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New Pyrimidine Derivatives of Cyanimidodithiocarbonates

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Summary. Several synthetic processes for some new pyrimidine derivatives of cyanimidodithiocarbonates are reported. Due to the formation of by-products, the optimization of reaction conditions is of importance.

Keywords. Cyanimidodithiocarbonate; Cyclization; Pyrimidine; Triazole; Triazine.

Neue Pyrimidinderivate von Cyanimidodithiocarbonaten

Zusammenfassung. Es werden einige Methoden zur Darstellung verschiedener neuer Pyrimidinderivate von Cyanimidodithiocarbonaten vorgestellt. Wegen der Entstehung von Nebenprodukten ist die Optimierung der Reaktionsbedingungen sehr wichtig.

Introduction

Cyanimidodithiocarbonates containing the S-CH_2-*X*-R′ system (*X* = O, S; *R*′ = alkyl, aryl, heteroaryl) are known as fungicides [1–3]. Their synthesis was carried out either by the reaction of potassium cyanimidodithiocarbonate monoester and chloromethylethers/thioethers or by (S-alkyl, S′-chloromethyl)-cyanimidodithiocarbonate and thiophenols.

On the other hand, cyanimidodithiocarbonic acid dimethylester is an important intermediate for the synthesis of compounds of medical interest with a N-cyanoisothiourea or N-cyanoguanidine structure [4–6]. The preparation of these materials can be carried out by nucleophilic substitution when the methylthio group is attacked with amines in a stepwise procedure. First, N-cyanoisothiourea [7–13] is formed and subsequently the guanidine [11, 14, 15].

The cyanimidodithiocarbonates show especially good reactivity in several ring closure reactions. The cyclocondensation of cyanimidodithiocarbonic acid dimethylester with substituted hydrazines (*R*-N^1H-N^2H_2) affords amino-methylthio-1,2,4-triazoles [16]. Similarly, several diamino-1,2,4-triazoles can be synthesized from isothioureas depending on the reaction conditions [17].

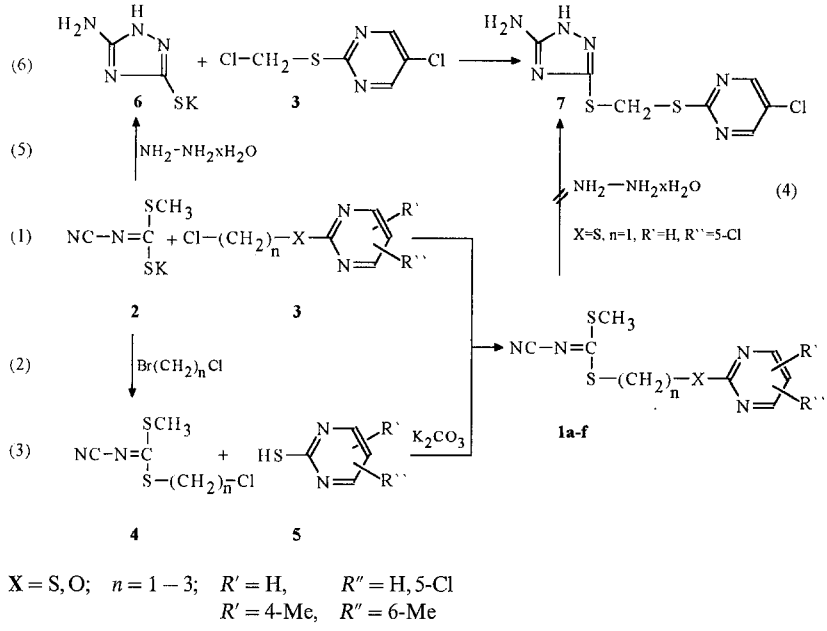
There are some references for the synthesis of triazine derivatives from cyanimidodithiocarbonic acid dimethylester: thio-*bis*-(formamidine) gives aminodithio-*s*-triazine derivatives in the presence of NaOEt [18], whereas chlorine produces in dichloromethane at −15 °C chlorinated amino-*s*-triazine derivatives

[19]. By application of acetamidine, a new process [20] was elaborated for the production of the important intermediate 2-amino-4-methoxy-6-methyl-1,3,5-triazine.

With knowledge of the above mentioned results, the aim of the present work was to introduce a series of variable syntheses for new pyrimidine derivatives of cyanimidodithiocarbonates which may have biological activity.

Results and Discussion

The pyrimidine ring can be introduced into the cyanimidodithiocarbonate molecule by nucleophilic substitution reactions: either by means of alkylation (dialkyl esters) or by an exchange between the alkylthio group and an amine derivative (isothioureas).



Scheme 1. Synthesis of (S-methyl, S'-(pyrimidin-2-yl)-thio/oxyalkyl)-cyanimidodithocarbonates **1a–f** and cyclization with hydrazine monohydrate

Two methods (**A** and **B**) are developed for the preparation of (S-methyl, S'-(pyrimidin-2-yl)-thio/oxyalkyl)-cyanimidodithiocarbonates (**1**). Method **A** was carried out according to Eq. 1 (Scheme 1) which required the synthesis of pyrimidine derivative **3**. The preparation of chloroalkyl thiopyrimidines (**3**, $X = S$) is possible either by chlorination of hydroxymethyl-pyrimidine derivatives with thionyl chloride or by alkylation of pyrimidine thiol with bromochloroalkanes [21]. The (chloroalkyl)-oxypyrimidines (**3**, $X = O$, $n = 2, 3$) were synthesized from 2-methylsulfonyl-pyrimidines and 2-chloro-ethanol or 3-chloro-propanol in the presence of NaH.

The application of method **A** is limited; in the case of $n = 2$, product **1** could neither be isolated in the case of $X = S$ nor of $X = O$. An inseparable complex

Table 1. (S-methyl, S′-(pyrimidin-2-yl)-thio/oxyalkyl)-cyanimidodithiocarbonates **1a–f**

	R′	R″	*n*	*X*	mp. (°C)	Yield (%)	^{1}H NMR ($CDCl_3$/*TMS*) δ (ppm)	IR (KBr) ν (cm^{-1}) C=N	(N)–C≡N
a	H	H	1	S	76–78	50	2.6 (3H, s, CH_3) 4.7 (2H, s, CH_2) 7.05 (1H, t, 5-H) 8.5 (2H, d, 4, 6-H)	1492	2190
b	4-Me	6-Me	1	S	115–120[a]	47	2.4 (6H, s, 4, 6-CH_3) 2.65 (3H, s, CH_3) 4.85 (2H, s, CH_2) 6.75 (1H, s, 5-H)	1493	2195
c	4-Me	6-Me	2	S	73–77	43	2.4 (6H, s, 4, 6-CH_3) 2.7 (3H, s, CH_3) 3.5 (4H, bs, CH_2–CH_2) 6.7 (1H, s, 5-H)	1495	2195
d	H	5-Cl	1	S	94–98	74	2.6 (3H, s, CH_3) 4.7 (2H, s, CH_2) 8.3 (2H, s, 4, 6-H)	1490	2190
e	H	5-Cl	2	S	85–89	44	2.7 (3H, s, CH_3) 3.5 (4H, bs, CH_2–CH_2) 8.45 (2H, s, 4, 6-H)	1478	2191
f	H	5-Cl	3	O	79–82	38	2.25 (2H, qi, O–CH_2–CH_2–CH_2–S) 2.65 (3H, s, CH_3) 3.36 (2H, t, O–CH_2–CH_2–CH_2–S) 4.45 (2H, t, O–CH_2–CH_2–CH_2–S) 8.45 (2H, s, 4, 6-H)	1485	2192

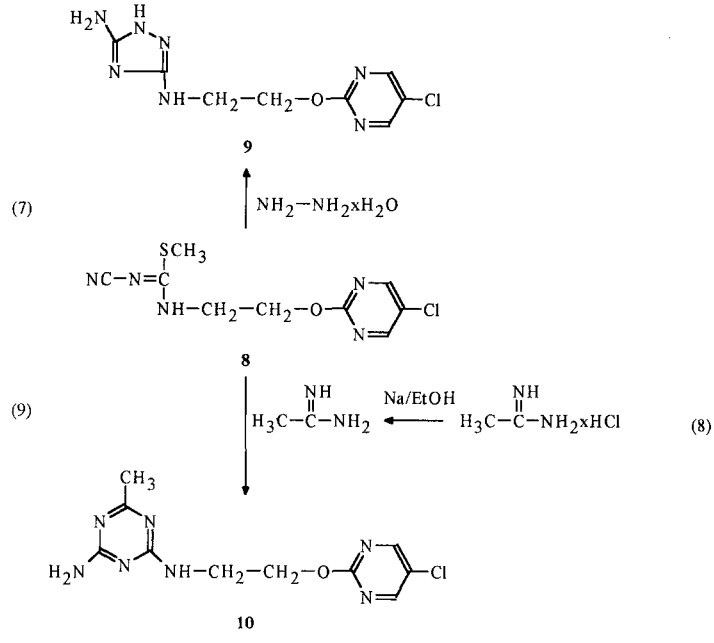
[a] Ref. [3]: mp.: 116–118 °C

reaction mixture was obtained due to an unexpected process. The ethylene bridge seems to be responsible for a side reaction which probably involves a cyclization.

This problem can be avoided by method **B** in the case of $X = S$. After preparing the chloroalkylthio derivatives of cyanimidodithiocarbonates (**4**) according to Eq. 2 a reaction is carried out with 2-thio-pyrimidine (**5**, Eq. 3, Scheme 1). The 2-hydroxy-pyrimidine, however, does not give the desired product even in this way (it is present in its oxo tautomer form). The products (**1a–f**) are summarized in Table 1.

Utilizing the ability of cyanimidodithiocarbonate for ring closure with hydrazine derivatives, the synthesis of compound **7** was attempted from **1d**; however, no pure product could be isolated (Eq. 4, Scheme 1). Since the S-CH_2-S system seems to be sensitive to basic conditions, another pathway was used to obtain this derivative. After successful synthesis of the triazole potassium salt **6**, product **7** was prepared as described in Eq. 6 (Scheme 1).

The isothiourea derivatives of pyrimidine have been described previously [22]. However, their ability for ring closure has not yet been studied. When the (5-chloropyrimidin-2-yl)-oxyethyl derivative **8** was reacted with hydrazine monohydrate, the desired triazole **9** was isolated (Eq. 7, Scheme 2). Since the NH-CH_2-CH_2-O system is stable under basic conditions, it is likely to take part in other cyclizations as well. For this reason, a reaction with acetamidine hydrochloride was carried out in the presence of Na/EtOH resulting in triazine **10** (Eq. 9, Scheme 2).



Scheme 2. Cyclization reactions of N-cyano-S-methyl-N′-(2-(5-chloropyrimidin-2-yl)-oxyethyl) isothiourea (**8**)

Amidines are rarely applied in ring closure reactions of cyanimidodithiocarbonates [18, 20]; their reaction with isothioureas is completely new. Diamino-1,3,5-triazines (substituted with OCH_3 or SCH_3) were obtained by the cyclization of cyanimidodithiocarbonic acid dimethylester with guanidine [23].

The pyrimidine derivatives of cyanimidodithiocarbonic acid showed fungicidal activity according to *in vivo* tests. **1a** proved to be the most valuable product: it killed *Podosphaera leucotricha* in a concentration of 125 mg/l.

Experimental

Melting points were determined on a Boëtus hotstage apparatus. A Varian EM 360A NMR spectrometer and a Pye Unicam SP-2000 IR spectrometer were used for spectroscopic studies. Starting materials having no reference number were purchased from Aldrich GmbH and used without further purification.

(S-methyl, S'-3-(5-chloropyrimidin-2-yl)-oxopropyl)-cyanimidodithiocarbonate (**1f**)

Method **A.** 11.4 g (0.06 mol) 5-chloro-2-methylsulfonyl-pyrimidine [24] and 18.9 g (0.2 mol) 3-chloro-1-propanol were dissolved in 60 ml dimethylformamide. 4.8 g (0.2 mol) NaH were added to the solution in small amounts under stirring. After one hour the precipitate was filtered and the filtrate was evaporated under vacuum. The residue was diluted with 100 ml chloroform and then washed with 3 × 50 ml of water. After drying over $MgSO_4$, it was chromatographed over 60 g Kieselgel 60 (0.063–0.2 mm, eluent: hexane). After evaporation of the solvent, white crystals formed from a diethyl ether – hexane mixture. Yield (intermediate **3**, $X = O$, $n = 3$, $R' = H$, $R'' = 5\text{-Cl}$): 5.4 g (44%); mp.: 55–58 °C; ^1H NMR ($CDCl_3/TMS$, δ): 2.3 (2H, qi, O–CH_2–CH_2–CH_2–Cl), 3.75 (2H, t, O–CH_2–CH_2–CH_2–Cl), 4.5 (2H, t, O–CH_2–CH_2–CH_2–Cl), 8.45 (2H, s, 4,6-H) ppm; IR (KBr): ν(pyrimidine) = 950, 1440, 1542, 1571, $\nu(C_{Ar}–O–C_{Al}) = 1043$, 1324 cm^{-1}.

3.4 g (0.02 mol) potassium S-methyl-cyanimidodithiocarbonate (**2**, [25]) and 3.0 g (0.015 mol) 5-chloro-2-(3-chloropropoxy)-pyrimidine (**3**, $X = O$, $n = 3$, $R' = H$, $R'' = 5\text{-Cl}$) were refluxed for 23 hours in ethyl methyl ketone in the presence of 0.1 g KI. The precipitate was filtered at room temperature and the filtrate was evaporated. The residue was crystallized from chloroform – petroleum ether. Yield: 1.7 g **1f** (38%); mp.: 79–82 °C; spectroscopic data are collected in Table 1.

(S-methyl, S'-2-(4,6-dimethylpyrimidin-2-yl)-thioethyl-cyanimidodithiocarbonate (**1c**)

Method **B.** To a solution of 8.5 g (0.05 mol) potassium S-methyl-cyanimidodithiocarbonate (**2**, [25]) and 50 ml acetone, 16.5 g (0.115 mol) bromochloroethane were added under stirring. The mixture was allowed to stand for 3 days, then filtered and evaporated. The residue was diluted with 50 ml benzene and washed with 3 × 25 ml of water. After drying over $MgSO_4$ and evaporation of the solvent, white crystals were obtained from a diethyl ether – hexane mixture. Yield (intermediate **4**, $n = 2$): 6.0 g (62%); m.p.: 50–52.5 °C; ^1H NMR ($CDCl_3/TMS$, δ): 2.65 (6H, s, CH_3); 3.3–3.9 (4H, m, CH_2–CH_2) ppm; IR (CCl_4: CS_2 = 1:1): ν'(N)–C≡N) = 2198, ν(C=N) = 1505 cm^{-1}.

To 20 ml of an acetonic solution of 3.0 g (0.015 mol) S-methyl, S'-(2-chloroethyl)-cyanimidodithiocarbonate (**4**, $n = 2$), 2.1 g (0.015 mol) K_2CO_3 and then 2.1 g (0.015 mol) 4,6-dimethyl-2-thio-pyrimidine in 20 ml acetone were added under stirring at room temperature. This reaction mixture was refluxed and stirred for 1 hour, then filtered, evaporated, diluted with 25 ml chloroform, and washed with water. After drying over $MgSO_4$, the organic phase was filtered, evaporated, and diluted with chloroform – diethyl ether. An oily precipitate was formed which was adsorbed on charcoal. The mixture was then filtered, and 1.9 g (43%) white crystals of **1c** were obtained from the filtrate. Mp.: 73–77 °C; spectroscopic data are collected in Table 1.

5-amino-1H-3-((5-chloropyrimidin-2-yl)-thiomethyl)-thio-1,2,4-triazole (**7**)

8.5 g (0.05 mol) potassium S-methyl-cyanimidodithiocarbonate (**2**, [25]) and 2.5 g (0.05 mol) hydrazine monohydrate (98%) were refluxed in 50 ml ethanol for 5 hours. After cooling to ambient temperature,

the crystals were filtered and washed with 10 ml ethanol. Yield (triazole salt **6**): 6.2 g (80%); mp.: 288–290 °C; IR (KBr): ν(C–S$^-$) = 450, ν(triazole) = 1025, 1265, 1315, 1440, 1540, ν($NH_{assoc.}$) = 2700, 2880, 3100, 3210, ν(NH_2) = 3320, 3410 cm^{-1}.

1.8 g (0.012 mol) **6** were heated with 2.3 g (0.012 mol) 5-chloro-2-(chloromethyl)-thiopyrimidine (**3**, X = S, n = 1, R' = H, R'' = 5-Cl, [21]) at the acetonitrile reflux temperature for 8 h 30 min. After cooling to 20 °C, the suspension was poured into cold water; the formed crystals were filtered, dissolved in chloroform – ethyl methyl ketone, and precipitated with diethyl ether. Yield: 2.0 g (61%); mp.: 172–175 °C; ^{1}H NMR (*DMSO*-d_6/*TMS*, δ): 4.75 (2H, s, CH_2), 6.05 (2H, s, NH_2), 8.8 (2H, s, 4,6-H) ppm; IR (KBr): ν(triazole) = 1008, 1290, 1390, 1528; 1580, ν($NH_{assoc.}$) = 2780, 2860, 3120, 3250, ν(NH_2) = 3370, 3480 cm^{-1}.

5-amino-1H-3-(2-(5-chloropyrimidin-2-yl)-oxyethyl)-amino-1,2,4-triazole (**9**)

3.4 g (0.0125 mol) N-cyano-S-methyl-N′-(2-(5-chloropyrimidin-2-yl)-oxyethyl) isothiourea (**8**, [22]) were reacted with 0.7 g (0.014 mol) hydrazine monohydrate (98%) at reflux temperature of acetonitrile (50 ml) for 4 h 30 min. The precipitated crystals were filtered at room temperature and washed with 3 × 5 ml acetonitrile. Yield: 2.8 g **9** (88%); mp.: 203–205 °C; ^{1}H NMR (*DMSO*-d_6/*TMS*, δ): 3.5 (2H, t, NH–CH_2–CH_2–O), 4.4 (2H, t, NH–CH_2–CH_2–O), 5.4 (2H, bs, NH_2), 5.7 (1H, bs, NH), 8.6 (2H, s, 4.6-H) ppm; IR (KBr): ν(heterocycle) = 800, 1430, 1555, 1570, ν($NH_{assoc.}$) = 2990, 3100, ν(NH_2) = 3300, 3440 cm^{-1}.

6-amino-2-(2-(5-chloropyrimidin-2-yl)-oxyethyl)-amino-4-methyl-1,3,5-triazine (**10**)

0.3 g (0.013 mol) Na was added in small amounts to 10 ml of absolute ethanol in which, after cooling to room temperature, 1.3 g (0.014 mol) acetamidine hydrochloride was dissolved. NaCl precipitated and was filtered off. To the filtrate, 3.2 g (0.12 mol) N-cyano-S-methyl-N′-(2-(5-chloropyrimidin-2-yl)-oxyethyl) isothiourea (**9**, [22]) were added. The mixture was refluxed for 6 hours. White crystals were obtained at room temperature which were filtered and washed with 3 × 5 ml ethanol. Yield: 1.9 g **10** (56%); mp.: 191–193 °C; ^{1}H NMR (*DMSO*-d_6/*TMS*, δ): 2.1 (3H, s, CH_3), 3.7 (2H, t, NH–CH_2–CH_2–O), 4.4 (2H, t, NH–CH_2–CH_2–O), 6.7 (2H, bs, NH_2), 7.3 (1H, bs, NH), 8.7 (2H, s, 4,6-H) ppm; IR (KBr): ν(heterocycle) = 815, 1435, 1560, ν(NH_2) = 3340, ν(NH) = 3190 cm^{-1}.

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References

[1] Walek W, Pallas M, Fieseler C, Müller W, Parche EM, Kochmann W, Steinke W (1986) Ger (East) DD 241 204, Chem Abstr **107**: 45 182g

[2] Walek W, Pallas M, Steinke W, Kemter P, Kochmann W (1986) Ger (East) DD 241 256, Chem Abstr **107**: 59 042w

[3] Walek W, Pallas M, Steinke W, Kochmann W, Schöppe G (1988) Ger (East) DD 256 693, Chem Abstr **111**: 7422h

[4] Durant GJ, Emmett JC, Ganellin CR (1972) Ger Offen DE 2 211 454, Chem Abstr **77**: 164 704y

[5] Kreidl J, Farkas M, Harsányi K, Benke B, Radó A, Domány G, Hegedüs B, Csongor É, Deutsch J, Pethö H (1983) Ger Offen DE Appl 3 235 459, Chem Abstr **99**: 10 848r

[6] Lam PYS, Eyermann CJ, Hodge CN, Jadhav PK, Delucca GV (1993) PCT Int Appl WO 93 07 128, Chem Abstr **120**: 134 540f

[7] Turner RW (1975) Synthesis 332
[8] Gompper R, Gäng M, Saygin F (1966) Tetrahedron Lett 1885
[9] Hartke K, Radau S (1974) Arch Pharm Ber Dtsch Pharm Ges **307**: 897
[10] Davidson JS (1965) Chem Ind 1977
[11] Gante J, Mohr G (1975) Chem Ber **108**: 174
[12] Wu MT (1977) J Heterocyclic Chem **14**: 443
[13] Davidson JS, Peak DA (1963) J Chem Soc 3327
[14] Birtwell S, Curd FHS, Hendry JA, Rose FL (1948) J Chem Soc 1645
[15] Petersen HJ (1976) Ger Offen DE 2 557 438, Chem Abstr **85**: 142 993e
[16] Reiter J, Somorai T, Jerkovich Gy, Dvortsák P (1982) J Heterocyclic Chem **19**: 1157
[17] Reiter J, Pongó L, Somorai T, Dvortsák P (1986) J Heterocyclic Chem **23**: 401
[18] Evers R, Fischer E (1979) Z Chem **19**: 290
[19] Trompen WP, Geevers J, Hackmann JTh (1971) Recl Trav Chim Pays-Bas **90**: 463
[20] Hevesi J, Nagy B, Földényi R, Vass A, Dudás J, Gyapai J, Molnár A, Szabó I, Tóth J (1991) HU 202 503, Chem Abstr (submitted to press)
[21] Goralski CT, Burk GA (1977) J Org Chem **42**: 3094
[22] Földényi R, Dudás J (1991) Monatsh Chem **122**: 745
[23] Suyama T, Odo K (1971) Yuki Gosei Kagaku Kyokai Shi **29**: 65
[24] Budesinsky Z, Vavrina J (1972) Coll Czech Chem Commun **37**: 1721
[25] Wittenbrook LS, Smith GL, Timmons RJ (1973) J Org Chem **38**: 465

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