyanates react with malonyl chlorides to give 4-chloropyrimidine-6-ones with an alkylthio or arylthio group in the 2-position. A mechanism for this as well as for the analog reaction with nitriles is discussed.

α-Methylene nitriles react with malonyl chloride at room temperature to give 3-substituted 2-chloro-4,6-dihydroxypyridines in the α-pyridone form.[1] A few α-methylene nitriles as well as a series of nitriles lacking α-methylene (*e.g.* having an α-halogen) form with malonyl chloride 2-substituted 4-chloropyrimidine-6-ones and with substituted malonyl chlorides 2,5-disubstituted 4-chloropyrimidine-6-ones.[2–4] A mechanism for these reactions has been postulated.[1,2]

Thiocyanates can be regarded as nitriles without an α-methylene group and they gave, in accord with the above picture and as mentioned earlier by Stensrud *et al.*[4] with malonyl chlorides 5-substituted 4-chloropyrimidine-6-ones with an alkylthio or an arylthio group in the 2-position as the sole products (I)



(I)

The yield in this synthesis ranged from 4 to 80 % and was highest when R^2 was a small primary alkyl group. ($R^2=CH_3$, yield 80 %; $R^2=C_7H_{15}$, yield 15 %.) Only the smallest secondary group, isopropyl, gave a yield (4 %) while phenyl thiocyanate yielded 40 % of the expected product. Chloromalonyl chloride gave products with a majority of the tested thiocyanates, while the yield from malonyl chloride was nil. The yields *etc.* are collected in Table 1.

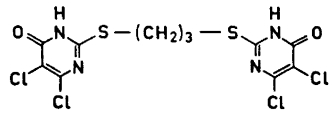
* Part I: Stensrud, T., Bernatek, E. and Johnsgaard, M. *Acta Chem. Scand.* **25** (1971) 523.

Table 1.

R^2	R^5	Reaction time (days)	Yield %	M.p. °C
CH_3	Cl	5	80	271 (subl. 260)
C_2H_5	»	7	60	204.5 – 205.5
n-C_3H_7	»	12	38	165.5 – 166.5
n-C_4H_9	»	10	25	149.5 – 151
n-C_7H_{15}	»	26	15	111.5 – 113
$CH_2-CH=CH_2$	»	6	16	172.5 – 174 (subl. 161)
C_6H_5	»	6	40	216.5 – 217.5 (subl. 205)
$CH_2C_6H_5$	»	12	35	222 – 223
$CH_2COOC_2H_5$	»	55	13	168 – 170 (subl. 162)
$CH_2CH_2COOC_2H_5$	»	20	8	130.5 – 132
$CH_2CH_2CH_2COOC_2H_5$	»	22	15	131 – 132
$CH(CH_3)_2$	»	52	4	192 – 194 (subl. 185)
$CH(CH_3)C_2H_5$	»	~400	0	
$CH(C_2H_5)COOC_2H_5$	»	~400	0	
$(CH_2)_2Br$	»	7	42	122.5 – 124.5
$(CH_2)_3Br$	»	12	30	154.5
C_2H_5	C_6H_5	120	5	160 – 161.5
n-C_4H_9	»	30	10	187.5 – 189
$CH_2C_6H_5$	»	3	30	211 – 218
C_2H_5	$CH_2C_6H_5$	11	36	167.5 – 169
n-C_3H_7	»	12	37	150.5 – 151
n-C_4H_9	»	20	20	128 – 129.5
$CH_2C_6H_5$	»	6	30	205 – 206.5
C_2H_5	H	>100	0	
$CH_2C_6H_5$	»	>100	0	

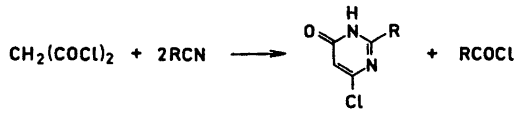
The reactions were all carried out at room temperature and the substances analysed correctly, either by elemental analysis or by high resolution mass spectrometry.

Of the three dithiocyanates – methylene, ethylene, and trimethylene dithiocyanate – tested in reaction with chloromalonyl chloride, only the latter gave a pyrimidine product. On the basis of its composition and spectral data it was assigned the structure (II).

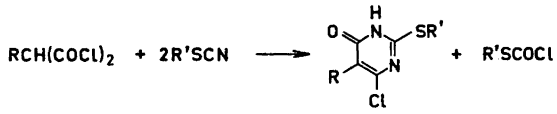


(II)

Elvidge and Zaidi [2] have postulated a mechanism for the formation of pyrimidines from nitriles and malonyl chloride involving an anionotropic rearrangement. The stoichiometry of the reaction was formulated by Bernatek *et al.*[3] as follows:

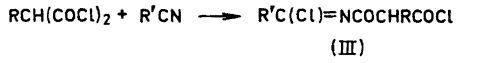


In close analogy to this the stoichiometry of the thiocyanate reaction is:



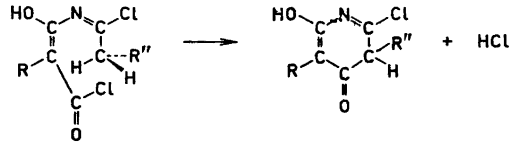
Two molecules of thiocyanate are involved as they are the only source of nitrogen in the pyrimidine ring. Chlorothiocarbonic acid S-esters are described in the literature.[5,6] In the reaction mixture from ethyl thiocyanate and chloromalonyl chloride the presence of *S*-ethyl chlorothiocarbonate could be demonstrated. Also in the reactions of propyl thiocyanate with chloromalonyl and benzylmalonyl chloride, respectively, the expected chlorothiocarbonic ester was formed.

There is evidently a close relationship between the pyridine and the pyrimidine synthesis (with nitriles as well as thiocyanates). It has been mentioned[3] that by increasing the ionic strength of the reaction mixture, chloroacetonitrile and benzoyloxyacetonitrile, which usually give pyrimidines, can be induced to produce pyridines exclusively. It is reasonable to assume that the first step in the mechanism is identical in both reactions. As already suggested[1] this step consists in an acylation of the nitrile by malonyl chloride.



(III)

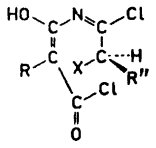
The intermediate (III) can be assumed to exist in several tautomeric forms and each of these can be envisaged in different conformations, *e.g.* (IV) (R′ = CH_2R'').



(IV) (V)

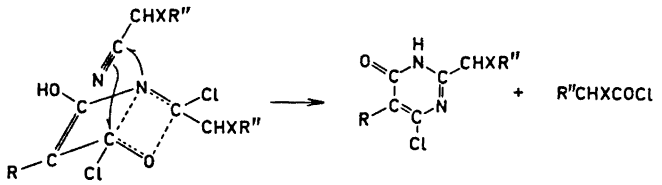
Here the steric conditions are such that a facile ring-closure with elimination of hydrogen chloride is to be expected. A pyridine derivative (V) (or tautomer) is thus formed. If the group next to CN in the nitrile is not methylene, but contains a halogen or another, bulky group X, the situation is different. In the

$-CHXR''$ group either R'' or X will be in *anti* position to the chlorine on the neighbouring carbon atom (VI). Thereby the region between the chlorocarbonyl group and $-CHXR''$ will be so crowded that the approximately



(VI)

coplanar entity (VI), which is necessary for the ring closure to a pyridine, becomes less probable. In such cases we know that the intermediate reacts with a second nitrile molecule and forms a pyrimidine. If in (VI) a partial bond is formed between the carbonyl carbon and nitrogen as well as between carbonyl oxygen and a carbon atom, the entity (VII) emerges.



(VII)

A second nitrile molecule can then react across the partially bridged ring as indicated and will force the elimination of the acid chloride R''CHXCOCl. However, it is possible that this acid chloride is split off before reaction with nitrile occurs, leaving a four-ring fragment (VIII), which in turn reacts in

(VIII) (IX)

a manner similar to that described. A support for this idea is found in the fact that a fragment corresponding to (IX) consistently appears in the mass spectra of the prepared pyrimidines.

The suggested mechanism of reaction has thus a common first step for the formation of pyridines and pyrimidines and rationalises the choice of divergent reaction paths of different nitriles. Thiocyanates are not specifically mentioned in the suggested reaction mechanism, but as they are incapable of forming pyridines in the described manner they must choose the path to pyrimidines.

The new compounds described in this work were tested for pharmacological activity, but apart from a slight antibacterial and antimycobacterial effect of (I) ($R^2 = n\text{-}C_7H_{15}$, $R^5 = Cl$) no such activity was found.

EXPERIMENTAL

Melting points were determined on a micro hot-stage. UV-spectra were recorded on a Perkin-Elmer 137UV Ultraviolet-Visible Spectrophotometer, infra-red spectra on a Perkin-Elmer 457 Grating Infrared Spectrophotometer, NMR spectra on a Varian A-60 A Spectrometer and the mass spectra on an AEI/EC MS 902 instrument. Elemental analyses were performed by J. Beetz, W. Germany.

Chloromalonyl chloride was prepared according to Conrad [7] from malonic acid by chlorination with sulphuryl chloride followed by treatment with phosphorus pentachloride. To ensure the quality of the product, the procedure was modified according to Stensrud *et al.*[4]

Benzylmalonyl and phenylmalonyl chloride are prone to loss of hydrogen chloride with formation of a ketene. To avoid this the substances were prepared according to Stensrud *et al.*[4]

Thiocyanates. The ethyl and benzyl compounds were obtained as commercial products. Methyl thiocyanate was prepared from methyl sulphate and potassium thiocyanate. B.p. 33°C/17 mmHg. The ten thiocyanates contained in Table 2 were prepared from the bromides and potassium thiocyanate in 80 to 100 % ethanol. The reaction was terminated when a sample gave only a faint red colour with $FeCl_3$.

Table 2. Thiocyanates from RBr and KSCN.

Product	B.p. °C/mmHg
C_3H_7SCN	163/760
$(CH_3)_2CHSCN$	50.5 – 51/20
C_4H_9SCN	185.5 – 187/760
$C_2H_5CH(CH_3)SCN$	59/12
$C_7H_{15}SCN$	120.5 – 121.5/17
$CH_2=CH-CH_2SCN$	69/31
$CH_2(COOC_2H_5)SCN$	123 – 125/20
$CH_2(CH_2COOC_2H_5)SCN$	135.0 – 135.8/20
$CH_2((CH_2)_2COOC_2H_5)SCN$	149 – 150/20
$C_2H_5CH(COOC_2H_5)SCN$	123 – 125/20

Phenyl thiocyanate was prepared from aniline by a Sandmeyer reaction. B.p. 232°C/760 mm. Methylene dithiocyanate was prepared from methylene iodide and potassium thiocyanate. M.p. 103 – 104°C. Ethylenedithiocyanate and 2-bromoethylthiocyanate were prepared in the same batch from ethylene dibromide and potassium thiocyanate. M.p. 90.0 – 90.5°C and b.p. 110 – 111°C/17 mm, respectively. The same type of reaction was utilised in the preparation of trimethylenedithiocyanate and 3-bromopropylthiocyanate. M.p. 1 – 5°C and b.p. 128°C/17 mm, respectively.

Pyrimidines. General procedure. The thiocyanate (5 – 15 g) was mixed with the malonyl chloride (5 – 10 g) in the molar ratio 2 : 1. The batch was distributed in several small capped vials and left at room temperature until the maximum amount of crystalline material had accumulated. This was washed, recrystallised from acetic acid and, if possible, sublimated *in vacuo*. The elemental analyses of the substances were correct within the usual limits of error. A few compounds were analysed by mass spectrometry.

1,3-Bis(4',5'-dichloropyrimidinyl-6'-one-2'-thio) propane. Trimethylenedithiocyanate (21.5 g) and chloromalonyl chloride (23 g) were reacted in the above manner. A low yield (10 %) of a yellow product was obtained. M.p. 257 – 263°C (dec.). The elemental analysis

was in fair agreement with the formula $C_9H_8N_4O_2S_2Cl_4$. The IR-spectrum was very similar to that of (I) ($R^2=CH_2CH_2CH_3$, $R^5=Cl$). The NMR-spectrum (in DMSO-d_6) had absorption at τ 6.74 (triplet) and at τ 7.90 (quintet), J 6.5 cps, signal ratio 2 : 1. This clearly indicates the central trimethylene chain.

Ethyl chlorothiocarbonate. The filtrate from the product of chloromalonyl chloride (15 g) and ethyl thiocyanate (15 g) was distilled *in vacuo*. B.p. 39°/20 mmHg. $\nu_{C=O}$ 1750 cm^{-1}. The NMR-spectrum in CCl_4 had 2H at τ 7.01 (quartet) and 3H at τ 8.46 (triplet), J 7 cps. The mass-spectrum gave the molecular ion *m/e* 124 containing one chlorine atom. High resolution: *m/e* 123.9747. Calc. for C_3H_5OSCl 123.9750.

Propyl chlorothiocarbonate. Isolated as in the foregoing experiment from the reaction mixture of benzylmalonyl chloride (25 g) and propyl thiocyanate (11 g). B.p. 41–43°C/24 mmHg. $\nu_{C=O}$ 1758 cm^{-1}. The NMR-spectrum in CCl_4 had 2 H at τ 7.05 (triplet), 2H at τ 8.25 (sextet) and 3H at τ 8.96 (triplet), J 7 cps. The mass spectrum gave the molecular ion *m/e* 138 with one chlorine atom. High resolution: *m/e* 137.9912. Calc. for C_4H_7OSCl: 137.9906. The same chlorothiocarbonate could be identified in the reaction mixture of chloromalonyl chloride and propyl thiocyanate.

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