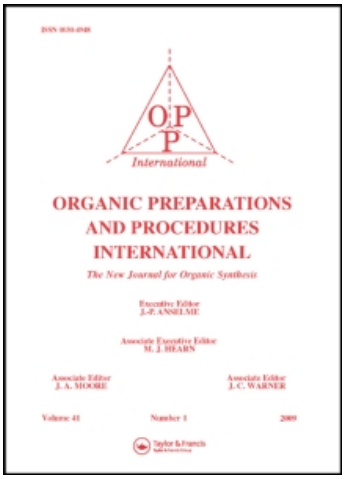

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SYNTHESIS OF THIENO[3,2-e]-1,2,4-TRIAZOLO[a]PYRIMIDINES

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SYNTHESIS OF THIENO[3,2-e]-1,2,4-TRIAZOLO[a]PYRIMIDINES

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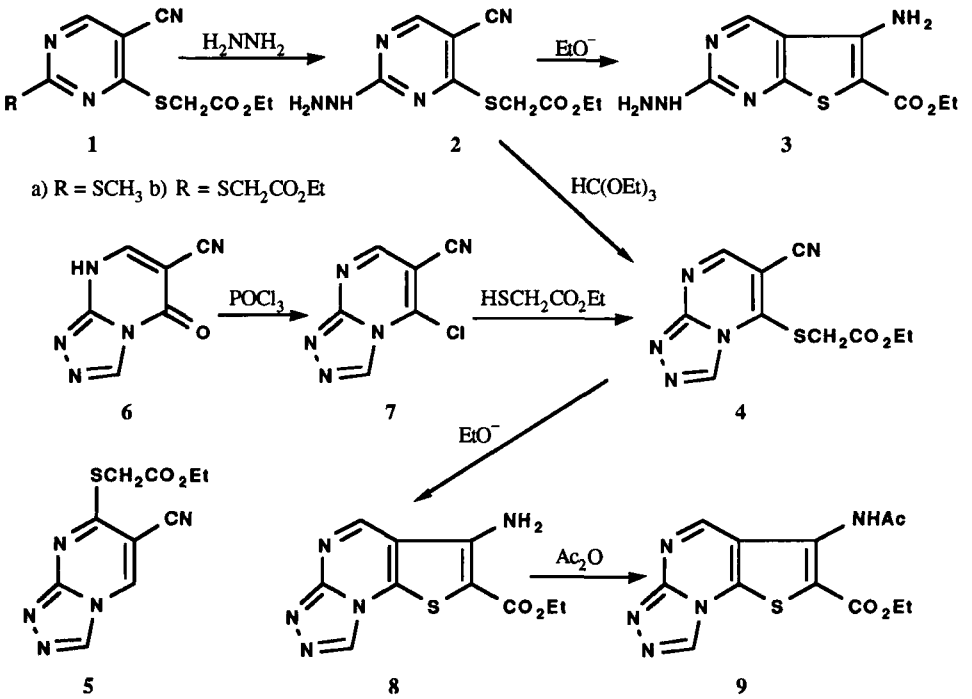
Several approaches have been developed for the synthesis of thieno-1,2,4-triazolopyrimidines. The methods can be classified into three groups. The first one involves formation of the triazolo ring starting from hydrazinothieno[2,3-d]pyrimidines[1,2] or from 3-amino-4-iminothieno[2,3-d]pyrimidines.[2,3] The second method involves formation of the pyrimidine ring by cyclization of 2-amino-3-(1H-1,2,4-triazol-3-yl)thiophenes[4] or by reaction of 5-amino-1,2,4-triazoles with thiophene β-ketoesters.[5] According to the third method, thieno[3,2-e]-1,2,4-triazolo[1,5-c]pyrimidines can be synthesized by recyclization of corresponding [4,3-c]isomers.[2,6] Nevertheless, 2,4,5-trisubstituted pyrimidines are versatile synthons for various heterocyclic systems, containing the pyrimidine nucleus. Recently, we have synthesized the N-amino derivatives of thieno[2,3-d:4,5-d']dipyrimidine starting from (2-alkylthio-5-cyanopyrimidinyl-4-thio)acetic acids esters.[7]

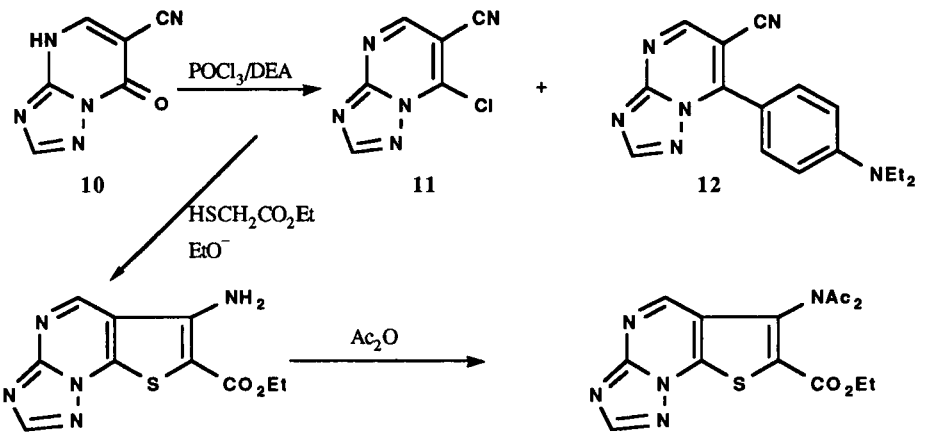
This paper describes the synthesis of isomeric thieno-[3,2-e]-1,2,4-triazolo[a]pyrimidines. The present work was also stimulated by the reports that a number of triazolo[a]pyrimidines[8] and thieno



[2,3-d]pyrimidines[9] display biological activity. Reaction of (2-alkylthio-5-cyanopyrimidinyl-4-thio)acetic acids esters (**1**) with hydrazine hydrate afforded the 2-hydrazino derivative **2**.

The structure of compound **2** was established by its cyclization to the known thieno[2,3-d]pyrimidine derivative **3**[7a] and by spectral methods. Upon treatment of **2** with triethyl orthoformate, cyclization between the 2-hydrazine group and the 3-position occurred to give ethyl ester of (6-cyano-1,2,4- triazolo[4,3-a]pyrimidinyl-5-thio)acetic acid (**4**), the isomeric 6,7-disubstituted derivative **5** was not formed. The structure of compound **4** was assigned on the basis of spectral assignments: the proton at position 3 in **4** was easily exchangeable with deuterium, and the pyrimidine ring proton in triazolopyrimidine appeared at s 8.33 and falls into a region s 7.84-8.34, characteristic of H(7), while H(5) appears invariably above δ 8.6.[10] In addition, the struct.ure of **4** was confirmed by its alternate synthesis from the known 6-cyano-1,2,4-triazolo[4,3-a]pyrimidin-5(8H)-one[11] (**6**) through the 5-chloro derivative **7**. Compound **4** was converted with sodium ethoxide to the ethyl ester of 6-aminothieno[3,2-e]-1,2,4-triazolo[4,3-a]pyrimidine-7-carboxylic acid (**8**), the first representative of this new heterocyclic system to our knowledge.

Taking into account that triazolo[4,3-a]pyrimidines undergo isomerization under basic or acidic conditions to the [1,5-a]isomers,[12] we accomplished the synthesis of ethyl ester of 6-aminothieno[3,2-e]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylic acid (**13**), isomeric to the compound **8**, from triazolo[1,5-a]pyrimidinone **10** through the chloro derivative **11**.



The two isomeric thienotriazolopyrimidines, **8** and **13**, showed no appreciable difference in the fragmentation pattern under electron impact. However, the ^{1}H NMR spectra showed considerable difference in the absorbtion of triazole proton. While the triazole proton of **8** resonates at δ 10.05, that of isomeric ring system **13** appears to be more shielded and exhibits a singlet at δ 9.35. Similar assignments have been reported in the thieno[3,2-e]-1,2,4-triazolo[c]pyrimidine series. The reaction of acetic andhydride with **8** and **13** afforded the monoacetyl- and diacetylamino derivatives **9** and **14** respectively (Schemes 1 and 2). An unexpected result was obtained in the reaction of **10** with phos-

phorus oxychloride in the presence of N,N-diethylaniline (DEA). Besides the formation of chloro derivative **11** the arylation of triazolopyrimidine occurred to give 6-cyano-5-(p-diethylamino)phenyl-1,2,4-triazolo[1,5-a]pyrimidine (**12**).

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as KBr pellets using a specord 75 IR spectrometer. UV spectra were obtained on a specord UV VIS spectrometer in ethanol. The ^{1}H NMR spectra were recorded on a Tesla BS 487C (80 MHz) spectrometer using hexamethyldisiloxane as the internal reference. The mass spectra were obtained on Kratos MS-50 (70 eV) instrument Fusing an introduction by direct insertion probe. Elemental analysis for C, H, N were performed on a CHN Analyser.

Ethyl Ester of (5-Cyano-2-hydrazinopyrimidinyl-4-thio)acetic acid (**2**).- A mixture of ethyl ester of (5-cyano-2-methylthiopyrimidinyl-4-thio)acetic acid (**1a**)[7a] (1 g, 3.7 mmol), ethanol (20 ml) and 99% hydrazine hydrate (0.19 g, 3.7 mmol) was stirred at room temperature for 5 hrs. After cooling to 5°, the precipitate was collected, washed with cold ethanol and recrystallized from ethanol to give 0.64 g (68%) of **2** as a colorless solid, mp. 151-152°. IR: 1716 (C=O), 2216 (C=N), 3328 (NH) cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 1.02 (t, 3H, CH_3), 3.98 (k, 2H, OCH_2), 4.02 (s, 2H, SCH_2), 4.5 (br.s, 2H, NH_2 exchangeable); 8.11 (s, 1H, 6-H), 8.44 (br.s, 1H, NH exchangeable); Ms: m/z (%) 253 M^+ (51), 207 (100), 180 (26), 179 (43), 165 (17), 151 (29).

Anal. Calcd. for $C_9H_{11}N_5O_2S$: C, 42.68. H, 4.38, N, 27.65

Found: C, 42.83, H, 4.43, N, 27.64

In the preparation of **2** from 5-cyano-2,4-bis(ethoxycarbonylmethylthio)pyrimidine (**1b**),[7b] a two-fold molar excess of hydrazine hydrate was used. The reaction time was 3 hrs and the yield was 81%.

Ethyl Ester of 5-Amino-2-hydrazinothieno[2,3-d]pyrimidine-6-carboxylic Acid (**3**).- To a warm solution of **2** (0.5 g, 2 mmol) in ethanol (15 ml) the 1M solution (0.1 ml) of $NaOC_2H_5$ in ethanol was added. The mixture was stirred at room temperature for 1 hr. The res.ulting precipitate was collected, washed with ethanol and recrystallized from a mixture of dimethylformamide-water to give 0.41 g (80%) of **3** as a yellow solid, mp. 238-239.5°, lit.[7a] mp. 238-239.5°. ^{1}H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3), 4.16 (k, 2H, OCH_2), 4.33 (br.s, 2H, NH_2 exchangeable), 7.23 (br.s, 2H, 5-NH_2 exchangeable), 8.75 (br.s, 1H, NH exchangeable), 8.95 (s, 1H, 4-H).

Ethyl Ester of (6-Cyano-1,2,3,4-triazolo [4,3-a]pyrimidinyl-5-thio)acetic Acid (**4**).- a) A mixture of **2** (2.68 g, 11 mmol), ethyl orthoformate (12.4 ml, 94 mmol) and 2 drops of acetic anhydride was refluxed for 9 hrs. The hot mixture was filtered the excess of ethyl orthoformate was removed *in vacuo*. Ethanol (7 ml) was added to the residue and the mixture was cooled to 5°; the precipitated solid was collected and recrystallized from ethanol to give 2.34 g (81%) of **4** as a colorless solid, mp. 138-139°. UV: λ_{max} (log ε) 221 (4.46), 244 (4.4), 258 (4.41), 273 sh (3.87), 313 (3.7) nm; IR: 1720 (C=O), 2220 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 4.1 (s, 2H, SCH_2), 4.18 (k, 2H, SCH_2), 8.34

(s, 1H, 7-H), 9.03 (s, 1H, 3-H), Ms: m/z (5) 263 M^+ (13), 217 (30), 190 (100), 177 (12), 164 (16).

Anal. Calcd. for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.45; N, 26.60

Found: C, 45.53; H, 3.34; N, 26.67

b) To a suspension of **7** (1 g, 5.58 mmol) in ethanol (12 ml), a solution of sodium salt of ethyl mercaptoacetate, prepared from sodium (0.12 g, 5.58 mmol), ethanol (5 ml), and ethyl mercaptoacetate (0.67 g, 5.58 mmol), was added dropwise. The mixture was stirred at room temperature for 20 min. After cooling the precipitated solid was collected, washed with cold water, ethanol and recrystallized from ethanol to give 1.17 g (80%) of **4** as a colorless solid, mp. 138-139°.

5-Chloro-6-cyano-1,2,4-triazolo[4,3-a]pyrimidine (**7**).- A mixture of 6-cyano-1,2,4-triazolo[4,3-a]pyrimidin-5(8H)-one (**6**)[11] (4 g, 24.8 mmol) and phosphorus oxychloride (15 ml) was refluxed for 1.5 hr. The excess of phosphorus oxychloride was removed *in vacuo*, and the residue poured onto ice. The precipitate was collected, washed with cold water until the washings were neutral and dried in a vacuum-desiccator ($CaCl_2$). The aqueous solution was extracted with chloroform (ca.500 ml), dried over $CaCl_2$, evaporated to give an additional crop (1 g) of **7**. The solids were combined and recrystallized from ethyl acetate to give 3.76 g (85%) of **7** as a colorless solid, mp. 156-157°. UV: λ_{max} (log ε) 228 (4.37), 310 (3.93) nm.

Anal. Calcd. for $C_6H_2N_5Cl$: C, 40.13; H, 1.12; N, 39.00

Found: C, 40.19; H, 0.93; N, 39.30

Ethyl Ester of 6-Aminothieno[3,2-e]-1,2,4-triazolo[4,3-a]pyrimidine-7-carboxylic Acid (**8**).- A mixture of **4** (1.5 g, 5.7 mmol), ethanol (15 ml), and 1M $NaOC_2H_5$ solution (0.15 ml) was refluxed under stirring for 1 hr. After cooling, the precipitate was collected, washed with ethanol and recrystallized from a mixture of dimethylformamide-water to give 1.39 g (93%) of **8** as a pale brown solid, mp. 260.5-263°. IR: 1690 (C=O), 3318, 3418 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.23 (t, 3H, CH_3), 4.2 (k, 2H, OCH_2), 7.15 (br.s, 2H, NH_2 exchangeable), 8.53 (s, 1H, 5-H), 10.05 (s, 1H, 1-H), Ms: m/z (%) 263 M^+ (94), 235 (21), 217 (100), 189 (38).

Anal. Calcd. for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.45; N, 26.60

Found: C, 45.73; H, 3.43; N, 26.67

Ethyl Ester of 6-Acetylaminothieno[3,2-e]-1,2,4-triazolo[4,3-a]pyrimidine-7-carboxylic Acid (**9**).- A mixture of **8** (0.5 g, 1.9 mmol) and acetic anhydride (5 ml) was refluxed for 2 hrs. After cooling to 5°, the precipitate was collected, washed with ethanol and recrystallized from dimethylformamide to give 0.35 g (61%) of **9** as a colorless solid, mp. 254-255°. ^1H NMR (DMSO-d_6): δ 1.28 (t, 3H, CH_2CH_3), 2.13 (s, 3H, $COCH_3$), 4.28 (k, 2H, CH_2CH_3), 8.58 (s, 1H, 5-H), 9.83 (s, 1H, 1-H), 9.95 (br.s, 1H, NH).

Anal. Calcd. for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.63; N, 22.94

Found: C, 47.26; H, 3.81; N, 22.77

5-Chloro-6-cyano-1,2,4-triazolo[1,5-a]pyrimidine (**11**) and 6-Cyano-5-(*p*-diethylamino)phenyl-1,2,4-triazolo[1,5-a]pyrimidine (**12**).- A mixture of 6-cyano-1,2,4-triazolo[1,5-a]pyrimidin-5(8H)-one

(**10**)[11] (1.2 g, 7.5 mmol), phosphorus oxychloride (26 ml), and N,N-diethylaniline (2.4 ml, 15 mmol) wasrefluxed for 2 hrs. The excess of phosphorus oxychloride was removed *in vacuo*, and a residue poured onto ice. The precipitate was collected and recrystallized from ethyl acetate to give 0.24 g (l8%) of **11** as a pale yellow solid, mp. 170°. ^{1}H NMR (CF_3CO_2D): δ 8.8 (s, 1H, 7-H), 8.93 (s, 1H, 2-H). The substance is very easily hydrolysed to **10**, even by the moisture in the air. The crude product **11** was used without further purification in the next reaction.

The aqueous filtrate was extracted with ca. 300 ml of chloroform, extract dried over $MgSO_4$. After evaporation of chloroform, the residue was chromotographed on silica gel (lx60 cm) L 100/160, using chloroform as eluent. The fraction with R_f 0.2 was collected. After evaporation of the chloroform, the residue was recrystallized from ethyl acetate to give 0.44 g (20%) of **12** as a red solid, mp. 174.5-177°. IR: 2222 (C=N) cm^{-1}; ^{1}H NMR (CF_3CO_2D): δ 0.9l (t, 6H, CH_3), 3.54 (k, 4H, CH_2), 7.55 (d, 2H, aromatic protons), 7.93 (d, 2H, aromatic protons), 8.8 (s, 1H, 7-H), 9.1 (s, 1H, 2-H). Ms: m/z (%) 292 M^+ (28), 277 (100), 249 (47).

Anal. Calcd. for $C_{16}H_{16}N_6$: C, 65.74, H, 5.52. N, 28.75
Found: C, 65.53. H, 5.67; N, 28.88

Ethyl Ester of 6-Aminothieno[3,2-e]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylic Acid (**13**).- To a suspension of **11** (1.4 g, 7.8 mmol) in ethanol (15 ml), a solution of sodium salt of ethyl mercaptoacetate, prepared from sodium (0.18 g, 7.8 mmol), ethanol (7 ml), and ethyl mercaptoacetate (0.94 g, 7.8 mmol), was added dropwise. The mixture was stirred at room temperature for 1 hr. The resulting precipitate was collected, washed with ethanol and recrystallized from a mixture of dimethylformamide-water to give 0.82 g (40%) of **13** as a colorless solid, mp. 273-274°. IR: 1670 (C=O), 3320, 3422 (NH_2) cm^{-1}, ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 3H, CH_3), 4.2 (k, 2H, OCH_2), 7.33 (br.s, 2H, NH_2 exchangeable), 8.55 (s, 1H, 5-H), 9.35 (s, 1H, 2-H), Ms: m/z (%) 263 M^+ (l00), 235 (28), 217 (95), 191 (20), 162 (38).

Anal. Calcd. for $C_{10}H_9N_5O_2S$: C, 45.62; H, 3.45; N, 26.60
Found: C, 45.17; H, 3.17; N, 26.39

Ethyl Ester of 6-Diacetylaminothieno[3,2-e]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylic Acid (**l4**).- A mixt.ure of **13** (1 g, 3.8 mmol) and acetic anhydride (10 ml) was refluxed for 10 hrs. After cooling to 5°, the precipitate was collected, washed with ethanol and recrystallized from dimethylformamide to give 0.59 g (45%) of **14** as a colorless solid, mp. 156.5-157.5°. ^{1}H NMR (DMSO-d_6): δ 1.23 (t, 3H, CH_2CH_3), 2.23 (s, 6H, $COCH_3$), 4.29 (k, 2H, CH_2CH_3), 8.74 (s, 1H, 5-H), 9.31 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{13}N_5O_4S$: C, 48.41; H, 3.77; N, 20.16
Found: C, 48.02; H, 4.11; N, 20.41

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