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Fused Pyrazolopyrimidines II[1]. Thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo-[1,5—a]pyrimidines

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The reaction of 3-amino-1 *H*-pyrazolo[3,4—d]thieno[2,3—b]pyridine with 1,3-dicarbonyl compounds and with ethoxy-methylene reagents gives the title ring system and its derivatives. The electrophilic substitutions occur in the thiophene ring of the system.

(Keywords: Cyclization; Electrophilic substitution; 1H-Pyrazolo[3,4—d]thieno[2,3—b]pyridine)

Kondensierte Pyrazolopyrimidine, 2. Mitt.: Thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]pyrimidine

Die Reaktion von 3-Amino-1 *H*-pyrazolo[3,4—d]thieno[2,3—b]pyridin mit 1,3-Dicarbonyl-Verbindungen und mit Ethoxymethylen-Reagentien ergibt das im Titel genannte Ringsystem und dessen Derivate. Elektrophile Substitution erfolgt im Thiophenring des Gesamtsystems.

Introduction

During our studies on thienopyridines and their cyclization reactions we had obtained 3-amino-1 *H*-pyrazolo[3,4—d]thieno [2,3—b]pyridine (**1**) by the reaction of 4-chloro-5-cycanothieno [2,3—b]pyridine with hydrazine[3]. This new aminoheterocycle (**1**) when reacted with the appropriate reagents, is capable of forming new heterocyclic systems with a nitrogen at the bridgehead. We had earlier reported[4] the formation of the title ring system from **1** and describe now the synthesis of thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]-pyrimidine (**2**), its various derivatives as well as some reactions of the ring system.

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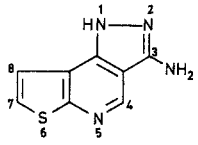
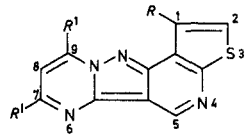
Results and Discussion

The amine **1** can react with 1,3-dicarbonyl and ethoxymethylene compounds. When **1** was allowed to condense with malondialdehyde tetramethyl acetal in the presence of zinc chloride and hydrochloric acid, thieno[3″,2″:5′,6′][pyrido-[4′,3′:3,4]pyrazolo[1,5-a]pyrimidine (**2**), the parent ring system was obtained in 76% yield. Its identity was established through its elemental analysis and the spectra.



1



2 $R=R^1=H$
3 $R=H$, $R^1=Me$
8 $R=NO_2$, $R^1=H$
9 $R=NO_2$, $R^1=Me$
10 $R=Br$, $R^1=H$
11 $R=Br$, $R^1=Me$

The infrared spectrum (IR) of **2** lacked the characteristic absorption peaks due to the amino group of **1**. The proton magnetic resonance spectrum (PMR) of **2** in *DMSO-d_6* displayed signals for the newly formed pyrimidine ring as a downfield double doublet (dd) at δ 9.52 with coupling constants of 1.9 and 4.5 Hz assigned to a proton at C 7, another dd at 8.94 with coupling constants of 1.9 and 7.0 Hz of the C 9-H and an upfield dd for C 8-H at 7.61 with coupling constants of 4.5 and 7.0 Hz. Other signals for the protons of the thiophene ring and the pyridine ring appeared as two singlets at 7.87 and 9.40 for the protons at C 1 and C 2, and C 5 respectively.

A condensation under similar conditions with 2,4-pentanedione gave the corresponding dimethyl derivative **3** in 93% yield and its structure was also confirmed by its elemental analysis and the IR and PMR spectra. The mass spectra of **2** and **3** showed the expected molecular ion peaks at *m/e* 226 and 254 respectively.

Ethoxymethylene compounds derived from "active" methylene containing esters were also used in the condensation reaction of **1**. Thus condensation of **1** with ethyl ethoxymethylenecyanoacetate in acetic acid led to the formation of 8-carbethoxy-9-amino derivative **4** of **2** as identified by its elemental analysis and IR spectrum.

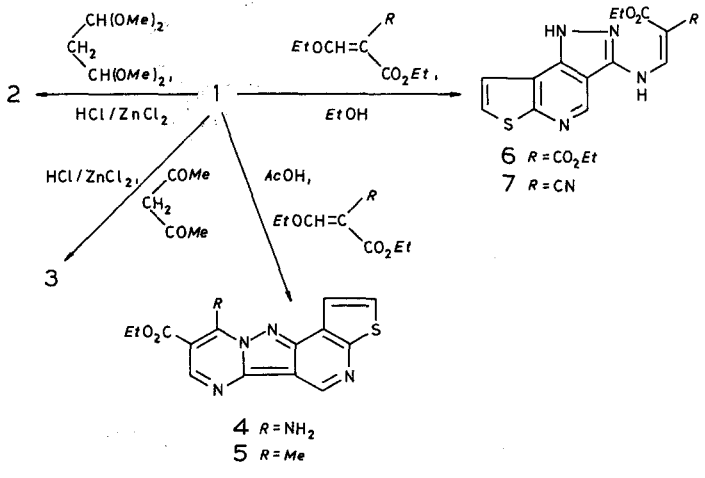
Absence of the cyano absorption and the presence of the amino absorption (3480 and 3300-3100 cm^{-1} the free and the associated stretchings) and the

carbonyl absorption of the ester group at 1690 cm^{-1} shifted to lower wavenumbers due to a hydrogen bonding with the amino group at C 9. The PMR spectrum displayed signals between 9.25 and 9.50 for the two protons at C 5 and C 8, at 8.15 for the two protons of the thiophene ring and the signals due to the protons of the ester group at 1,59 (t, 3 H) and at 4.73 (q, 2 H) with a coupling constant of 7.0 Hz.

Similarly the condensation of **1** with ethyl ethoxymethyleneacetoacetate in acetic acid led to the cyclic product **5** which was identified through its elemental and spectral analysis.

An attempted condensation of **1** with diethyl ethoxymethylenemalonate in acetic acid even with prolong refluxing (14 h) gave only the acyclic product, the aminoacrylate **6** whose structure was elucidated by its elemental and spectral analysis (see Exp.). This aminoacrylate **6** could, however, be obtained by refluxing **1** and diethyl ethoxymethylenemalonate in ethanol. Under these conditions **1** in refluxing ethanol reacted with ethyl ethoxymethylenecyanoacetate to give the corresponding aminoacrylate **7**. The structure of **7** was confirmed by its PMR spectrum, IR absorption spectrum ($\nu_{C\equiv N}$ 2220 cm^{-1} and $\nu_{C=O\ (ester)}$ 1690 cm^{-1}) and elemental analysis. Under these conditions **1** reacted with ethyl ethoxymethylene-acetoacetate to give the cyclized product **5** and no corresponding aminoacrylate was detected. This indicates that the acetyl group is much more reactive than the cyano or the ester group in these reactions. These reactions are shown in the Scheme 1.

Scheme 1



To test the reactivity of this new ring system towards electrophilic reagents some nitrations and brominations were attempted. The nitration of **2** with "mixed acids" at 25° or at 95° led to the same mononitro product **8**. Analysis of the PMR spectrum of **8** revealed that the attack of the electrophile occurs in the thiophene ring since the product showed the usual signals for the protons of the pyrimidine ring (dd at 9.83 and 8.13 with coupling constants of 1.9 and 7.0 Hz for C 7-H and 4.5 and 7.0 Hz for C 8-H and a dd at 9.48, 1.9 and 4.5 Hz, for C 9-H) and the pyridine ring (s at 10.07 for C 5-H) while the proton of the thiophene ring showed a s of 1 H at 8.96. The nitration of **3** under similar conditions also gave a mononitro product **9** which on analysis of its PMR spectrum showed that in this case also the entering nitro group attacks the thiophene ring. The bromination of **2** and **3** with bromine and acetic acid also gave monobromo products **10** and **11** respectively and once again the PMR spectra indicate the attack occuring in the thiophene moiety of this ring system. Since in condensed thiophenes such as benzothiophene[5] and thieno[2,3—b]pyridine[6] and thieno [2,3—c]pyridine[7] the preferred position for electrophilic attack has been shown to be at the β-position, we assume that in the title ring system also this position (one position) is preferred in the nitration and bromination reactions.

Acknowledgements

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Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 MHz (*TMS* as internal standard). The infrared absorption spectra (IR) were taken by the Perkin-Elmer model 727 spectrophotometer. The samples were measured in potassium bromide disks. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240 and are in full agreement with the calculated values.

Thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]pyrimidine (**2**)

3-Amino-1 *H*-pyrazolo[3,4—d]thieno[2,3—b]pyridine[3] (**1**) (0.69 g) was dissolved in 8 ml of ethanol containing 0.1 g of anhydrous zinc chloride and a few drops of concentrated hydrochloric acid and the mixture brought to reflux. A solution of malondialdehyde tetramethyl acetal (1 ml) in 3 ml of ethanol was added to the refluxing mixture and let reflux for an hour. The reaction mixture, after cooling, was inverted over ice, basified with ammonia and extracted with chloroform (3 × 20 ml). The chloroform extract was dried and on removal of the

solvent a light yellow solid was obtained which was crystallized from ethanol giving cream colored needles of **2**, $C_{11}H_{16}N_4S$, m. p. 270-271°. yield 0.62 g; 76.5%. IR (cm ^{1}): 3070, 1630, 1590, 1519, 1470, 1380, 1345, 1190, 1120, 980, 795, 760, 720; PMR δ (*DMSO-d*$_6$, 125°): 7.87 (2 H, s, H-1 and H-2), 8.94 (1 H, dd, J = 1.9 and 4.5 Hz, H-9), 9.40 (1 H, s, H-5), 9.52 (1 H, dd, J = 7.0 and 1.9 Hz, H-7), 7.61 (1 H, dd, J = 4.5 and 7.0 Hz, H-8).

7,9-Dimethylthieno[3",2":5',6']pyrido[4',3':3,4]pyrazolo[1,5—a]pyrimidine (**3**)

Using the experimental conditions for the preparation of **2**, 1 g of **1** and 3 ml of 2,4-pentamedione gave 1.25 g (93% yield) of **3**, $C_{13}H_{10}N_4S$ as yellow crystals m. p. 231-232° (ethanol, activated carbon). IR (cm^{-1}): 3100, 1629, 1600, 1590, 1510, 1451, 1440, 1381, 1160, 975; PMR δ (CF_3CO_2H): 9.95 (1 H, s, H-5), 8.15 (1 H, d, J = 6.0 Hz, H-1), 7.98 (1 H, d, J = 6.0 Hz, H-2), 7.76 (1 H, s, H-8), 3.28 (3 H, s, C**H**$_3$-9), 3.09 (3 H, s, C**H**$_3$-7).

Ethyl 9-aminothieno[3",2":5',6']pyrido[4',3':3,4]pyrazolo[1,5—a]pyrimidine-8-carboxylate (**4**)

A mixture of 0.32 g of **1** and 0.3 g of ethyl ethoxymethylenecyanoacetate in 5 ml of acetic acid was heated under reflux for 1.5 h and cooled. The yellow precipitate was filtered and crystallized from *DMSO* to give **4**, $C_{14}H_{11}N_5O_2S$, m. p. 290-292%. yield, 0.38 g (72%). IR (cm^{-1}): 3480 and 3300-3100 (NH), 1690 (C = O), 1630, 1610, 1575, 1370, 1340, 1320, 1300, 1270, 1200, 1180, 1060, 975, 715; PMR δ (CF_3CO_2H): 9.5 (1 H, s, H-5), 9.25-9.45 (1 H, br., H-7), 8.15 (2 H, s, H-1 and H-2), 4.73 (2 H, q, J = 7.0 Hz,—OC**H**$_2$CH$_3$), 1.59 (3 H, t, J = 7.0 Hz,—OCH$_2$C**H**$_3$).

Ethyl 9-methylthieno[3",2":5',6']pyrido[4',3':3,4]pyrazolo[1,5—a]pyrimidine-8-carboxylate (**5**)

A mixture of 0.21 g of **1**, 0.45 g ethyl ethoxymethyleneacetoacetate in 5 ml of acetic acid was heated under reflux for 1.5 h, cooled, filtered and crystallized from ethanol to give 0.29 g (84%) of **5**, $C_{15}H_{12}N_4O_2S$, as cream colored needles, m. p. 207-208°. IR (cm^{-1}): 1730 (C=O), 1620 and 1260; PMR δ (CF_3CO_2H): 9.99 (1 H, s, H-7), 9.75 (1 H, s, H-5), 8.23 (1 H, d, J = 6.0 Hz, H-2), 8.05 (1 H, d, J = 6.0 Hz, H-1), 4.76 (2 H, q, J = 7.0 Hz,—OC**H**$_2$CH$_3$), 1.51 (3 H, t, J = 7.0 Hz,—OCH$_2$C**H**$_3$).

Ethyl α-carbethoxy-β-(N-pyrazolo[3,4—d]thieno[2,3—b]pyrid-3-yl)aminocrylate (**6**)

A mixture of 0.4 g of diethyl ethoxymethylenemalonate and 0.36 g of **1** in 5 ml of ethanol was heated under reflux for 1.5 h. On cooling the solid was filtered and crystallized from ethanol to give 0.34 g (50% yield) of **6**, $C_{16}H_{16}N_4O_4S$, m. p. 266-267°. IR (cm^{-1}): 3260 (NH), 1690 (C=O), 1660 (C=O), 1610, 1305, 1250, 1225, 1160, 1080; PMR δ (*DMSO-d*$_6$) (100 MHz on Varian XL-100 spectrometer): 9.06 (1 H, s, H-4), 8.10 (1 H, d, J = 13.0 Hz, H-β), 10.96 (1 H, d, J = 13.0 Hz, N**H**-β), 13.59 (1 H, s, H-1), 7.93 (1 H, d, J = 7.0 Hz, H-7), 7,67 (1 H, d, J = 7.0 Hz, H-8), 4.02-4.44 (4 H, m, —OC**H**$_2$CH$_3$). 1.10-1.46 (6 H, m, —OCH$_2$C**H**$_3$).

Ethyl α-cyano-β-(N-pyrazolo[3,4—d]thieno[2,3—b]pyrid-3-yl)aminoacrylate (**7**)

On heating 0.3 g ethyl ethoxymethylenecyanoacetate and 0.32 g of **1** in 5 ml of ethanol for 1.5 h a solid was obtained which was filtered and crystallized from ethanol to give 0.23 g (43%) of **7**, $C_{14}H_{11}N_5O_2S$, m.p. 269-270°. IR (cm^{-1}): 3500-3100 (NH), 2220 (C≡N), 1690 (C=O), 1625, 1270, 1170; PMR δ (CF_3CO_2H): 9.48 (1 H, s, H-4), 9.13-9.35 (1 H, m, H-β), 8.00-8.30 (2 H, m, H-7 and H-8), 4.72 (2 H, q, J = 7.0 Hz,—O**C**$\mathbf{H_2}$C$\mathbf{H_3}$), 1.58 (3 H, t, J = 7.0 Hz, —OC$\mathbf{H_2}$C**H**$_3$).

1-Nitrothieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]pyrimidine (**8**)

0.1 g of **2** was dissolved in a 2.2 ml of nitric and sulfuric acid (1:10, *v/v*) and let it react under agitation at 25° for 0.5 h and then inverted over crushed ice, filtered and washed with water to give a yellow solid which was crystallized from *DMSO* to give 0.09 g (79%) of **8**, $C_{11}H_5N_5O_2S$, m.p. > 300°. IR (cm^{-1}): 3050, 1630, 1520 (NO_2), 1475, 1370, 1350, 1330 (NO_2), 1280, 820; PMR δ (CF_3CO_2H): 10.17 (1 H, s, H-5), 9.83 (1 H, dd, J = 1.9 and 7.0 Hz, H-7), 9.48 (1 H, dd, J = 1.9 and 4.5 Hz, H-9), 8.96 (1 H, s, H-2), 8.13 (1 H, dd, J = 4.5 and 7.0 Hz, H-8).

7,9-Dimethyl-1-nitrothieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]pyrimidine (**9**)

The nitration of 0.124 g of **3** under similar conditions used for the nitration of **2** above gave 0.118 g (81%) of **9**, $C_{13}H_9N_5O_2S$, m.p. > 300° (*DMSO*). IR (cm^{-1}): 1630, 1601, 1520 (NO_2), 1475, 1430, 1380, 1330, 1315 (NO_2), 1280, 1165, 1065, 940, 720; PMR δ (CF_3CO_2H): 10.08 (1 H, s, H-5), 8.91 (1 H, s, H-2), 7.80 (1 H, s, H-8), 3.38 (3 H, s, C$\mathbf{H_3}$-9), 3.19 (3 H, s, C$\mathbf{H_3}$-7).

1-Bromothieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]pyrimidine (**10**)

0.2 g of **2** was added to 5.5 ml solution of bromine in acetic acid (1:10, *v/v*) and stirred at 25° for 45 min, treated with potassium bisulfite and filtered. The cream colored precipitate was filtered, washed with water, crystallized from *DMSO* and repurified by subliming *in vacuo* (230°/25 mm Hg) to give 0.2 g (75%) of **10**, $C_{11}H_5N_4BrS$, m.p. 288-290°. IR (cm^{-1}: 3070, 1630, 1510, 1380, 1352, 1340, 1185, 1120, 935, 780; PMR δ (CF_3CO_2H): 9.95 (1 H, s, H-5), 9.85 (1 H, d, J = 7.0 Hz, H-7), 9.40 (1 H, d, J = 4.5 Hz, H-9), 8.18 (1 H, s, H-2), 7.90-8.20 (1 H, m, H-8).

1-Bromo-7,9-dimethylthieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5—a]-pyrimidine (**11**)

In a similar manner as for the bromination of **2** above, 0.124 g of **3** was brominated to give after sublimation at 260°/28 mm Hg, 0.113 g (70% yield) of **11**, $C_{13}H_9N_4BrS$, m.p. 258-260°. IR (cm^{-1}): 3070, 1630, 1601, 1480, 1460, 1380, 1360, 1310, 1185, 990, 920; PMR δ (CF_3CO_2H): 9.98 (1 H, s, H-5), 8.15 (1 H, s, H-2), 7.80 (1 H, s, H-8), 3.29 (3 H, s, C$\mathbf{H_3}$-9), 3.10 (3 H, s, C$\mathbf{H_3}$-7).

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