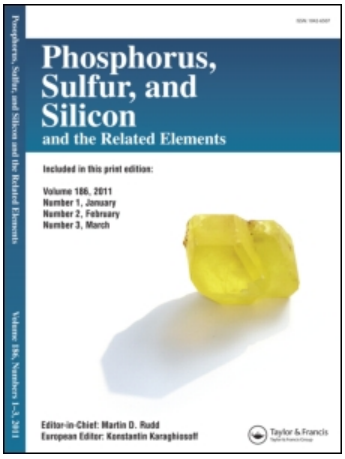

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Synthesis of Some Thioxopyrimidines, Thiazolopyrimidines, Thiazolodipyrimidines and Pyrazolothiazolopyrimidines

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*Thioxopyrimidines **4(a–c)** were synthesized by using the Biginelli three-component cyclocondensation reaction of an appropriate β-diketone, arylaldehyde, and thiourea. Reaction of thioxopyrimidines **5** with bromomalononitrile under strong basic solution afforded thiazolopyrimidines **7(a–c)**. On condensation of thiazolopyrimidines **7** with hydroxylamine hydrochloride in acetic acid and in the presence of sodium acetate thiazolodipyrimidines **8(a–b)** were obtained. However reaction of **7** with formic acid gave the corresponding pyrazolothiazolopyrimidine **9a**.*

Keywords Pyrazolothiazolopyrimidine; thiazolopyrimidines; thioxopyrimidines

INTRODUCTION

The pyrimidine nucleus, which is a useful structure for further molecular exploration and for the development of new derivatives with different biological activities, has received much attention in recent years.[1]

Pyrimidine derivatives are of interest because of their pharmacological properties[1–12] including antiviral,[2] antitumor,[5] antibacterial,[6,10] and antihypertensive[4] effects. Several synthetic strategies have been reported for the preparation of pyrimidine derivatives.[10,13–19] Most of them are based on the modification of the classical one-pot Biginelli reaction[10,14–18] and in some cases based on the more complex multi steps processes[19,20] which may involve use of some expensive commercially nonavailable materials. Owing to the versatility of pyrimidines and as a continuation of our work, we have extended the convenient

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Biginelli reaction for preparation of some different, fused pyrimidine and dipyrimidine derivatives containing a thiazole or pyrazole ring.

RESULTS AND DISCUSSION

Different pyrimidine derivatives containing a thiazole or pyrazole ring were synthesized under reflux temperature. Reaction of β-diketone **1**, appropriate arylaldehyde **2**, and thiourea under reflux condition afforded thioxopyrimidines **4(a–c)**. Also reaction thiazolopyrimidines **7** with hydroxylamine hydrochloride and formic acid gave thiazolodipyrimidines **8(a–b)** and pyrazolothiazolopyrimidine **9a** respectively as shown in Scheme 1.

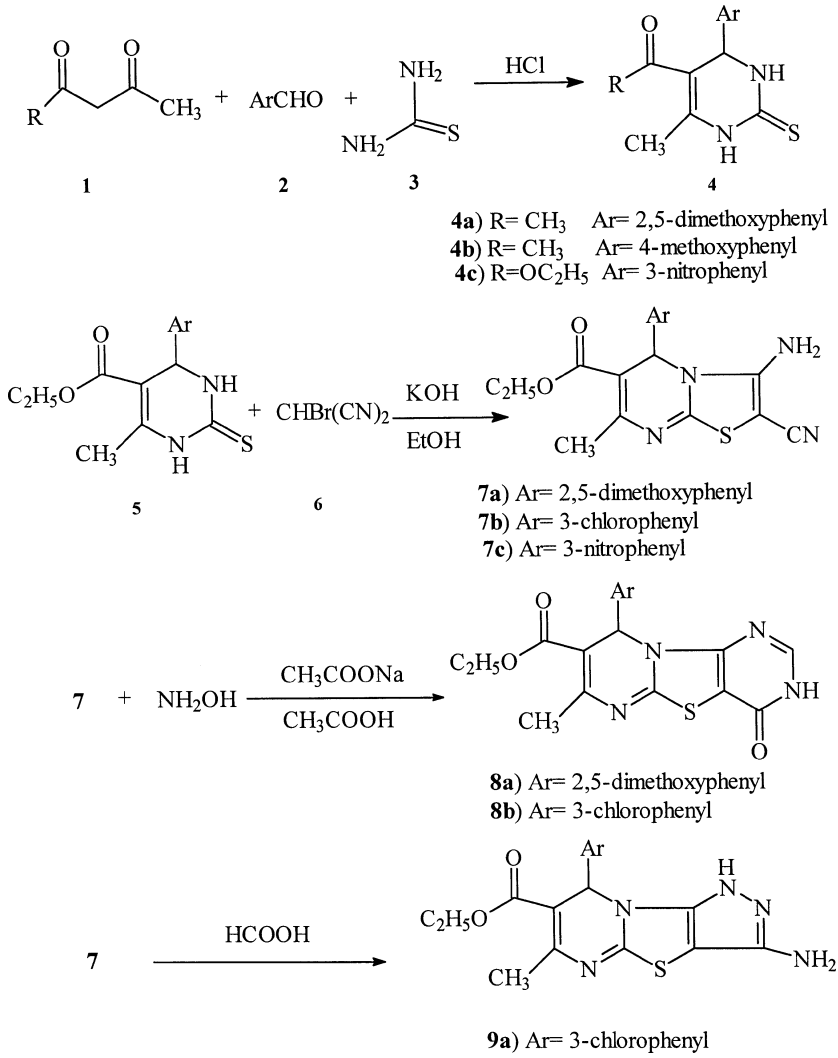
On reaction of pyrimidine derivatives **5** with bromomalononitrile two, isomeric products may be expected from an attack of the nucleophile on N-1 and N-3 nitrogen. However, in this reaction we obtained only thiazolopyrimidines **7(a–c)** as a result of nucleophilic attack on N-3 nitrogen. It is well established[15,18,21,22] that the N-3 position in pyrimidine **5** is more reactive towards electrophiles than the N-1 position, which is conjugated with the ester group in 5-position of the pyrimidine ring.

Also on the basis of ^{1}H NMR spectra the structures of **7(a–c)** are in support of nucleophilic attack on the N-3 nitrogen. Thus the chemical shift of the pyrimidine H-4 proton in **7** compared to that of **4** or **5** appeared at lower shift.

Condensation of thiazolopyrimidine **7** with hydroxylamine hydrochloride in acetic acid and in the presence of sodium acetate gave thiazolodipyrimidines **8(a–b)** in a quantitative yield. However, condensation of **7** with formic acid afforded the corresponding pyrazolothiazolopyrimidine **9a**. The IR spectra of **8(a–b)** display two absorption bands at *ca* 1660 and 1710 cm^{-1}, which are assigned to two carbonyl groups, and are in support of the expected reactions. Also in the IR spectra of **8(a–b)** and **9a** absence of the absorption around 2190 cm^{-1}, the characteristic absorption of the CN group of the starting material, is in support of the expected reaction.

EXPERIMENTAL

Pyrimidine derivatives were prepared using the procedure in our earlier reports.[23,24] Melting points were determined with an electrothermal digital melting point apparatus. IR spectra were taken on a Galaxy series FT-IR 5000 spectrophotometer in potassium bromide pellets. ^{1}H NMR spectra were recorded at 25°C on Bruker 400 and 500 MHz spectrometers with using Me_4Si (TMS) as an internal standard. Reaction



1 2 3 4

4a) R= CH_3 Ar= 2,5-dimethoxyphenyl
4b) R= CH_3 Ar= 4-methoxyphenyl
4c) R=OC_2H_5 Ar= 3-nitrophenyl

5 6

7a) Ar= 2,5-dimethoxyphenyl
7b) Ar= 3-chlorophenyl
7c) Ar= 3-nitrophenyl

8a) Ar= 2,5-dimethoxyphenyl
8b) Ar= 3-chlorophenyl

9a) Ar= 3-chlorophenyl

SCHEME 1

courses and product mixtures were monitored by thin layer chromatography.

PREPARATION OF 4(a–c)

For the preparation of **4(a–c)** a mixture of aryl aldehyde (0.1 mol), thiourea (0.12 mol) and appropriate β-diketone (0.1 mol) in ethanol

(25 mL) containing a catalytic amount of concentrated hydrochloric acid (37%, 4–5 drops) was refluxed for 6, 7, and 8 h, respectively. The reaction mixture was kept at room temperature for overnight. The solid products was filtered, washed with a mixture of ethanol and water (1:1), and recrystallized from ethanol.

PREPARATION OF 7(a–c)

To a warm solution of potassium hydroxide (0.01 mol) and pyrimidine derivative **5** (0.01 mol) in ethanol (30 mL), bromomalononitrile (0.011 mol) was added drop wise with stirring. The reaction mixture was stirred for 2, 2, and 3 h, respectively. The solution was allowed to stand overnight at room temperature and the solid product precipitated upon dilution with water. The precipitate was filtered off and recrystallized from dilute DMF.

PREPARATION OF 8(a–b)

For the preparation of **8(a–b)** a mixture of the appropriate thiazolopyrimidine derivative **7** (0.01 mol) and formic acid (3 mL) was heated under reflux for 10 and 12 h, respectively. The solid product was filtered off and recrystallized from ethanol.

PREPARATION OF 9a

A mixture of the thiazolopyrimidine **7a** (0.01 mol), hydroxylamine hydrochloride (0.012 mol), sodium acetate (0.01 mol) and acetic acid (15 mL) was refluxed for 7 h, then left overnight at room temperature and poured into cold water. The solid precipitate which formed was filtered off and recrystallized from ethanol.

5-ACYL-4-(2,5-DIMETHOXYPHENYL)-6-METHYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE (4a)

Yield 87%, m.p. 190–192°C
IR (KBr): $\nu = 3350, 3200, 3100, 1637, 1574, 1498\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 2.17$ (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.81, 4.18 (s, 6H, $2OCH_3$), 5.95 (s, 1H, H-4), 6.69–7.25 (m, $3H_{aromat}$), 7.81 (s, 1H, NH), 8.71 (s, 1H, NH)

5-ACYL-4-(4-METHOXYPHENYL)-6-METHYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE (4b)

Yield 78%, m.p. 183–184°C
IR (KBr): $\nu = 3320, 3240, 3100, 2900, 1640, 1540\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 2.12$ (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 5.23 (s, 1H, H-4), 6.89–7.14 (m, $4H_{aromat}$), 9.69 (s, 1H, NH), 10.23 (s, 1H, NH)

ETHYL-4-(3-NITROPHENYL)-6-METHYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE (4c)

Yield 75%, m.p. 173–174°C
IR (KBr): $\nu = 3380, 3200, 3160, 2940, 1730, 1600\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.12$ (t, J = 7.2 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.02 (q, J = 7.2 Hz, 2H, CH_2), 5.33 (d, 1H, H-4), 7.68–8.17 (m, $4H_{aromat}$), 9.77 (s, 1H, NH), 10.50 (s, 1H, NH)

ETHYL-3-AMINO-2-CYANO-5-(2,5-DIMETHOXYPHENYL)-7-METHYL-5H-THIAZOLO[a-2,3]PYRIMIDINE-5-CARBOXYLATE (7a)

Yield 88%, m.p. 228–229°C
IR (KBr): $\nu = 3500, 3369, 3126, 2987, 2191, 1705, 1604\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.18$ (t, J = 7.2 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.47 (s, 6H, $2OCH_3$), 4.04 (q, j = 7.2 Hz, 2H, CH_2), 6.38 (s, 1H, H-4), 7.29–7.37 (m, $3H_{aromat}$), 7.71 (s, 2H, NH_2)

ETHYL-3-AMINO-5-(3-CHLOROPHENYL)-2-CYANO-7-METHYL-5H-THIAZOLO[a-2,3]PYRIMIDINE-5-CARBOXYLATE (7b)

Yield 85%, m.p. 209–210°C
IR (KBr): $\nu = 3472, 3371, 3063, 2976, 2191, 1710, 1650\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.19$ (t, J = 7.2 Hz, 3H, CH_3), (s, 3H, CH_3), 4.03 (q, 2H, CH_2), 6.34 (s, $1H_{pyrimidine}$, H-4), 7.26–7.46 (m, $4H_{aromat}$), 7.68 (s, 2H, NH_2)

ETHYL-3-AMINO-5-(3-NITROPHENYL)-2-CYANO-7-METHYL-5H-THIAZOLO[a-2,3]PYRIMIDINE-5-CARBOXYLATE (7c)

Yield 85%, m.p. 259–260°C
IR (KBr): $\nu = 3380, 3285, 3020, 2991, 2200, 1710, 1560\ cm^{-1}$

HNMR (DMSO-d_6): $\delta = 1.18$ (t, J = 7.2 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.02 (q, J = 7.2 Hz, 2H, CH_2), 6.35 (s, $1H_{pyrimidine}$, H-4), 7.29–7.34 (m, $4H_{aromat}$), 7.65 (s, 2H, NH_2)

ETHYL-9-(2,5-DIMETHOXYPHENYL)-4-OXO-7-METHYL-9H-3,4-DIHYDROTHIAZOLO[a-2,3:b-4,5]DIPYRIMIDINE-8-CARBOXYLATE (8a)

Yield 70% m.p. 267–268°C
IR (KBr): $\nu = 3440, 3160, 2940, 1720, 1670, 1530\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.18$ (t, J = 7.2 Hz, 3H, CH_3), 3.68 (s, 6H, OCH_3), 4.05 (q, J = 7.2 Hz, 2H, CH_2), 6.58 (s, $1H_{pyrimidine}$, H-9), 6.88–7.48 (m, $3H_{aromat}$), 8.14 (s, 1H, NH), 8.29 (s, $1H_{pyrimidine}$, H-2)

ETHYL-9-(3-CHLOROPHENYL)-4-OXO-7-METHYL-9H-3,4-DIHYDROTHIAZOLO[a-2,3:b-4,5]DIPYRIMIDINE-8-CARBOXYLATE (8b)

Yield 75%, m.p. 269–270°C
IR (KBr): $\nu = 3300, 3180, 2980, 1710, 1660, 1580, 1500\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.12$ (t, J = 7.2 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.02 (q, 2H, J = 7.2 Hz, CH_2), 6.36 (s, $1H_{pyrimidine}$, H-9), 7.23–7.44 (m, $4H_{aromat}$), 8.27 (s, 1H, NH), 9.68 (s, $1H_{pyrimidine}$, H-2)

ETHYL-3-AMINO-8-(3-CHLOROPHENYL)-6-METHYL-1H,8H-PYRAZOLO[d-3,4]THIAZOLO[a-2,3]PYRIMIDINE-7-CARBOXYLATE (9a)

Yield 70%, m.p. 199–200°C
IR (KBr): $\nu = 3310, 3180, 2980, 1670, 1570\ cm^{-1}$
HNMR (DMSO-d_6): $\delta = 1.14$ (t, J = 7.2 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3), 4.03 (q, J = 7.2 Hz, 2H, CH_2), 5.19 (s, $1H_{pyrimidine}$, H-8), 7.17–7.42 (m, $4H_{aromat}$), 9.68 (s, 1H, NH-exchangeable), 10.41 (s, 1H, NH_2)

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