1,2,4-Triazolo[4,3-*c*]pyrimidines From 4-Acylhydrazinopyrimidines

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The reaction of N^1-acetylacetamidrazones **1** with *N*-[bis(methylthio)methylene]cyanamide (**2**) at room temperature in the presence of potassium carbonate in dimethyl sulfoxide affords good yields of ethyl 4-acylhydrazino-2-amino-6-methylthio-5-pyrimidine carboxylate **3**. By briefly refluxing compounds **3** in dimethyl sulfoxide, 1,2,4-triazolo[4,3-*c*]pyrimidine derivatives **4** were obtained. When equimolecular amounts of N^1-acylacetamidrazones and compounds **2** were refluxed in dimethyl sulfoxide/toluene, compounds **4** were obtained directly.

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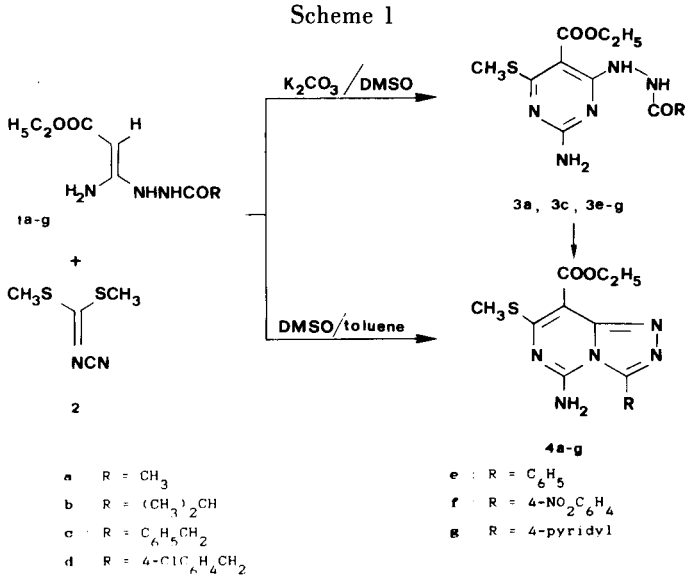
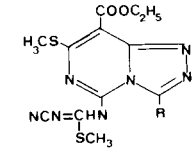
Polysubstituted pyrimidines are versatile synthons for various heterocyclic systems. Particularly 4-hydrazinopyrimidines are suitable precursors in the formation of azolepyrimidine. The reaction of 4-hydrazinopyrimidines with ortho esters lead to 1,2,4-triazolo[4,3-*c*]pyrimidines and under certain conditions to rearranged products of the [1,5-*c*] series [1]. In recent years these bicyclic systems have acquired great importance due to the range of their different biological activities (bronchospasmolytic [2], diuretic [3], antiviral [4]).

In this paper we report a new, easy synthesis of polysubstituted pyrimidines and their condensation to 1,2,4-triazolo[4,3-*c*]pyrimidines starting from the N^1-acylacetamidrazones **1**. The precursors of the triazolopyrimidines, the 4-acylhydrazinopyrimidines **3**, are obtained by reacting equimolecular amounts of N^1-acylamidrazones **1** and *N*-[bis(methylthio)methylene]cyanamide (**2**) at room temperature in the presence of potassium carbonate in dimethyl sulfoxide. Formation of compounds **3** depends on the amidrazone and on the reaction time, as reported in Table 1. When reacted longer, apart from the pyrimidines **3**, varying amounts of 1,2,4-triazolo[4,3-*c*]pyrimidine **4** are formed (Scheme 1).

Scheme 1



When cyanamide **2** reacts with amidrazone **1b**, after dilution of the reaction mixture with water, compound **4b** is obtained as the main product. When the basic solution is acidified a further product separated, which is identified as 5-[(cyanoimino(methylthio)methyl)amino]-1,2,4-triazolo[4,3-*c*]pyrimidine (**5b**).



5b,5d

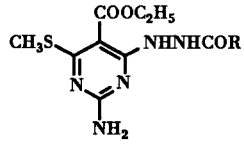
Compound **5d** is the only product obtained from the reaction between amidrazone **1d** and cyanamide **2**. Compounds **5b** and **5d** are also obtained on heating in dimethyl sulfoxide equimolecular amounts of the respective amidrazones **1b** and **1d** and cyanamide **2**. The 4-acylhydrazinopyrimidines **3** are transformed into 1,2,4-triazolo[4,3-*c*]pyrimidines **4** by short heating in dimethyl sulfoxide. Compounds **4** (Table 3) are also obtained by refluxing equimolecular amounts of amidrazones **1** and cyanamide **2** in toluene/dimethyl sulfoxide in 1:2 solution (Scheme 1). Compounds **4** are stable both to acids and heat. No rearrangement was observed, not even after prolonged boiling (24 hours) in formic acid. The structure of compounds **3** and **4** agree with the microanalytical and spectral data (Table 2, 4).

The ^{1}H nmr spectra of compounds **4** show at downfield two singlets for the protons of the NH_2 group in position 5. The non-equivalence of these protons can be attributed to the interaction with the substituents in position 3, and to a hindered rotation around the N-H bond. Compounds **4a-c** and **4e** were then submitted to acetylation with acetic anhydride in pyridine to give compounds **6a-c** and **6e** respectively (Scheme 2).

The ^{1}H nmr spectra of compounds **6a-c,e** show a singlet between 11.11 and 10.87 ppm due to the NH group and a singlet at 2.53-2.48 ppm due to the protons of the $COCH_3$ group. The chemical shifts of the other groups present in

Table 1

Physical and Analytical Data of Compounds **3**



Compound No	R	Reaction time (minutes)	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N
3a	CH_3	45	65	185 [a]	$C_{10}H_{15}N_5O_3S$	42.10	5.30	24.55
						42.15	5.28	24.52
3c	$C_6H_5CH_2$	45	63	170 [b]	$C_{16}H_{19}N_5O_3S$	53.18	5.30	19.38
						53.21	5.32	19.35
3e	C_6H_5	45	95	205 [c]	$C_{15}H_{17}N_5O_3S$	51.87	4.93	20.17
						51.84	4.92	20.14
3f	$4\text{-}NO_2C_6H_4$	3	70	240 [c]	$C_{15}H_{16}N_6O_5S$	45.92	4.11	21.42
						45.97	4.13	21.45
3g	4-pyridyl	3	75	215 [d]	$C_{14}H_{16}N_6O_3S$	48.27	4.63	24.13
						48.24	4.61	24.10

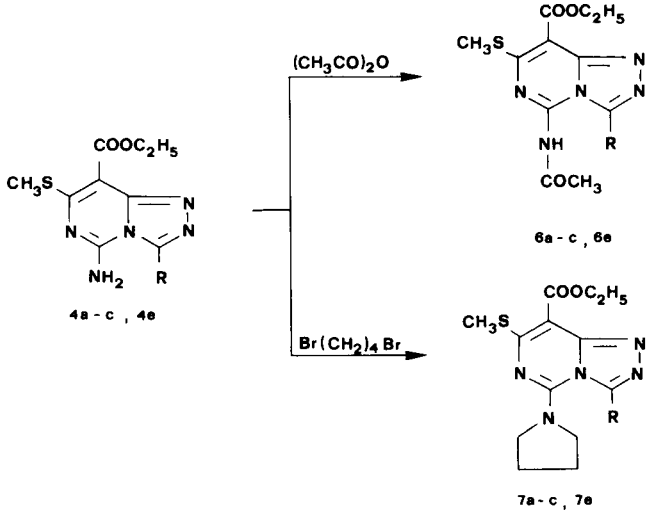
[a] From ethanol. [b] From acetonitrile. [c] From 2-ethoxyethanol. [d] From 1-propanol.

Table 2

Spectroscopic Data of Compounds **3**

Compound	IR (nujol) ν (cm^{-1})	^{1}H-NMR δ (ppm) $COOC_2H_5$	SCH_3	NH_2	NHNH	R
3a	3380, 3240, 1690, 1645, 1575	1.26 (t), 4.26 (q)	2.33 (s)	7.70 (s)	8.40 (s)	1.76 (s, CH_3)
3c	3420, 3310, 3260 1685, 1630, 1590	1.26 (t), 4.25 (q)	2.33 (s)	7.25 (s)	8.44 (s)	3.28 (s, CH_2) 7.20 (m, Ar)
3e	3480, 3410, 3350, 1695, 1660, 1640, 1610	1.28 (t), 4.27 (q)	2.37 (s)	7.48 (s)	8.49 (s)	7.32 and 8.00 (m, Ar)
3f	3420, 3300, 3230, 1670, 1640, 1610	1.29 (t), 4.28 (q)	2.38 (s)	7.71 (s)	8.55 (s)	8.17 and 8.23 (d, Ar)
3g	3400, 3280, 3220, 1690, 1670, 1625, 1615	1.27 (t), 4.27 (q)	2.36 (s)	7.68 (s)	8.50 (s)	7.86 and 8.53 (d, pyridyl)

Scheme 2



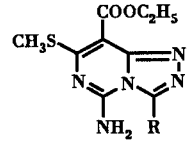
the molecule do not show any significative differences with respect to those of the compounds **4a-c,e**.

Compounds **4a-c** and **4e** are treated with 1,4-dibromobutane using hexamethylphosphoramide (HMPA) as solvent to obtain the alkylation compounds **7a-c** and **7e** (Scheme 2).

For the pyrrolidine group, three multiplets can be seen in the ^{1}H nmr spectra of compounds **7a-c,e**. The multiplet resonating at higher fields (1.90 ppm) is due to the CH_2-CH_2 protons, while the signal widened to 3.87-3.75 ppm and the multiplet at higher fields (2.45-2.42 ppm) are attributed to the protons CH_2NCH_2. The fact that the chemical shifts of the CH_2NCH_2 protons are different suggests that, because of the steric hindrance due to the substituent in position 3, the pyrrolidine ring tends to arrange perpendicularly to the plane of the central ring system. Consequently two of the CH_2NCH_2 protons undergo a re-

Table 3

Physical and Analytical Data of Compounds **4**



Compound No	R	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./Found C	H	N
4a	CH_3	65	185 [a]	$C_{10}H_{13}N_5O_2S$	44.94	4.90	26.21
					44.90	4.88	26.19
4b	$(CH_3)_2CH$	65	150 [b]	$C_{12}H_{17}N_5O_2S$	48.80	5.80	23.72
					48.84	5.82	23.69
4c	$C_6H_5CH_2$	97	183 [a]	$C_{16}H_{17}N_5O_2S$	55.97	4.99	20.40
					55.95	4.97	20.37
4d	4-$ClC_6H_4CH_2$	56	180 [a]	$C_{16}H_{16}ClN_5O_2S$	50.86	4.26	18.53
					50.84	4.28	18.51
4e	C_6H_5	85	195 [a]	$C_{15}H_{15}N_5O_2S$	54.71	4.59	21.27
					54.75	4.57	21.30
4f	4-$NO_2C_6H_4$	98	250 [c]	$C_{15}H_{14}N_6O_4S$	48.31	3.77	22.45
					48.35	3.75	22.41
4g	4-pyridyl	45	280 [a]	$C_{14}H_{14}N_6O_2S$	50.91	4.27	25.45
					50.93	4.25	25.48

[a] From ethanol. [b] From acetonitrile. [c] From 2-ethoxyethanol.

Table 4

Spectroscopic Data of Compounds **4**

Compound	IR (nujol) ν (cm^{-1})	^{1}H-NMR δ (ppm) $COOC_2H_5$	SCH_3	NH_2	R-
4a	3420, 1680, 1650, 1585	1.25 (t), 4.24 (q)	2.39 (s)	8.38 (s), 8.60 (s)	2.39 (s, CH_3)
4b	3340, 3140, 1695, 1625, 1580	1.27 (t), 4.30 (q)	2.35 (s)	8.20 (s), 8.35 (s)	1.30 and 3.03 (m, $CH(CH_3)_2$)
4c	3340, 3130, 1690, 1655, 1620	1.25 (t), 4.22 (q)	2.41 (s)	8.40 (s), 8.70 (s)	4.11 (s, CH_2), 7.30 (m, Ar)
4d	3410, 3330, 3180, 1710, 1670, 1630	1.20 (t), 4.20 (q)	2.39 (s)	8.39 (s), 8.65 (s)	4.10(s, CH_2), 7.32 (m, Ar)
4e	3470, 3340, 3300, 1700, 1670, 1625	1.31 (t), 4.27 (q)	2.43 (s)	8.40 (s), 8.63 (s)	7.49 and 8.16 (m, Ar)
4f	3440, 3300, 1700, 1680, 1640	1.30 (t), 4.33 (q)	2.39 (s)	8.70 (s)	8.33 (m, Ar)
4g	3460, 3400, 1680, 1640, 1590	1.31 (t), 4.26 (q)	2.42 (s)	8.50 (s), 8.85 (s)	8.02 and 8.73 (d, pyridyl)

markable shielding effect by interaction with the substituent in 3, typical of the *peri*-substituent repulsive interaction [5].

On the other hand it is known that the rearrangement of the *s*-triazolo[4,3-*c*]pyrimidines to the [1,5-*c*] isomers depends not only on the reaction conditions (heating, acidity of the medium) but also on the type of substituent in the pyrimidine ring: it increases with electron depletion of the ring and decreases with its electron enrichment [6]. Moreover it is still more difficult when the triazole ring is substituted [7].

The reaction between the amidrazone **1h** and cyanamide **2** in potassium carbonate and dimethyl sulfoxide leads to a mixture of compounds that depend only on the reaction time.

After 30 minutes, adduct **8** is isolated by dilution of the reaction mixture with water. In the ir this adduct is characterized by the absorption bands of the NH_2 and NHNH-$COOC_2H_5$ groups at 3480, 3410, 3295 and 3210 cm^{-1}, by absorption of the CN group at 2180 cm^{-1} and of the CO groups at 1690 and 1645 cm^{-1}. The ^{1}H nmr spectrum of compound **8** is characterized by two triplets and two quartets relating to the protons of two $COOC_2H_5$ groups and the four exchangeable protons of the NH_2 and NHNH-

Scheme 3

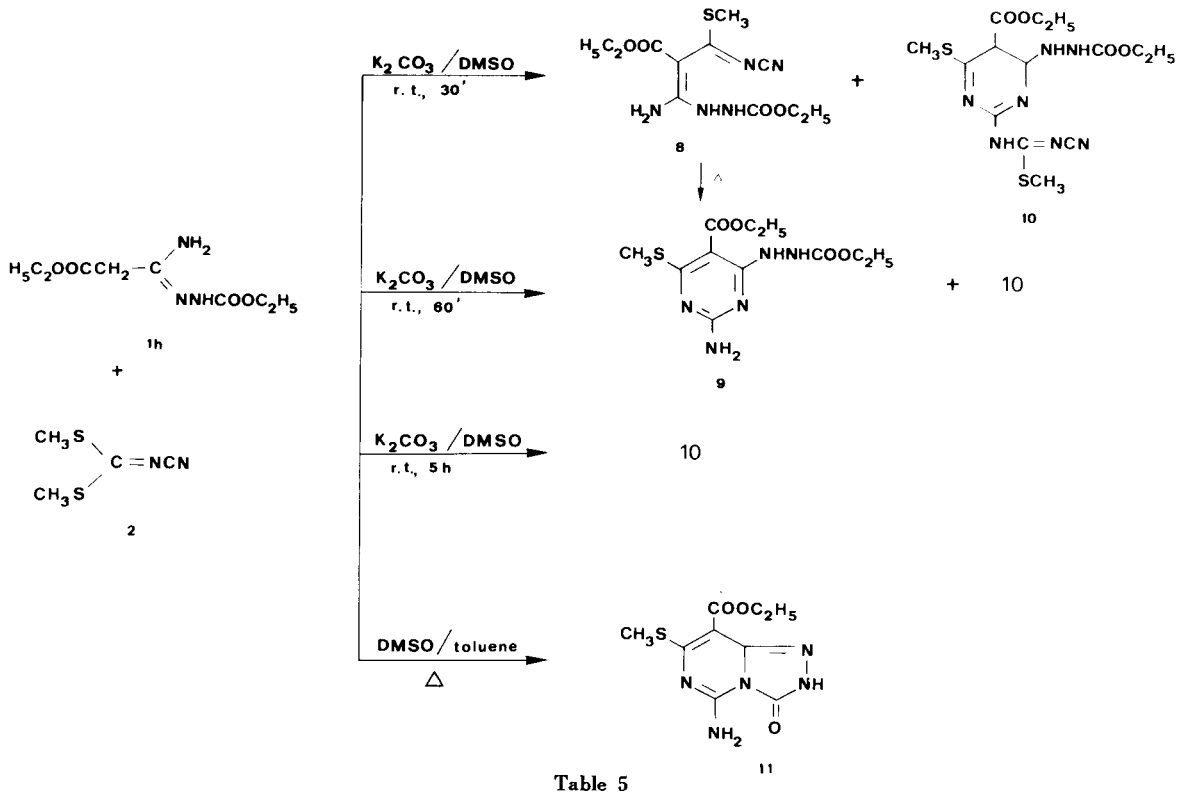
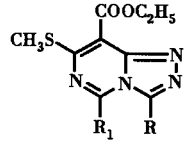


Table 5

Analytical Data of Compounds **5,6,7**



Compound No	R	R_1	Formula	Analysis % Calcd./Found C	H	N
5b	$(CH_3)_2CH$	NHC(=NCN)SCH$_3$	$C_{15}H_{19}N_7O_2S_2$	45.78 45.80	4.86 4.84	24.92 24.89
5d	4-$ClC_6H_4CH_2$	NHC(=NCN)SCH$_3$	$C_{19}H_{18}ClN_7O_2S_2$	47.94 47.90	3.81 3.83	20.60 20.58
6a	CH_3	$NHCOCH_3$	$C_{12}H_{15}N_5O_3S$	46.60 46.58	4.89 4.83	22.65 22.60
6b	$(CH_3)_2CH$	$NHCOCH_3$	$C_{14}H_{19}N_5O_3S$	49.84 49.80	5.68 5.65	20.76 20.77
6c	$C_6H_5CH_2$	$NHCOCH_3$	$C_{18}H_{19}N_5O_3S$	56.10 56.07	4.97 4.95	18.17 18.14
6e	C_6H_5	$NHCOCH_3$	$C_{17}H_{17}N_5O_3S$	54.98 54.95	4.61 4.62	18.86 18.84
7a	CH_3	pyrrolidino	$C_{14}H_{19}N_5O_2S$	52.33 52.30	5.96 5.98	21.80 21.78
7b	$(CH_3)_2CH$	pyrrolidino	$C_{16}H_{23}N_5O_2S$	55.00 55.04	6.64 6.67	20.05 20.01
7c	$C_6H_5CH_2$	pyrrolidino	$C_{20}H_{23}N_5O_2S$	60.44 60.40	5.83 5.80	17.62 17.65
7e	C_6H_5	pyrrolidino	$C_{19}H_{21}N_5O_2S$	59.52 59.55	5.52 5.50	18.27 18.25

$COOC_2H_5$ groups. Adduct **8** is quickly transformed into 4-ethoxycarbonylhydrazinopyrimidine **9**. This compound is obtained in 40% yields when the reaction mixture is kept under stirring for one hour. Apart from compounds **8** and **9**, compound **10** is also isolated by acidification of the respective solutions. This compound is the only product obtained when the reaction time is extended to 5 hours. Compound **10** is also obtained by addition of cyanamide **2** to compound **9**.

The 1,2,4-triazolo[4,3-*c*]pyrimidine-3-one, **11**, is obtained either by refluxing equivalent amounts of amidrazone **1h** and cyanamide **2** in a dimethyl sulfoxide/toluene solution, or by heating of 4-acylhydrazinopyrimidine **9** in dimethyl sulfoxide.

Table 6

Analytical Data of Products From the Reaction Between **1h** and **2**

Compound No	Formula	Analysis % Calcd. C	H	N	Found C	H	N
8	$C_{11}H_{17}N_5O_4S$	41.90	5.43	22.21	41.93	5.45	22.19
9	$C_{11}H_{17}N_5O_4S$	41.90	5.43	22.21	41.87	5.40	22.18
10	$C_{14}H_{19}N_7O_4S_2$	40.66	4.63	23.71	40.64	4.60	23.73
11	$C_9H_{11}N_5O_3S$	40.15	4.12	26.02	40.11	4.10	26.00

EXPERIMENTAL

The melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in nujol with a Perkin-Elmer 398 spectrophotometer. The ^1H nmr spectra were recorded on a Varian Unity 300 spectrometer with shifts in ppm downfield from the internal hexamethyldisiloxane. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. The N^1-acylacetamidrazones were obtained with a previously described procedure [8].

General Procedure for the Preparation of Ethyl 6-(2-acylhydrazino)-2-amino-4-methylthio-5-pyrimidinecarboxylates **3a,c,e,f,g**.

Forty percent aqueous potassium carbonate (3.5 ml) was added to a stirred solution of the appropriate N^1-acylacetamidrazone **1** (10 mmoles) and compound **2** (10 mmoles) in dimethyl sulfoxide (10 ml). The mixture was stirred at room temperature for the time shown in Table 1 and then diluted with ice-water. The precipitate was collected by filtration, washed, dried and recrystallized to give compounds **3**.

In the case of amidrazone **1b**, following the general procedure with a reaction time of 30 minutes, ethyl 5-amino-3-isopropyl-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**4b**) (50% yield) was obtained.

With a reaction time of 3 hours, compound **4b** precipitates with a 34% yield (based on compound **2**), and after neutralization of the solution with 10% aqueous hydrochloric acid, ethyl 5-[(cyanoimino(methylthio)methyl)amino]-3-isopropyl-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**5b**) was obtained, mp 240° (acetonitrile), yield 26% (based on compound **2**); ir (nujol): 3300, 2250, 1715, 1700, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.06 (m, 6H, $2CH_3$), 1.19 (t, 3H, CH_3), 2.43 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3), 2.86 (m, 1H, CH), 4.13 (q, 2H, CH_2), 7.45 (br s, 1H, NH), 11.24 (s, 2H, 2NH).

As far as regards amidrazone **1d**, after a reaction time of 3 minutes, only ethyl 3-(4-chlorophenylmethyl)-5-[(cyanoimino(methylthio)methyl)amino]-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**5d**) was obtained, mp 210° (1-propanol), yield 72% (based on compound **2**); ir (nujol): 3260, 2240, 1710, 1620, 1580 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.03 (t, 3H, CH_3), 2.44 (s, 6H, $2CH_3$), 3.85 (s, 2H, CH_2), 3.94 (q, 2H, CH_2), 7.33 (m, 5H, Ar + NH), 11.62 (s, 2H, 2NH).

Products **5b,d** were obtained also from the reaction of compounds **4b,d** (10 mmoles) and **2** (10 mmoles). The reagents were refluxed in dimethyl sulfoxide (10 ml) in the presence of 40% aqueous potassium carbonate for 10 hours. The reaction mixture was cooled and diluted with water to obtain **5b,d** in 20% yields.

General Procedure for the Preparation of the 1,2,4-Triazolo[4,3-*c*]pyrimidine Derivatives **4a-g**.

Method A.

A solution of **2** (10 mmoles) and the appropriate amidrazone **1** (10 mmoles) in dimethyl sulfoxide/toluene 2:1 (15 ml) was refluxed for 30 minutes. After cooling, crushed ice was added. The formed precipitate was filtered off and recrystallized from a suitable solvent to give compounds **4** in the yields reported in Table 3.

Method B.

Thermal Cyclization of Compounds **3**.

A solution of **3** in dimethyl sulfoxide (5 ml) was refluxed for 5 hours. After cooling water was added to the reaction mixture. The resulting solid was collected by suction and recrystallized from an appropriate solvent to give compounds **4** in quantitative yields.

Method C.

A 40% aqueous potassium carbonate solution (3.5 ml) was added to a solution of amidrazones **1f,g** (10 mmoles) and compound **2** (10 mmoles) in dimethyl sulfoxide (10 ml). The resulting mixture was stirred at room temperature for 30 minutes and then diluted with water. The formed solid was filtered and after recrystallization gave the corresponding 1,2,4-triazolo[4,3-*c*]pyrimidine **4f,g** in quantitative yields.

Reactions of Amidrazone **1h** with **2** in Dimethyl Sulfoxide/Potassium Carbonate.

A solution of 40% aqueous potassium carbonate (3.5 ml) was added to a stirred solution of **1h** (10 mmoles) and **2** (10 mmoles) in dimethyl sulfoxide (10 ml). The mixture was stirred at room temperature for 30 minutes, then diluted with ice-water. The formed solid was filtered, washed with water and dried to give ethyl 3-amino-2-[cyanoimino(methylthio)methyl]-3-(2-ethoxycarbonylhydrazino)propenoate **8**, mp 120°, yield 50% (based on compound **2**); ir (nujol): 3480, 3410, 3290, 3230, 2160, 1690, 1645, 1615, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.11 (t, 3H, CH_3), 1.26 (t, 3H, CH_3), 2.33 (s, 3H, SCH_3), 3.91 (q, 2H, CH_2), 4.25 (q, 2H, CH_2), 7.75 (br s, 2H, NH_2), 8.47 (s, 2H, NHNH).

The remaining solution was acidified with 10% hydrochloric acid and ethyl 2-[(cyanoimino(methylthio)methyl)amino]-6-(2-ethoxycarbonylhydrazino)-4-methylthio-5-pyrimidinecarboxylate

(**10**) was obtained, mp 310° (2-ethoxyethanol), yield 70% (calculated on compound **2**); ir (nujol): 3270, 2240, 1730, 1620, 1580 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_3), 1.21 (t, 3H, CH_3), 2.46 (s, 3H, SCH_3), 4.14 (q, 2H, CH_2), 4.18 (q, 2H, CH_2), 9.90 (br s, 1H, NH), 11.20 (br s, 1H, NH), 11.40 (br s, 1H, NH).

When the reaction time reached 1 hour, after dilution with ice-water, an initial precipitate was obtained. It was separated by filtration, washed with acetone and dried to give ethyl 2-amino-6-(2-ethoxycarbonylhydrazino)-4-methylthio-5-pyrimidinecarboxylate (**9**), mp 295° (from diethyleneglycol), yield 40% (based on compound **2**); ir (nujol): 3410, 3280, 3210, 1680, 1655, 1620, 1585 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.11 (t, 3H, CH_3), 1.27 (t, 3H, CH_3), 2.33 (s, 3H, SCH_3), 3.91 (q, 2H, CH_2), 4.25 (q, 2H, CH_2), 7.81 (br s, 2H, NH_2), 8.48 (br s, 2H, NHNH).

From the acidified solution product **10** was obtained, yield 58% (calculated on product **2**).

When the reaction time reached 5 hours, only product **10** was obtained, yield 98%.

Pyrimidine derivative **9** was also obtained in quantitative yields by refluxing an ethanolic solution of compound **8** for 5 minutes.

Preparation of 5-Amino-2,3-dihydro-8-ethoxycarbonyl-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-3-one (**11**).

Method A.

A solution of amidrazone **1h** (10 mmoles) and compound **2** (10 mmoles) in dimethyl sulfoxide/toluene 2:1 (15 ml) was refluxed for 30 minutes. The formed precipitate was filtered off and recrystallized from diethyleneglycol to give compound **11**, mp 315° dec, yield 95%; ir (nujol): 3400, 3280, 1650, 1620, 1590 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (t, 3H, CH_3), 2.43 (s, 3H, SCH_3), 8.10, 8.30 (br s, 2H, NH_2), 11.90 (br s, 1H, NH).

Method B.

A solution of compound **9** (10 mmoles) in dimethyl sulfoxide (10 ml) was refluxed for 12 hours. After cooling ice-water was added. The solid obtained was treated as described in method A to give compound **11** in 80% yields.

Acetylation of Compounds **4a-c,e**.

Acetic anhydride was added to a solution of 1,2,4-triazolo[4,3-*c*]pyrimidines **4a-c,e** (10 mmoles) in pyridine (4 ml), and the resulting mixture was refluxed for 6 hours. After cooling, ice-water was added and the formed precipitate was collected by filtration and recrystallized from a suitable solvent to give compounds **6a-c,e**.

Ethyl 5-(Acetylamino)-3-methyl-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**6a**).

The title product was obtained (70%), mp 164° (from acetonitrile); ir (nujol): 3240, 1710, 1685 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.26 (t, 3H, CH_3), 2.32 (s, 3H, $COCH_3$), 2.45 (s, 3H, SCH_3), 2.50 (s, 3H, CH_3), 4.32 (q, 2H, CH_2), 11.11 (br s, 1H, NH).

Ethyl 5-(Acetylamino)-3-isopropyl-7-methylthio-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**6b**).

The title product was obtained (65%), mp 150° (from acetonitrile); ir (nujol): 3200, 1700, 1680 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (m, 9H, $3CH_3$), 2.34 (s, 3H, SCH_3), 2.48 (s, 3H, $COCH_3$), 3.14 (m, 1H, CH), 4.30 (q, 2H, CH_2), 10.87 (s, 1H, NH).

Ethyl 5-(Acetylamino)-7-methylthio-3-phenyl-1,2,4-triazolo[4,3-*c*]pyrimidine-8-carboxylate (**6c**).

The title compound was obtained (80%), mp 225° (from 2-ethoxyethanol); ir (nujol): 3340, 1710, 1685, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.35 (t, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 2.53 (s, 3H, SCH_3), 4.34 (q, 2H, CH_2), 7.52, 8.22 (m, 5H, Ar), 11.01 (s, 1H, NH).

Ethyl 5-(Acetylamino)-7-methylthio-3-phenylmethyl-1,2,4-triazolo-[4,3-*c*]pyrimidine-8-carboxylate (**6e**).

The title compound was obtained (90%), mp 145° (from benzene); ir (nujol): 3220, 1700, 1680, 1600, 1540 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (t, 3H, CH_3), 2.33 (s, 3H, SCH_3), 2.49 (s, 3H, $COCH_3$), 4.15 (s, 2H, CH_2), 4.27 (q, 2H, CH_2), 7.26 (m, 5H, Ar), 11.10 (s, 1H, NH).

Alkylation of Compounds **4a-c,e**.

1,2,4-Triazolo[4,3-*c*]pyrimidines **4a-c,e** (10 mmoles) were dissolved in 10 ml of dry HMPA. A 100% excess of sodium bicarbonate was added, as well as 1,4-dibromobutane (10 mmoles), and the reaction mixture was heated at 70-80° for 5 hours. After cooling, ice-water was added and the product was extracted with ethyl ether, and concentrated. Purification of the product was achieved by recrystallization from a suitable solvent.

Ethyl 3-Methyl-7-methylthio-5-pyrrolidino-1,2,4-triazolo[4,3-*c*]-pyrimidine-8-carboxylate (**7a**).

The title product was obtained (80%), mp 175° (from cyclohexane); ir (nujol): 1670, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.24 (t, 3H, CH_3), 1.90 (m, 4H, $2CH_2$), 2.35 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 2.45 and 3.75 (m, 4H, CH_2NCH_2), 4.21 (q, 2H, CH_2).

Ethyl 3-Isopropyl-7-methylthio-5-pyrrolidino-1,2,4-triazolo[4,3-*c*]-pyrimidine-8-carboxylate (**7b**).

The title compound was obtained (70%), mp 140° (from cyclohexane); ir (nujol): 1670, 1610, 1555 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.26 (m, 9H, $3CH_3$), 1.89 (m, 4H, $2CH_2$), 2.36 (s, 3H, SCH_3), 2.99 (m, 1H, CH), 2.42 and 3.78 (m, 4H, CH_2NCH_2), 4.22 (q, 2H, CH_2).

Ethyl 7-Methylthio-3-phenyl-5-pyrrolidino-1,2,4-triazolo[4,3-*c*]-pyrimidine-8-carboxylate (**7c**).

The title compound was obtained (80%), mp 160° (from benzene); ir (nujol): 1680, 1650, 1610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31 (t, 3H, CH_3), 1.91 (m, 4H, $2CH_2$), 2.37 (s, 3H, SCH_3), 2.42 and 3.86 (m, 4H, CH_2NCH_2), 4.26 (q, 2H, CH_2), 7.49, 8.14 (m, 5H, Ar).

Ethyl 7-Methylthio-3-phenylmethyl-5-pyrrolidino-1,2,4-triazolo-[4,3-*c*]pyrimidine-8-carboxylate (**7e**).

The title product was obtained (90%), mp 175° (from acetonitrile); ir (nujol): 1670, 1600, 1560 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23 (t, 3H, CH_3), 1.90 (m, 4H, $2CH_2$), 2.38 (s, 3H, SCH_3), 2.45 and 3.78 (m, 4H, CH_2NCH_2), 4.05 (s, 2H, CH_2), 4.19 (q, 2H, CH_2), 7.29 (m, 5H, Ar).

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