# β-Enaminoesters as Building Blocks in Heterocyclic Synthesis. A Novel Synthesis of Fused Azines by Using Blaise Reaction as a Key Step

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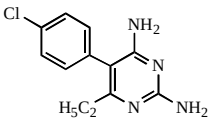
Received April 28th, 1998, respectively July 30th, 1998

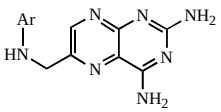
**Keywords:** Bioorganic chemistry, Heterocycles, Antimalarial agents, β-Enaminoesters, Pyrimethamine

**Abstract.** Ethyl bromoacetate **4** reacts with nitriles in the presence of activated zinc dust to afford the beta-enaminoesters **7** and **19**. Compounds **7** and **19** show high reactivity towards a variety of reagents to give polyfunctional heterocyclic compounds. For example, the enaminoesters **7** and **19** react with benzaldehyde to give the 1,4 dihydropyridine derivatives **9** and **20**, respectively. Isothiocyanates **24** (R = Ph, OEt) added to **19** to furnish pyrimidine-thiones **26** and **27** respectively. Structures and conceivable mechanisms are discussed.

Pyrimethamine **1** is a folic acid reductase inhibitor. In this molecule the ring nitrogen is flanked by two functional groups, which is essential to the biological activity of pyrimethamine. Also, a *plethora* of aminopterin **2** and 2,4-diamino-6-substituted quinazoline antifolates **3** exhibit strong antimalarial effects against sensitive and drug-resistant lines of *plasmodium berghei* in mice, *plasmodium gallinaceum* in chicks and *plasmodium cyanomolgi* in rhesus monkeys [1–5]. In spite of the importance of bifunctionally substituted heterocycles the synthetic approach of these compounds are rather limited. In this paper a novel and convenient synthesis of bi-functionally heterocycles are reported using Blaise reaction as a key step.



**1**



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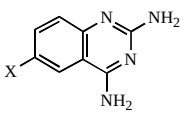
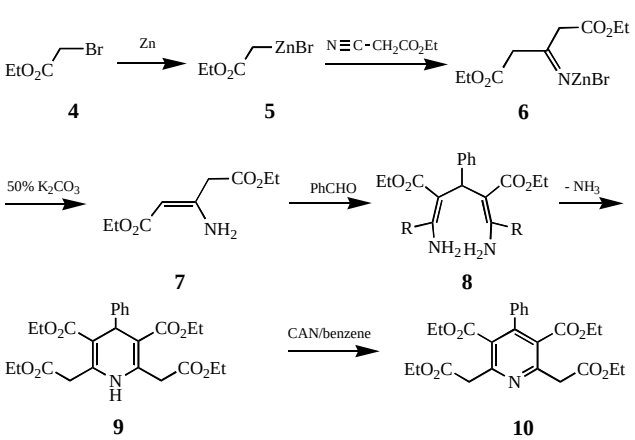


**3**

Treatment of ethyl cyanoacetate with 3–5 molar excess of ethyl bromoacetate **4** in the presence of activated zinc dust in refluxing THF yielded the corresponding enaminoester **7** *via* the iminatozinc bromide intermediate **6**. This enaminoester with its active methylene group could be used as versatile reagent for the synthesis of several antifolates. The enaminoester **7** reacted with benzaldehyde to give only the 1:2 condensation product, the dihydropyridine **9**. The latter resembles the well-known Hantzsch type synthesis of 1,4-dihydropyridine-3,5-diesters [6, 7]. The reaction apparently involves the formation of diamine **8** as an intermediate, which cyclizes *via* loss of $NH_3$ to give the 1,4-dihydropyridine derivative **9**. Further, the oxidation of **9** was attempted. When compound **9** was stirred with ceric ammonium nitrate [8] in acetone at room temperature, the pyridine derivative **10** was obtained. Compound **10** with its ester and active methylene groups reacted readily with a variety of electrophiles to give unique heterocyclic compounds. Thus, fusion of **10** with ammonium acetate at 120 °C afforded a product *m.p.* 210 °C, the mass spectral data of which revealed a molecular formula $C_{17}H_{11}N_3O_4$ (*m/z* 321) consistent with the pyrido [3,4: 2',3']pyrido[3,4-*b*]-pyridine derivative **11**.



**Scheme 1**

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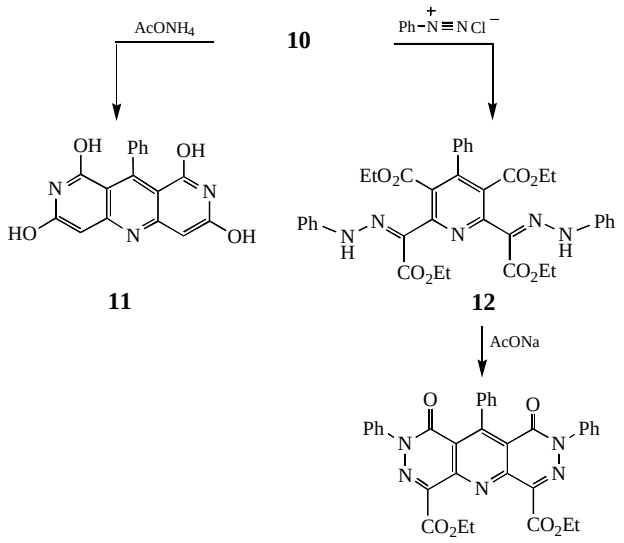
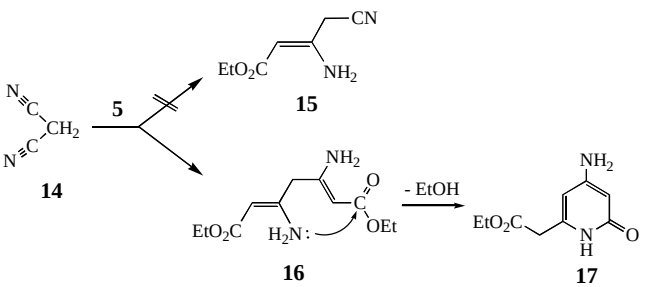
Compound **10** was readily coupled with benzenediazonium salt to give the hydrazone **12** which cyclized readily on boiling in ethanol/sodium acetate to give the highly conjugated fused heterocyclic compound **13**.



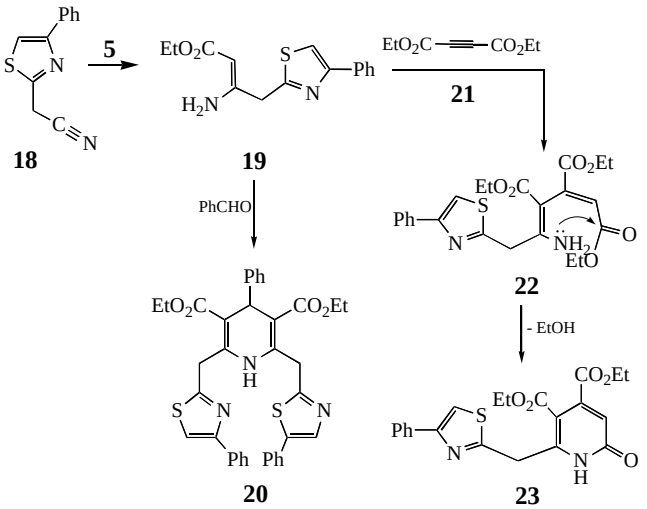
**Scheme 2**

Attempts to prepare the 1:1 condensation product **15** *via* the reaction of malononitrile **14** with ethyl bromoacetate in the presence of activated Zn dust failed; the reaction giving instead the 1:2 condensation product **17**. Compound **17** is believed to be formed *via* the addition of the $\alpha$-halozinc ester **5** to both cyano groups in malononitrile to give the acyclic intermediate **16**. The latter cyclized under the reaction conditions by loss of ethanol to afford the final isolable pyridine derivative **17**.

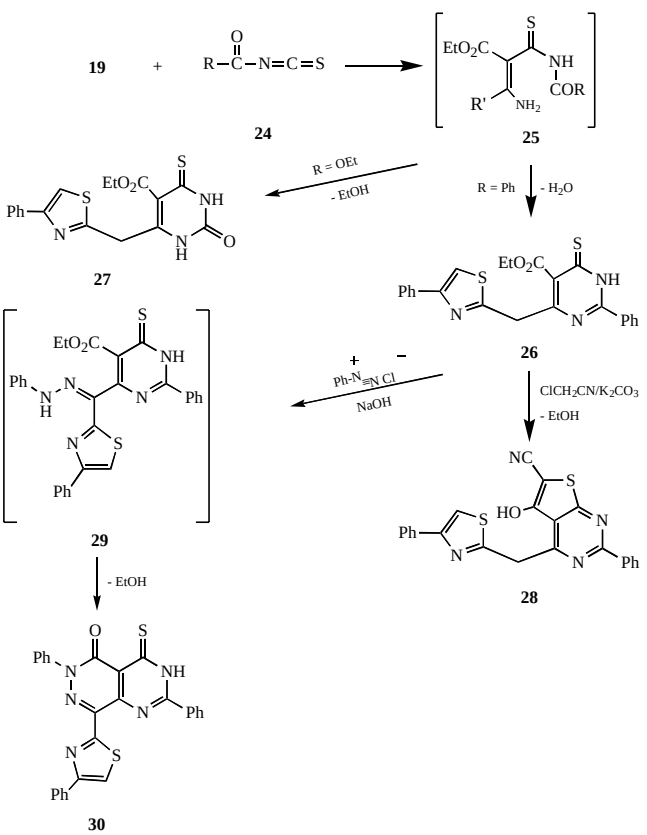


**Scheme 3**

Next, it was important to study the effect of the Blaise reaction on a heterocyclic compound having an acetonitrile moiety. A novel synthesis of a $\beta$-enaminoester having a heterocyclic moiety was achieved. Thus, 4-phenylthiazole-2-acetonitrile **18** reacted with ethyl bromoacetate in the presence of activated zinc to afford the $\beta$-enaminoester **19**. Compound **19** was found to undergo a wide variety of further transformations. It readily reacted with benzaldehyde to afford the dihydropyridine **20**. Compound **19** reacted also with diethyl acetylenedicarboxylate **21** to afford the pyridine derivative **23**. It is believed that compound **23** was obtained *via* Michael addition of the $\beta$-amino-crotonate **19** to the acetylenic moiety in **21** to give the adduct **22**, which under the reaction conditions would cyclize to afford the final isolable pyridine **23**.



**Scheme 4**



**Scheme 5**

Isothiocyanates **24** reacted with **19** in acetonitrile with the formation of 1:1 cyclocondensation product **26** *via* addition intermediates **25**. In the case of ethoxycarbonyl isothiocyanate the isolated product was the pyrimidinone derivative **27**. *S*-Alkylation of the compound **26** with equimolar of chloroacetonitrile in ethanol/$K_2CO_3$ solution under reflux results in the formation of the corresponding thieno[2,3-*d*]pyrimidine derivative **28** *via* loss of ethanol. Also, the methylene group in **26** proved to be highly reactive towards electrophilic reagents. For instance, compound **26** underwent electrophilic substitution upon coupling with equimolar amounts of the appropriate benzenediazonium chloride in ethanol/NaOH solutions gives the acyclic hydrazone intermediate **29**, which spontaneously intramolecularly cyclized *via* ethanol elimination to yield the final isolable pyrimidinopyridazine **30** (Scheme 5). This is the first reported simple and convenient synthesis of a β-enaminoester [1] by using the *Blaise* reaction which at the same time, leads to a key step in preparation of compounds having a thiamine-type structure [9, 10].

## Experimental

All melting points are uncorrected. IR spectra were recorded from KBr pellets on a Pa-9712 IR-spectrophotometer. $^1$H NMR spectra were recorded on a Varian EM-360 (60 MHz) and Jeol (270 MHz) spectrometer with DMSO-$d_6$ and $CDCl_3$ as solvents and TMS as internal reference. $^{13}$C NMR spectra were measured on a Jeol (MHz) spectrometer. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The mass spectra were recorded on a Kratos (75 eV) Ms spectrometer.

### Enaminoesters 7 and 19 (General Procedure)

To prepare the activated zinc, zinc dust was washed sequentially with 3N hydrochloric acid, distilled water, ethanol, and ether and drying *in vacuo*. Next, the α-bromoester is added over 30–60 min to minimize self-condensation. To a suspension of 327 mg (5 equiv.) of activated zinc dust in 3 ml of refluxing anhydrous THF under $N_2$ were added 4 drops of the α-bromoester (0.1 g, 0.6 mmol). After the appearance of a green color, 1 mmol of the nitrile was added in one portion, and then α-bromoester (0.6 g, 4 mmol) were injected by syringe pump over 45 min. The mixture was refluxed for additional 10 min, diluted with 9 ml of THF, quenched with 1.3 ml of 50% aqueous $K_2CO_3$ and rapid stirred for 30 min. to give two sepa-rated layers. The upper organic layer was separated and dried with $MgSO_4$, then concentrated and purified by passing through a short silica gel column and eluted with a (1:1) hexa-ne : $Et_2O$ mixture to give an almost pure (95%) enaminoester product.

*Diethyl 3-aminopent-2-endioate* (**7**)

Yield 1.4 g (70%). – *m.p.* 27 °C. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3350, 3300 ($NH_2$), 1720 (C=O), 1695 (C=O). – $^1$H NMR ($CDCl_3$): δ/ppm = 1.21 (t, 3H, *J*/Hz = 7.7, $CH_3$), 1.30 (t, 3H, *J*/Hz = 7.7, $CH_3$), 2.67 (s, 2H, $CH_2$), 4.05 (q, 2H, *J*/Hz = 7.7, $CH_2$), 4.31 (q, 2H, *J*/Hz = 7.7, $CH_2$), 4.53 (s, 1H, CH), 6.15 (br, s, 2H, $NH_2$). – $^{13}$C NMR ($CDCl_3$): δ/ppm = 14.32, 14.52 ($2CH_3$); 60.12, 60.42 ($2CH_2$); 69.58 ($CH_2$); 110.61 (C-2); 142.38 (C-3); 197.42, 202.45 (2C=O). – MS: *m/z* = 201 ($M^+$).

| | | | | |
|---|---|---|---|---|
| $C_9H_{15}NO_4$ | calcd.: | C 53.72 | H 7.46 | N 6.96 |
| (201.22) | found: | C 54.10 | H 7.40 | N 6.80. |

*Ethyl 3-amino-4-(4'-phenylthiazol-2'-yl)but-2-enoate* (**19**)

Yield 1.8 g (62%). – *m.p.* 76 °C (benzene). – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3400, 3350 ($NH_2$), 1680 (C=O). – $^1$H NMR ($CDCl_3$): δ/ppm = 1.20 (t, 3H, *J*/Hz = 8.1, $CH_3$), 2.34 (s, 2H, $CH_2$), 4.19 (q, 2H, *J*/Hz = 8.1, $CH_2$), 4.68 (s, 1H, CH), 6.61 (s, 1H, thiazole H), 6.71–6.95 (m, 7H, Ph protons and $NH_2$). – MS: *m/z* = 288 ($M^+$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{15}H_{16}N_2O_2S$ | calcd.: | C 62.50 | H 5.55 | N 9.72 | S 11.11 | | |
| (288.47) | found: | C 62.20 | H 5.40 | N 9.80 | S 11.30. | | |

*Diethyl (3,5-diethoxycarbonyl-1,4-dihydro-4-phenylpyridin-2,6-diyl)-2,6-diacetate* (**9**)

To a solution of **7** (4 g, 0.02 mol) in 20 ml ethanol/acetic acid (1:1), benzaldehyde (1.06 g, 0.01 mol) was added. The reaction mixture was refluxed for 15 min and then left at room temperature overnight. The crystals obtained were filtered off and crystallized from ethanol. – *m.p.* 125 °C yield 65%. IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3250 (NH), 1715, 1685 (C=O), 1650 (C=C). – $^1$H NMR ($CDCl_3$): δ/ppm = 0.83 (t, 6H, *J*/Hz = 7.8, $2CH_3$), 1.19 (t, 6H, *J*/Hz = 7.8, $2CH_3$), 2.37 (s, 4H, $2CH_2$), 3.87 (q, 4H, $2CH_2$), 4.05 (q, 4H, $2CH_2$), 5.13 (s, 1H, CH), 6.12 (br, s, 1H, NH), 6.70–6.87 (m, 5H, aromatic protons). – MS: *m/z* = 473 ($M^+$).

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|---|---|---|---|---|---|
| $C_{25}H_{31}NO_8$ | calcd.: | C 63.42 | H 6.55 | N 2.95 | |
| (473.52) | found: | C 63.20 | H 6.50 | N 3.10. | |

*Diethyl (3',5'-diethoxycarbonyl-4'-phenylpyridin-2',6'-diyl)-2,6-diacetate* (**10**)

To a solution of the dihydropyridine **9** (0.95 g, 0.002 mol) in acetone (15 ml) was added a solution of ceric ammonium nitrate (CAN; 2.19 g, 4 mmol) in $H_2O$ (3.5 ml) fairly rapidly dropwise at room temperature. The orange color of the reagent disappeared immediately on addition of each drop. After stirring for 10 min, the resulting solution was concentrated to a small volume under reduced pressure. $H_2O$ (20 ml) was added, and the mixture was extracted with chloroform. The organic phase is washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. The resulting pyridine crystallized from benzene/petroleum ether (40–60 °C). – *m.p.* 115 °C, yield 70%. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 1695, 1670 (C=O), 1660, 1645 (C=C). – $^1$H NMR ($CDCl_3$): δ/ppm = 1.09–1.28 (m, 12H, $4CH_3$), 2.72 (s, 4H, $2CH_2$), 4.10–4.35 (m, 8H, $4CH_2$), 6.91–7.10 (m, 5H, aromatic protons). – MS: *m/z* = 471 ($M^+$).

| | | | | | |
|---|---|---|---|---|---|
| $C_{25}H_{29}NO_8$ | calcd.: | C 63.69 | H 6.15 | N 2.97 | |
| (471.50) | found: | C 63.80 | H 6.30 | N 3.20. | |

*1,3,7,9-Tetrahydroxy-10-phenylpyrido[3,4:3',2']pyrido [3,2-c]pyridine* (**11**)

A mixture of **10** (2.35 g, 0.005 mol) and ammonium acetate (2 g, 0.02 mol) was heated in an oil bath at 120 °C for 2 h. The resulting residue was dissolved in ethanol and then diluted with water. The aqueous solution was neutralized by sodi-

um carbonate. The precipitate was filtered off and crystallized from DMF. – *m.p.* 255 °C, yield 55%. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3450–3300 (OH), 1660, 1620, 1600 (C=C). – $^1$H NMR [$(CD_3)_2SO$]:$\delta$/ppm = 3.50 (br, 4H, 4OH), 6.82–7.89 (m, 7H, aromatic protons). – MS: *m/z* = 321 ($M^+$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{17}H_{11}N_3O_4$ | calcd.: | C | 63.50 | H | 3.42 | N | 13.08 |
| (471.50) | found: | C | 63.20 | H | 3.40 | N | 12.80. |

*Diethyl (3',5'-diethoxycarbonyl-4'-phenylpyridin-2',6'-diyl)-2,6-diphenylhydrazono-diacetate* (**12**)

To a solution of **10** (4.7 g, 0.01 mol) in ethanol (30 ml) containing sodium acetate (5 g, 0.06 mol), an ice-cold solution of benzenediazonium chloride [0.02 mol, prepared by adding sodium nitrite (2.7 g, 0.04 mol) to the appropriate quantity of aniline (1.86 g, 0.02 mol) in 10 ml concentrated hydrochloric acid] was added dropwise with stirring. After 30 min the solid product was collected by filtration and crystallized from ethanol. – *m.p.* 221 °C; yield (80%). – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3400, 3350 (NH), 1695–1685 (C=O), 1660, 1630, 1600 (C=C). – $^1$H NMR [$(CD_3)_2$ SO]: $\delta$/ppm = 0.85–1.16 (m, 12H, 4$CH_3$), 3.95–4.16 (m, 8H, 4$CH_2$), 6.85–7.31 (m, 10H, aromatic H); 7.45–7.69 (m, 5H, aromatic H), 12.4 (br, 2H, 2NH). – MS: *m/z* = 679 ($M^+$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{37}H_{37}N_5O_8$ | calcd.: | C | 65.39 | H | 5.44 | N | 10.30 |
| (679.72) | found: | C | 65.50 | H | 5.50 | N | 10.20. |

*Diethyl 1,9-dioxo-1,2,8,9-tetrahydro-2,8,10-triphenylpyridazino[3,5:2',3']pyrido[2,3-d]pyridazine-4,6-dicarboxylate* (**13**)

A solution of **12** (6.7 g, 0.01 mol), in ethanol (20 ml) was refluxed with sodium acetate (3 g, 0.03 mol) for 1 h. The solid formed during reflux was collected by filtration and crystallized from acetic acid. – *m.p.* 265 °C; yield 95%. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 1695, 1665 (C=O), 1640 (C=C). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 1.02 (t, 6H, 2$CH_3$), 4.15 (q, 4H, 2$CH_2$), 6.81–7.42 (m, 11H, aromatic protons), 7.50–7.71 (m, 4H, aromatic protons).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{32}H_{25}N_5O_6$ | calcd.: | C | 66.78 | H | 4.34 | N | 12.17 |
| (575.58) | found: | C | 66.90 | H | 4.20 | N | 12.40. |

*Ethyl 4-amino-1,6-dihydro-6-oxopyridine-2-acetate* (**17**)

To a suspension of 327 mg (5 equiv.) of activated zinc dust in 3 ml of refluxing anhydrous THF under $N_2$ atmosphere were added 4 drops of ethyl bromoacetate (0.1 g, 0.6 mmol). After the appearance of the green color, malononitrile (0.66 g, 0.01 mol) was added and then ethyl bromoacetate (0.6 g, 4 mmol) were injected by syringe pump over 45 min. The mixture was refluxed for an additional 10 min, diluted with THF (9 ml) and 50% aqueous $K_2CO_3$ (10 ml) was added. The brown solid product was formed on dilution with $K_2CO_3$ solution. The precipitate obtained was filtered off and crystallized from ethanol : DMF (1:1) mixture. – *m.p.* 235 °C; yield 45%. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3400, 3350, 3300 (NH), 1715 (C=O), 1665 (C=O). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 1.16 (t, 3H, *J*/Hz = 8.0, $CH_3$), 3.60 (s, 2H, $CH_2$), 4.16 (q, 2H, *J*/Hz = 8.0, $CH_2$), 6.31 (s, 1H, pyridine H), 6.51 (s, 1H, pyridine H), 7.29 (br, 2H, $NH_2$), 12.40 (s, 1H, NH). – MS: *m/z* = 196 ($M^+$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_9H_{12}N_2O_3$ | calcd.: | C | 55.10 | H | 6.12 | N | 14.28 |
| (196.20) | found: | C | 54.80 | H | 6.00 | N | 14.40. |

*Diethyl 1,4-dihydro-2,6-di(4'-phenylthiazol-2'-ylmethyl)-4-phenylpyridine-3,5-di-carboxylate* (**20**)

To a solution of **19** (2.8 g, 0.01 mol) in acetic acid (20 ml), benz-aldehyde (1.06 g, 0.01 mol) was added. The reaction mixture was refluxed for 15 min, and the formed precipitate was filtered off and crystallized from acetic acid. – *m.p.* 210 °C; yield 70%. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3350 (NH), 1695 (C=O), 1600 (C=O). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 0.89 (t, 6H, *J*/Hz = 7.8, 2$CH_3$), 2.51 (s, 4H, 2$CH_2$), 3.89 (q, 4H, *J*/Hz = 7.8, 2$CH_2$), 5.19 (s, 1H, CH), 6.61 (s, 2H, thiazole H), 6.81–7.25 (m, 12H, aromatic protons and NH), 7.45–7.70 (m, 4H, aromatic protons). – MS: *m/z* = 647 ($M^+$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{37}H_{33}N_3O_4S_2$ | calcd.: | C | 68.62 | H | 5.10 | N | 6.49 S 9.89 |
| (647.81) | found: | C | 68.50 | H | 5.00 | N | 6.60 S 10.10. |

*Diethyl 1,2-dihydro-6-(4'-phenylthiazol-2'-ylmethyl)-2-oxo-pyridine-4,5-dicarboxylate* (**23**)

To a solution of **19** (2.8 g, 0.01 mol) in 20 ml dioxane, diethylacetylene dicarboxylate (1.7 g, 0.01 mol) and a few drops of acetic acid were added. The reaction mixture was refluxed for 2 h., left to cool and the precipitate was filtered off and crystallized from dioxane. – *m.p.* 195 °C; yield (70%). – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3320 (NH), 1720, 1680 (C=O). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 0.96–1.21 (m, 6H, 2$CH_3$), 2.62 (s, 2H, $CH_2$), 3.98–4.10 (m, 4H, 2$CH_2$), 6.61 (s, 1H, thiazole H), 6.71–7.19 (m, 6H, aromatic protons), 12.40 (s, 1H, NH);

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{21}H_{20}N_2O_5S$ | calcd.: | C | 61.16 | H | 4.85 | N | 6.79 S 7.76 |
| (412.46) | found: | C | 60.80 | H | 4.90 | N | 6.60 S 7.50. |

**Synthesis of Pyrimidine-thiones 26 and 27 (General Procedure)**

To a suspension of ammonium thiocyanate (0.77 g, 0.0l mol) in acetonitrile (25 ml), benzoyl chloride (1.4 g, 0.01 mol) or ethyl chloroformate (1.08 g, 0.01 mol) was added. The reaction mixture was refluxed for 5 min, then treated with $\beta$-enaminoester (2.8 g, 0.01 mol). The reaction mixture was refluxed for an additional 15 min. To the reaction mixture sodium hydroxide (0.2 g, 5 mmol) was added, and reflux continued for further 2 min. The cooled reaction mixture was poured into water. The solid products were collected by filtration and crystallized from ethanol.

*Ethyl 1,6-dihydro-2-phenyl-4-(4'-phenylthiazol-2'-yl)methyl-6-thiopyrimidine-5-carboxylate* (**26**)

Yield (65%). – *m.p.* 228 °C. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3350 (NH), 1685 (C=O), 1620 (C=C). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 1.2 (t, 3H, *J*/Hz = 7.6, $CH_3$), 2.55 (s, 2H, $CH_2$), 2.91 (s, 1H, NH), 4.20 (q, 2H, *J*/Hz = 7.6, $CH_2$), 6.61 (s, 1H, thiazole proton), 6.78–7.45 (m, 8H, aromatic proton), 8.20–8.35 (m, 2H, aromatic proton).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{23}H_{19}N_3O_2S_2$ | calcd.: | C | 63.74 | H | 4.38 | N | 9.69 S 14.78 |
| (433.55) | found: | C | 63.90 | H | 4.40 | N | 9.60 S 15.00. |

*Ethyl 6-(4'-phenylthiazol-2'-ylmethyl)-2-oxo-1,2,3,4-tetrahydro-4-thiopyrimidine-5-carboxylate* (**27**)

Yield (70%). – *m.p.* 240 °C. – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3400, 3350 (NH), 1690 (C=O). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 1.21 (t, 3H, *J*/Hz = 7.6, $CH_3$), 2.61 (s, 2H, $CH_2$), 2.95 (s, 1H, NH), 4.20 (q, 2H, *J*/Hz = 7.6, $CH_2$), 6.61 (s, 1H, thiazole proton), 6.70–6.9 (m, 5H, aromatic proton), 12.42 (br, 1H,

NH). – MS: *m/z* = 373 ($M^+$).

| | | | | | |
|---|---|---|---|---|---|
| $C_{17}H_{15}N_3O_3S_2$ | calcd.: | C 54.69 | H 4.02 | N 11.26 | S 17.15 |
| (373.45) | found: | C 54.50 | H 3.90 | N 11.40 | S 17.20. |

*3-Hydroxy-4-(4'-phenylthiazol-2'-yl)methyl-6-phenylthieno[2,3-d]pyrimidine-2-carbonitrile* (**28**)

To a solution of **26** (0.86 g, 0.002 mol) in ethanol (30 ml), $K_2CO_3$ (0.3 g, 0.002 mol) in 1 ml $H_2O$ and chloroacetonitrile (1.5 g, 0.002 mol) were added. The reaction mixture was refluxed for 2 h, left to cool at room temperature and poured onto water. The solid product so-formed was collected by filtration and crystallized from dioxane. – *m.p*. 261 °C: yield (70%). – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3500–3450 (OH), 2221 (CN). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 2.61 (s, 2H, $CH_2$), 4.6 (s, 1H, OH), 6.68 (s, 1H, thiazole-H), 6.72–7.92 (m, 10H, aromatic protons).

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|---|---|---|---|---|---|
| $C_{23}H_{14}N_4OS_2$ | calcd.: | C 64.78 | H 3.28 | N 13.14 | S 15.02 |
| (426.52) | found: | C 64.80 | H 3.10 | N 13.30 | S 14.90. |

*2,6-Diphenyl-8-(4'-phenylthiazol-2'-yl)methyl-1,4,5,6-tetrahydro-6-thioxopyrimidino[4,5-d]pyridazin-5-one* (**30**)

To a stirred solution **26** (2 g, 0.005 mol) in ethanol (50 ml) containing NaOH (2 g, 0.05 mol), the appropriate benzenediazonium chloride (0.005 mol) [prepared by adding $NaNO_2$ (0.3 g, 0.005 mol) to the appropriate aniline (0.46 g, 0.005 mol) in concentrated HCl (2 ml) at 0–5 °C while stirring] was added dropwise while cooling at 0–5 °C and stirring. The reaction mixture was kept at 0–5 °C for 2 h, whereby the solid product was collected by filtration and crystallized from acetic acid. – *m.p*. 235 °C: yield (55%). – IR (KBr): $\nu_{max}$/cm$^{-1}$ = 3430 (NH), 1665 (C=O). – $^1$H NMR [$(CD_3)_2SO$]: $\delta$/ppm = 3.20 (s, 1H, NH), 6.62 (s, 1H, thiazole-H), 6.74–8.22 (m, 15H, aromatic protons).

| | | | | | |
|---|---|---|---|---|---|
| $C_{27}H_{17}N_5OS_2$ | calcd.: | C 65.98 | H 3.46 | N 14.25 | S 13.03 |
| (491.59) | found: | C 66.10 | H 3.40 | N 14.10 | S 13.20. |

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