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Synthesis of new pyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,4-*c*]pyrimidines and a 5,6-dihydro-1,2,4-triazolo[4″,3″:1′,2′]pyrido[4′,3′:4,5]thieno[2,3-*d*]-pyrimidine ring system

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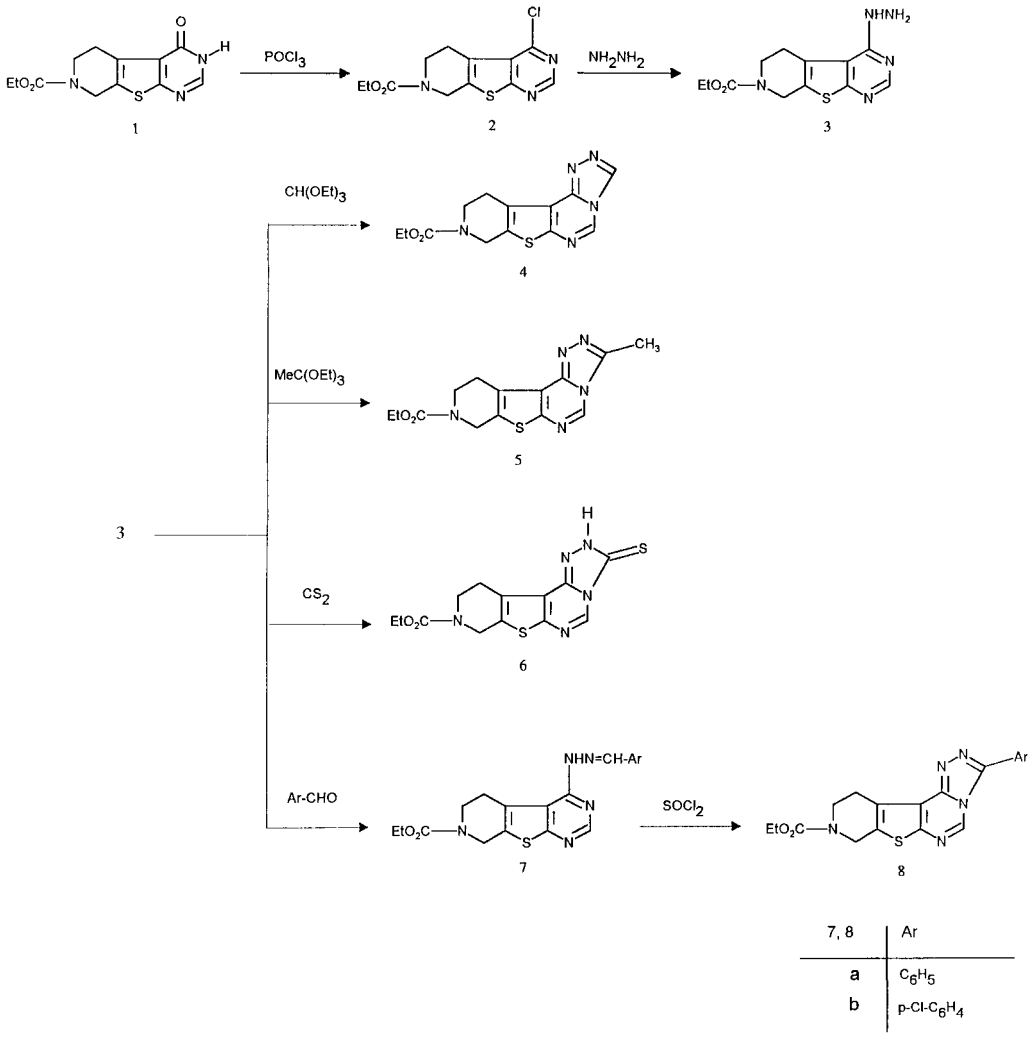
A series of substituted pyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,4-*c*]pyrimidines **4**–**6**, **8**, pyrido[4′,3′:4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,4-*c*]pyrimidines **11**–**13** and 5,6-dihydro-1,2,4-triazolo[4″,3″:1′,2′]pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidines **16**–**19** have been synthesized from **3**, **10** and **15** through the reaction with orthoesters and carbon disulphide, respectively.

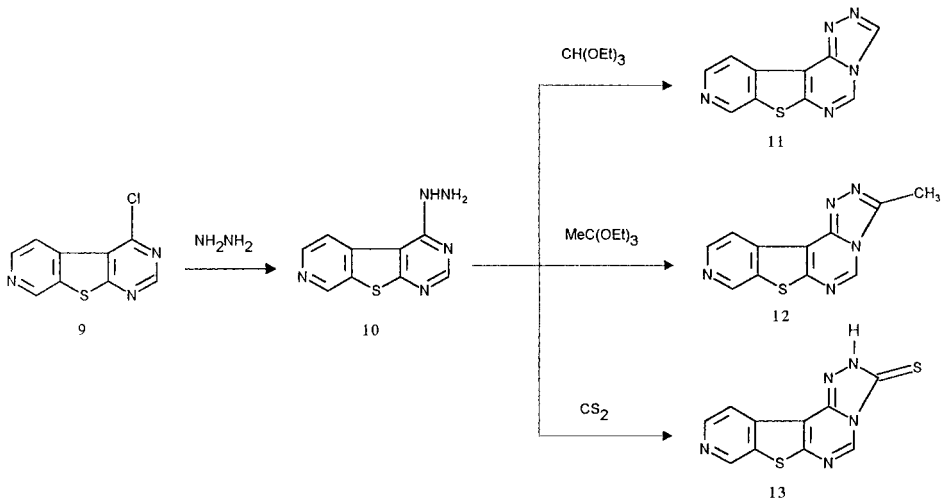
1. Introduction

Pyridothienopyrimidines have been the subject of chemical and biological studies on account of their interesting pharmacological properties. A number of syntheses for substituted derivatives of this triheterocyclic ring system have been developed. Such derivatives have antiinflammatory [1–3], antipyretic [4, 5], analgesic [6] and antianaphylatic [7, 8] activity. Also, some are clinically effective antiallergic [9] or potentially antineoplastic agents [10] and a few possess significant hypocholesterolemic [11] activity. On the other hand, 1,2,4-triazoles are considered a very interesting heterocyclic ring system because of their therapeutic importance. Recently, derivatives of 1,2,4-triazole have been found to have significant analgesic [12] and antiseptic [13] activity. Therefore we wanted to develop an efficient procedure for the synthesis of new heterocyclic systems containing a 1,2,4-triazolo moiety condensed with a pyridothienopyrimidine nucleus, pyridothienotriazolopyrimidines.

Scheme 1



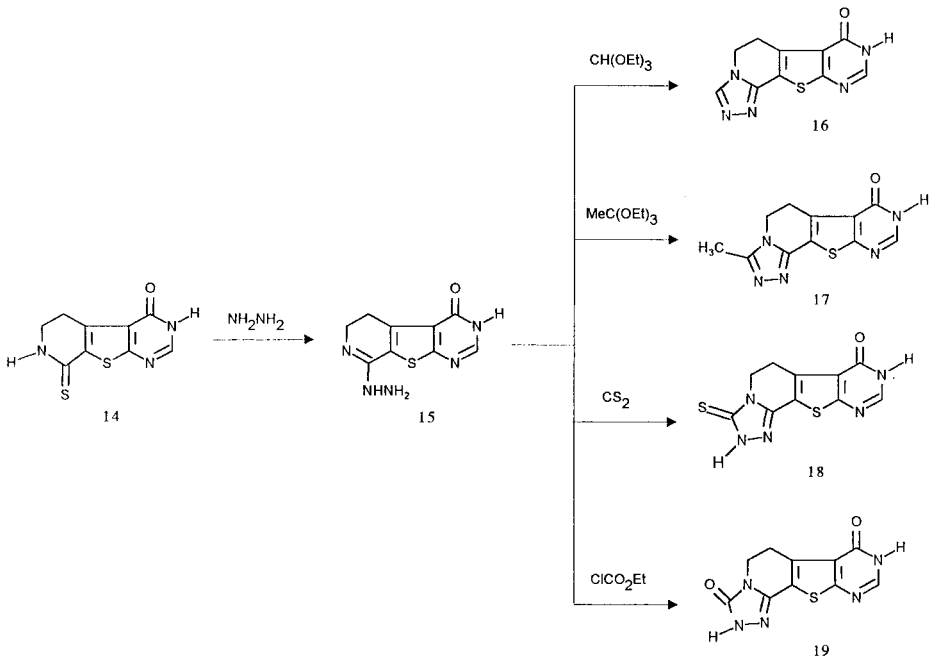
Scheme 2



2. Investigations, results and discussion

The key intermediate is 4-hydrazino-5,6-dihydro-8 H-pyrido[4′, 3′ : 4,5]thieno[2,3-*d*]pyrimidine-7(6 *H*)-carboxylic acid ethyl ester (**3**) which is obtained from 3,4,5,8-tetrahydro-4-oxopyrido[4′, 3′: 4,5]-thieno[2,3-*d*]pyrimidine-7(6 *H*)-carboxylic acid ethyl ester **1** [14], via chlorination with phosphoryl chloride to give the corresponding chloro compound **2**. Refluxing **2** with an excess of hydrazine hydrate in ethanol gave **3**, through the nucleophilic substitution of the chloro atom at C-4 in **2** with hydrazine. The resulting compound **3** was refluxed with triethyl orthoformate to afford pyridothienotriazolopyrimidines **4**. In the same manner, compound **3** refluxed with triethyl orthoacetate gave 3-methyl-10,11-dihydro-8 *H*-pyrido[4′,3′ : 4,5]thieno-[2,3-*d*]-1,2,4-triazolo-[3,4-*c*]pyrimidine-9(8 *H*)-carboxylic acid ethyl ester (**5**). Refluxing **3** with carbon disulphide in methanol and in the presence of an equivalent of potassium hydroxide yields 10,11-dihydro-8 *H*-pyrido-[4′,3′ : 4,5]thieno[2,3-*d*]-1,2,4-triazolo[3,4-*c*]pyrimidine-3(2 *H*)-thione-9(8 *H*)-carboxylic acid ethyl ester (**6**). Condensation of **3** with aromatic aldehydes in refluxing ethanol and in the presence of a catalytic amount of piperidine yielded the corresponding carbohydrazones **7a**, **b** which are subjected to intramolecular cyclocondensation, using thionyl chloride, to give the triazolo derivatives **8a**, **b** (Scheme 1). On the other hand, pyridothienotriazolopyrimidines **11**–**13** were obtained when 4-hydrazinopyridothienopyrimidine (**10**) which was prepared by reacting the chloro compound **9** [14] with an excess of hydrazine hydrate in ethanol at reflux temperature, was subjected to a reaction with triethyl orthoformate, triethyl orthoacetate and carbon disulphide in refluxing methanol, respectively. Our interest in developing synthetic approaches to the interesting tetracyclic triazolopyridothienopyrimidines **16**–**19** led us to synthesize the 8-hydrazino derivative **15** by hydrazinolysis of **14** [14]. Thus, reacting **15** with ethyl orthoformate, ethyl orthoacetate, carbon disulphide in

Scheme 3



methanol and ethyl chloro formate in pyridine gave the triazolopyridothienopyrimidines **16**–**18** and **19**, respectively, as a new tetracyclic ring system. Structural assignments of all new compounds were made on the basis of spectral data (see Experimental).

3. Experimental

M.p's were recorded on a Gallenkamp apparatus and are uncorrected. IR Spectra were recorded on a Shimadzu 470 spectrophotometer (KBr pellets). ^{1}H NMR spectra were recorded on a JEOL (270 MHz) spectrometer with TMS as internal standard and chemical shifts are expressed in δ values.

3.1. 4-Chloro-5,6-dihydro-8 H-pyrido[4′,3′ : 4,5]thieno[2,3-d]pyrimidine-7(6 H)-carboxylic acid ethyl ester (2)

A solution of **1** (0.56 g, 2 mmol) in $POCl_3$ (10 ml) was refluxed for 1 h. The reaction mixture was concentrated to dryness in vacuo. The oily residue was poured into ice/water. The precipitated product was filtered off, washed well with water, dried and recrystallized from ethanol to give colorless crystals; yield 85%: m.p.: 91–92 °C. IR(KBr): ν = 3000 (arom. CH), 2900 (aliph. CH), 1700 (ester C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.21 (t, 3 H, CH_3), 3.12 (t, 2 H, H-5), 3.74 (t, 2 H, H-6), 4.14 (q, 2 H, CH_2), 4.79 (s, 2 H, H-8), 8.85 (s, 1 H, H-2).
$C_{12}H_{12}ClN_3O_2S$

3.2. Synthesis of hydrazinopyrido[4′,3′ : 4,5]thieno[2,3-d]pyrimidine 3, 10 *and* 15 *(general procedure)*

A mixture of **2**, **9** or **14** (0.001 mol) and hydrazine hydrate (0.022 mol) in ethanol (5 ml) was refluxed for 2–4 h. Then the solvent was removed in vacuo and the resulting solid product was washed with water, dried and recrystallized from methanol.

3.2.1. 4-Hydrazino-5,6-dihydro-8 H-pyrido[4′,3′ : 4,5]thieno[2,3-d]pyrimidine-7(6 H)-carboxylic acid ethyl ester (3)

Colorless powder; yield 63%; m.p.: 160–162 °C. IR(KBr): ν = 3250–3400 (NH, NH_2), 3000 (arom. CH), 2900 (aliph. CH), 1690 (ester C=O), 1625 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.12 (t, 3 H, CH_3), 3.01 (t, 2 H, H-5), 3.67 (t, 2 H, H-6), 4.13 (q, 2 H, CH_2), 4.75 (s, 2 H, H-8), 7.71–8.20 (br, 3 H, $NHNH_2$), 8.36 (s, 1 H, H-2).
$C_{12}H_{15}N_5O_2S$

3.2.2. 4-Hydrazinopyrido[4′,3′ : 4,5]thieno[2,3-d]pyrimidine (10)

Yellow crystals; yield 66%; m.p.: 224–225 °C. IR: ν = 3200–3350 (NH, NH_2), 1625 (C=N) cm^{-1}. ^{1}H NMR: δ = 5.15 (br, 2 H, NH_2), 8.38 (s, 1 H, H-2), 8.55 (d, 1 H, H-5), 8.70 (d, 1 H, H-6), 8.75 (s, 1 H, H-8), 9.40 (br, 1 H, NH).
$C_9H_7N_5S$

3.2.3. 8-Hydrazino-5,6-dihydropyrido[4′,3′ : 4,5]thieno[2,3-d]pyrimidine-4(3 H)-one (15)

Yellow crystals; yield 80%; m.p.: 281–282 °C; IR ν = 3200–3350 (NH, NH_2), 1680 (C=O), 1610 (C=N) cm^{-1}. ^{1}H NMR: δ = 3.15 (t, 2 H, H-5), 3.47 (t, 2 H, H-6), 7.11 (br, 2 H, NH_2), 7.71 (br, 1 H, NH), 8.45 (s, 1 H, H-2).
$C_9H_9N_5OS$

3.3. Synthesis of pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo[3,4-c]pyrimidines, 4, 5, 11 *and* 12, *and 1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[4′,3′ : 4,5]-thieno[2,3-d]pyrimidines* 16, 17 *(general procedure)*

A mixture of **3**, **10** or **15** (0.002 mol) and triethyl orthoformat or triethyl orthoacetate (10 ml) was refluxed for 2–4 h. After cooling at room temperature, the formed product was filtered off, dried and recrystallized from a suitable solvent.

3.3.1. 10,11-Dihydro-8 H-pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]pyrimidine-9(8 H)carboxylic acid ethyl ester (4)

Yellow powder from ethanol; yield 66%; m.p.: 213–214 °C. IR: ν = 3090, 3030 (arom. CH), 2930 (aliph. CH), 1720 (ester C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.23 (t, 3 H, CH_3), 3.15 (t, 2 H, H-11), 3.81 (t, 2 H, H-10), 4.11 (q, 2 H, CH_2), 4.49 (s, 2 H, H-8), 9.32 (s, 1 H, H-5), 9.42 (s, 1 H, H-3).
$C_{13}H_{13}N_5O_2S$

3.3.2. 3-Methyl-10,11-dihydro-8 H-pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]pyrimidine-9(8 H)carboxylic acid ethyl ester (5)

Yellow powder from ethanol; yield 56%; m.p.: 124–125 °C. IR: ν = 3070 (arom. CH), 2975 (aliph. CH), 1710 (ester C=O), 1610 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.23 (t, 3 H, CH_3), 2.78 (s, 3 H, CH_3), 3.13 (t, 2 H, H-11), 3.82 (t, 2 H, H-10), 4.11 (q, 2 H, CH_2), 4.78 (s, 2 H, H-8), 9.23 (s, 1 H, H-5).
$C_{14}H_{15}N_5O_2S$

3.3.3. Pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]pyrimidine (11)

Yellow powder from DMF; yield 75%; m.p.: 268–269 °C. IR: ν = 3100 (arom. CH), 1610 (C=N) cm^{-1}. ^{1}H NMR: δ = 8.45 (d, 1 H, H-11), 8.78 (s, 1 H, H-5), 9.45 (d, 1 H, H-10), 9.76 (s, 1 H, H-8), 9.78 (s, 1 H, H-3).
$C_{10}H_5N_5S$

3.3.4. 3-Methyl-pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]-pyrimidine (12)

Yellow powder from DMF; yield 86%; m.p.: 238–239 °C. IR: ν = 3020 (arom. CH), 2995 (aliph. CH), 1610 (C=N) cm^{-1}. ^{1}H NMR: δ = 2.82 (s, 3 H, CH_3), 8.35 (d, 1 H, H-11), 8.75 (s, 1 H, H-5), 9.40 (d, 1 H, H-10), 9.55 (s, 1 H, H-8).
$C_{11}H_7N_5S$

3.3.5. 5,6-Dihydro-1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[4′,3′ : 4,5]thieno[2,3-d]-pyrimidine-7(8 H)-one (16)

Yellow crystals from ethanol; yield 60%, m.p.: 295–296 °C. IR: ν = 3050 (arom. CH), 1690 (ester C=O), 1610 (C=N) cm^{-1}. ^{1}H NMR: δ = 3.50 (t, 2 H, H-6), 4.38 (t, 2 H, H-5), 8.50 (s, 1 H, H-9), 8.64 (s, 1 H, H-3).
$C_{10}H_9N_5OS$

3.3.6. 3-Methyl-5,6-dihydro-1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[4′,3′ : 4,5] thieno[2,3-d]pyrimidine-7(8 H)-one(17)

Yellow crystals from ethanol; yield 59%; m.p.: 182–183 °C, IR: ν = 3050 (arom. CH), 2950 (aliph. CH), 1690 (C=O) cm^{-1}. ^{1}H NMR: δ = 2.08 (s, 3 H, CH_3), 3.13 (t, 2 H, H-6) 3.44 (t, 2 H, H-5), 8.42 (s, 1 H, H-9).
$C_{11}H_9N_5OS$

3.4. Synthesis of pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo[3,4-c]pyrimidines, 6, 13 *and 1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[4′,3′ : 4,5]-thieno[2,3-d]pyrimidines* 18 *(general procedure)*

To a mixture of **3**, **10** or **15** (0.002 mol), and potassium hydroxide (0.112 g, 0.002 mol) in methanol (10 ml), carbon disulphide (0.003 mol) was added. The mixture was refluxed for 2–5 h. After concentration, the mixture was diluted with water and acidified with conc. hydrochloric acid. The resulting solid product was filtered off, washed well with water, dried and recrystallized from suitable solvent.

3.4.1. 10,11-Dihydro-8 H-pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]pyrimidine-3(2 H)-thione-9(8 H)-carboxylic acid ethyl ester (6)

Yellow crystals from ethanol; yield 61%, m.p.: 207–209 °C. IR: ν = 3000 (arom. CH), 2950 (aliph. CH), 1690 (ester C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.22 (t, 3 H, CH_3), 3.00 (t, 2 H, H-11), 3.77 (t, 2 H, H-10), 4.12 (q, 2 H, CH_2), 4.78 (s, 2 H, H-8), 8.94 (s, 1 H, H-5), 14.62 (s, 1 H, NH).
$C_{13}H_{13}N_5O_2S_2$

3.4.2. Pyrido[4′,3′ : 4,5]thieno[2,3-d]-1,2,4-triazolo-[3,4-c]pyrimidine-3(2 H)-thione (13)

Yellow crystals from DMF; yield 58%; m.p.: >360 °C. IR: ν = 3000 (arom. CH), 1625 (C=N) cm^{-1}. ^{1}H NMR: δ = 8.35(d, 1 H, H-11), 8.72 (s, 1 H, H-5), 9.40 (d, 1 H, H-10), 9.50 (s, 1 H, H-8).
$C_{10}H_5N_5S_2$

3.4.3. 5,6-Dihydro-1,2,4-triazolo[4″,3″ : 1′,2′]pyrido[4′,3′ :4,5]thieno[2,3-d]-pyrimidine-3(2 H)-thione-7(8 H)-one (18)

Yellow crystals from ethanol; yield 75%, m.p.: 260–261 °C. IR: ν = 3050 (arom. CH), 1670 (C=O) cm^{-1}. ^{1}H NMR: δ = 3.16 (t, 2 H, H-6), 3.52 (t, 2 H, H-5), 8.43 (s, 1 H, H-9).
$C_{10}H_7N_5OS_2$

3.5. 5,6-Dihydro-8 H-4-(arylidene hydrazino)pyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-7(6 H)-carboxylic acid ethyl ester 7a, b *(general procedure)*

To a mixture of **3** (0.58 g, 0.002 mol) and the appropriate aromatic aldehyde (0.002 mol) in ethanol (10 ml), a catalytic amount of piperidine was added. The reaction mixture was refluxed for 2 h. After concentration and cooling at room temperature, the precipitated product was filtered off, dried and recrystallized from a proper solvent.

3.5.1. 5,6-Dihydro-8 H-4-[benzylidene hydrazino]pyrido[4′,3′:4,5]-thieno[2,3-d]-pyrimidine-7(6 H)-carboxylic acid ethyl ester (7a)

Yellow crystals from methanol; yield 94%; m.p.: 176–178 °C. IR: ν = 3400 (NH), 3070 (arom. CH), 1700 (ester C=O), 1620 (C=N) cm^{-1}. ^{1}H NMR: δ = 1.23 (t, 3 H, CH_3), 3.15 (t, 2 H, H-5), 3.80 (t, 2 H, H-6),

4.11 (q, 2 H, CH_2), 4.75 (s, 2 H, H-8), 6.80–7.60 (m, 6 H, 5 ArH + CH=N), 8.32 (s, 1 H, H-2), 9.25 (s, 1 H, NH).
$C_{19}H_{19}N_5O_2S$

3.5.2. 5,6-Dihydro-8 H-4-[4-chorobenzylidene hydrazino]pyrido[4′,3′:4,5]-thieno[2,3-d]-pyrimidine-7(6 H)-carboxylic acid ethyl ester (**7b**)

Pale yellow crystals from methanol; yield 92%; m.p.: 224–225 °C. IR: ν = 3400 (NH), 3000 (arom. CH), 2900 (aliph. CH), 1675 (ester C=O), 1620 (C=N) cm^{-1}. ^1H NMR: δ = 1.23 (t, 3 H, CH_3), 3.15 (t, 2 H, H-5), 3.81 (t, 2 H, H-6), 4.11 (q, 2 H, CH_2), 4.75 (s, 2 H, H-8), 7.40–7.62 (m, 3 H, 2 ArH + CH=NH), 7.90 (d, 2 ArH), 8.33 (s, 1 H, H-2), 9.27 (s, 1 H, NH).
$C_{19}H_{18}ClN_5O_2S$

3.6. 3-Aryl-10,11-dihydro-8 H-pyrido[4′,3′:4,5]thieno[2,3-d]-1,2,4-triazolo[3,4-c]pyrimidine-9(8 H)-carboxylic acid ethyl ester 8a, b *(general procedure)*

A mixture of **7a**, **b** (0.001 mol) and thionyl chloride (10 ml) was heated at 70–80 °C for 2 h. The excess of thionyl chloride was removed by distillation under reduced pressure. The resulting solid product was collected by filtration, washed with water, dried and recrystallized from the suitable solvent.

3.6.1. 3-Phenyl-10,11-dihydro-8 H-pyrido[4′,3′:4,5]thieno[2,3-d]-1,2,4-triazolo[3,4-c]pyrimidine-9(8 H)-carboxylic acid ethyl ester (**8a**)

Yellow crystals from ethanol; yield 72%; m.p.: 164 °C. IR: ν = 3100 (arom. CH), 2900 (aliph. CH), 1700 (ester C=O), 1620 (C=N) cm^{-1}. ^1H NMR: δ = 1.23 (t, 3 H, CH_3), 3.35 (t, 2 H, H-11), 3.80 (t, 2 H, H-10), 4.11 (q, 2 H, CH_2), 4.75 (s, 2 H, H-8), 6.8–7.6 (m, 5 ArH), 8.35 (s, 1 H, H-5).
$C_{19}H_{17}N_5O_2S$

3.6.2. 3-(4 Chlorophenyl)-10,11-dihydro-8 H-pyrido[4′,3′:4,5]thieno[2,3-d]-1,2,4-triazolo[3,4-c]pyrimidine-9(8 H)-carboxylic acid ethyl ester (**8b**)

Yellow crystals from ethanol; yield 81%; m.p.: 168 °C. IR: ν = 3000 (arom. CH) 2950 (aliph. CH), 1700 (ester C=O) cm^{-1}. ^1H NMR: δ = 1.23 (t, 3 H, CH_3), 3.23 (t, 2 H, H-11), 3.80 (t, 2 H, H-10), 4.11 (q, 2 H, CH_2), 4.75 (s, 2 H, H-8), 7.63 (d, 2 ArH), 7.95 (d, 2 ArH), 8.30 (s, 1 H, H-5).
$C_{19}H_{16}ClN_5O_2S$

3.7. 5,6-Dihydro-1,2,4-triazolo[4″,3″:1′,2′]pyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-3(2 H)-oxo-7(8 H)-one (**19**)

A mixture of **15** (0.47 g, 0.002 mol) and ethyl chloroformate (2 ml) was refluxed in dry pyridine (10 ml) for 5 h. After cooling at room temperature and dilution with water, the resulting solid product was filtered off, dried and recrystallized from DMF to give yellow crystals yield 74%; m.p.: >360 °C. IR: ν = 3250 (NH), 3050 (arom. CH), 1710 (C=O), 1685 (C=O), 1660 (C=N) cm^{-1}. ^1H NMR: Insoluble in commen solvents.
$C_{10}H_7N_5O_2S$

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References

1 Leistner, S.; Wagner, G.; Gütschow, M.; Glusa, E.: Pharmazie **41**, 54 (1986)
2 Chaykovsky, M.; Lin, M.; Rosowsky, A.; Modest, E.: J. Med. Chem. **10**, 188 (1973)
3 Eslager, E. F.; Jacob, P. W.; Leslic, M.: J. Heterocyclic Chem. **9**, 775 (1972)
4 Bousquet, E.; Romero, G.; Guerrera, F.; Caruso, A.; Roxas, M. A.: Farmaco Ed. Sci. **40**, 869 (1985)
5 Bousquet, E.; Guerrera, F.; Siracusa, N. A.; Caruso, A.; Roxas, M. A.: Farmaco Ed. Sci. **39**, 110 (1984)
6 Dave, C. G.; Shah, P. R.; Dave, C. K.; Patel, J. V.: J. Indian Chem. Soc. **66**, 48 (1989)
7 Vieweg, H.; Leistner, S.: Wagner, G.; Boehm, N.; Krasselt, U.; Grupe, R.; Lohmann, D.; Laban, G.: East German Patent, DD 257, 830 (1988); C.A. **110**, 95262p (1989)
8 Vieweg, H.; Leistner, S.; Wagner, G.; Boehm, N.; Krasselt, U.; Grupe, R.; Lohmann, D.; Laban, G.: East German Patent, DD 258, 234 (1988); C.A. **110**, 95263q (1989)
9 Madding, D, G.; Thomposon, D. M.: J. Heterocyclic Chem. **24**, 581 (1987)
10 Cheng, C. C., in: Ellis, B. G.; West, B. G. (eds.): Progress in Medicinal chemistry, vol. **25**; H. Elsevier Science Publishers, Amsterdam 1985
11 Sshoo, J. C.; Devani, B. M.; Bhadti, S. V.: Indian Patent **151**, 456 (1983); C.A. **100**, 209858 (1984)
12 Dobosz, M.; Pachuta, A.; Rekas, J.: Acta Polon. Pharm. **50**, 225 (1993)
13 Dobosz, M.; Rekas, J.; Pachuta, A.: Acta Polon. Pharm. **46**, 40 (1989)
14 Sauter, F.; Jordis, U.; Frohlich, G.; Gewald, K.; Grohmann, F.; Ahmed, E. Kh.: ACH-Models in Chemistry **131**, 489 (1994)

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