# Efficient Synthesis of Pyrimido[5,4-c]pyridazines and of Thiino[2,3-d]pyrimidines Based on an Aza-Wittig Reaction/Heterocyclization Strategy
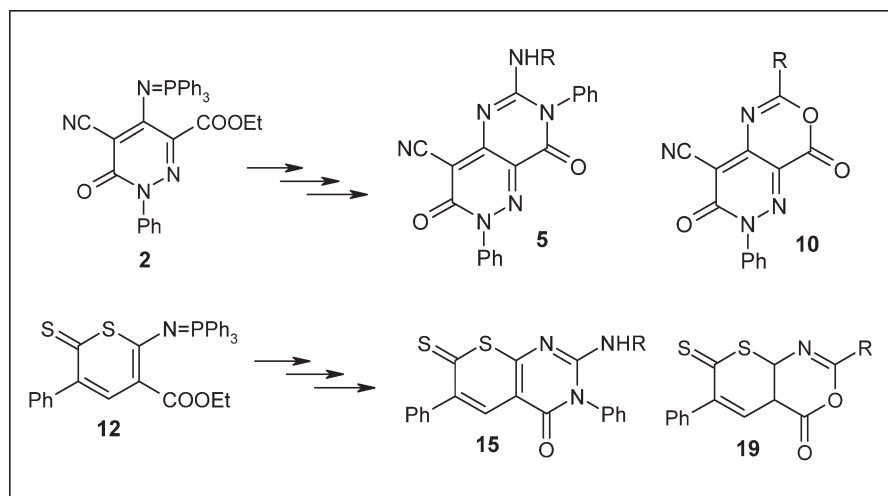
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A simple one-pot and efficient method is described for the synthesis of pyrimido[5,4-c]pyridazines **5** and of thiino[2,3-d] pyrimidines **15** by a domino process involving an aza-Wittig reaction/heterocyclization. The iminophosphorane **2** reacted with phenylisocyanate, followed by heterocyclization on addition of amines to give the corresponding guanidine intermediates **4**. The guanidine intermediates were cyclized in the presence of catalytic amount of sodium ethoxide to pyrimido[5,4-c]pyridazines **5**. Similarly, iminophosphorane **12** reacted with phenylisocyanate and amines to give thiino[2,3-d]pyrimidines **15** in moderate yields. Furthermore, pyridazino[4,3-d]oxazines **10** and thiino[2,3-d]oxazines **19** were synthesized by the intremolecular aza-Wittig reaction of phosphazenes **2** and **12**, respectively, with acid chlorides followed by heterocylization *via* imidoyl chloride intermediates.

## INTRODUCTION

The pyrimidine moiety have been widely used in the design of biologically active agents, structures containing such units often play an essential role owing to their wide range of biological activity particularly in cancer and virus research [1,2]. The presence of a fused pyrimidine scaffold in the framework of various pharmacologically active compounds continues to spur synthetic efforts regarding their acquisition [3,4].

On the other hand, pyridazines and heterocyclic annulated pyridazines have been investigated intensively for their applications in agriculture and in particular for their biological activity for use as potential drugs [5–8]. In particular, fused bicyclic pyrimidopyridazines are of great importance because of their remarkable biological activities. For example, some derivatives of pyrimido[4,5-c]pyridazines have shown good antimicrobial and antifungal activ-

ities [9] while several pyrimido[4,5-d]pyridazines are useful as diuretics [10]. From these isomers, pyrimido[5,4-c]pyridazines are less studied and they show antifungal activities and also have effective diuretic action [10,11].

So far the methods described for the preparation of some representative derivatives of this ring system involve as either the conversion of pyrimidine or uracil moiety to pyrimido[5,4-c]pyridazines, by treatment with a formylating agent [12], from Hofmann reaction on 6-methypyridazine-3,4-dicarboxamid or from 4-aminopyridazine-3-carboxylate on fusion with urea [13]. However, these methods are conducted under harsh conditions, incur expensive materials, and involve several steps in which a mixture of pyrimidopyridazine isomers were inevitably obtained, which lead us to the investigation of the alternative, more regioselective, synthesis of pyrimido[5,4-c]pyridazines *via* the intermolecular aza-Wittig reaction heterocyclization.

Nitrogen- and sulfur-containing rings are among the most useful heterocycles and their utility have been widely demonstrated as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance [14,15].

Whereas pyrimidine annulated sulfur containing heterocycles have been studied, surprisingly aza-analogous compounds incorporating a six-membered S-heterocycle fused to a pyrimidine nucleus have remained relatively rare. Among these heterocycles, thiopyranopyrimidines are an important class of compounds in pharmaceutical discovering research. Some of them show excellent hypoglycemic activity, blood sugar lowering activity platelet aggregation inhibitory activity, antihistamine, anti-inflammatory, and antilergiy activities. They also have beta-adrenergic blocking properties proving useful in the treatment of cardiovascular ailments known to be amenable to beta-blocker therapy. Certain compounds are useful in the treatment of elevated intraocular pressure [16–20].

In the development of strategies for the preparation of heterocycles, the aza-Wittig reaction has proved to be a powerful tool for the synthesis of five-to-eight-membered nitrogen heterocycles [21–30] including natural products [31–36]. The iminophosphorane of heterocyclic and heteroaromatic β-enamino esters have proved to be very versatile intermediates for the construction of manifold hetero-condensed system. Synthesis of many important nitrogen heterocycles *via* aza-Wittig reaction of β-ethoxy carbonyl iminophosphorane with aromatic isocyanate and subsequent heterocyclization on reaction with various nucleophiles under mild condition have been utilized [37–47].

## RESULTS AND DISCUSSION

The starting compound for the aza-Wittig reaction/heterocyclization sequence, iminophosphorane **2** was prepared in 97% yield using Appel's method [48,49] (the modified Kirsanov reaction) from the readily available ethyl 4-amino-1,6-dihydro-5-cyano-6-oxo-1-phenyl-pyridazino-3-carboxylate (**1**) [50] with *in situ* generated dichlorophenylphosphorane using a hexachloroethane/triphenylphosphine/triethylamine reagent system by refluxing in dry benzene for 1 h.

When the resulting iminophosphorane **2** reacted with phenylisocyanate, triphenylphosphine oxide was formed. On addition of primary amines in dry ethylene chloride in presence of a catalytic amount of NaOEt at room temperature to the carbodiimide function, heterocyclization occurred *via* nucleophilic displacement of the ester ethoxide group to give the corresponding pyrimido[5,4-*c*]pyridazine.

While two isomeric pyrimido[5,4-*c*]pyridazine **5** and **6** may be produced in the reaction of iminophosphorane

**Scheme 1**



5a, R = Ethyl
b, R = n-Butyl
c, R = n-Hexyl
d, R = n-Octyl
e, R = Benzyl
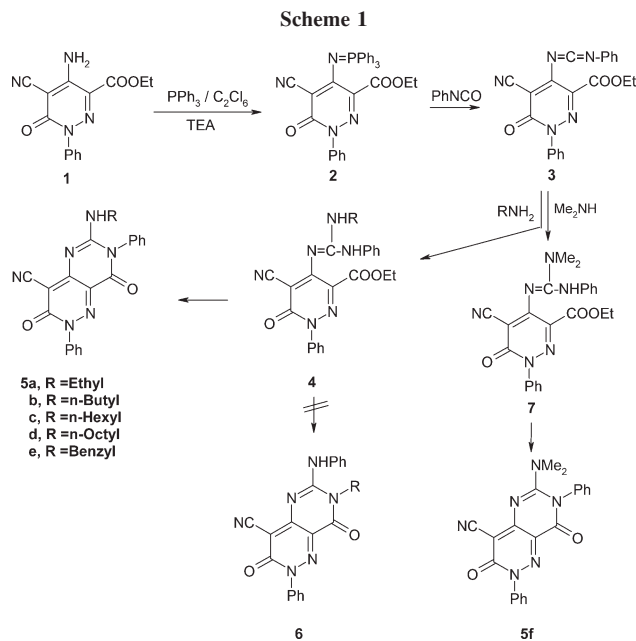
**2** with primary amines *via* a guanidine-type intermediate, it is interesting to note that the reaction is chemoselective to afford **5** in excellent yields.

The EI mass spectrum for **5a** showed the expected molecular ion peaks in moderate to high intensity and the fragmentation pattern is in accord with the proposed structure, it showed *m/z* at 384 (M$^+$, 70%). The IR spectrum (KBr) showed a strong absorption at $\nu = 3220$ cm$^{-1}$ attributed to the NH group, 1690 and 1703 cm$^{-1}$ assigned to the CO groups. In the $^1$H-NMR spectrum, the NH proton appears at δ 4.14 ppm as a broad singlet, in addition to the aromatic proton multiplet.

Likewise, reaction of iminophosphorane **2** with phenylisocyanate and dimethylamine at room temperature resulted in the formation of triphenylphosphine oxide and the corresponding guanidine-type intermediate **7**. In the presence of NaOEt, **7** underwent heterocyclization across the electrophilic ester functionality to give the fused pyrimidine **5f** (Scheme 1).

On the other hand, when iminophosphorane **2** was treated with acid chlorides by refluxing in acetonitrile in presence of small excess of triethylamine, pyridazino[4,3-*d*]oxazines **10a,b** were readily obtained in 69% and 67%, respectively. Here, the tertiary amine seems to be essential for the reaction as only 15% products were obtained without Et$_3$N. The IR spectrum of **10a** resulting from the reaction of iminophosphorane **2** with acetyl chloride revealed absorption bands at $\nu = 2220$, 1692, and 1638 cm$^{-1}$ due to cyano and two carbonyl groups, respectively. Moreover, its $^1$H-NMR spectrum revealed a signal at δ 2.11 corresponding to CH$_3$, in addition to the phenyl H multiplet at δ 7.17–7.89.

**Scheme 2**



10 a, R = Me
b, R = Ph
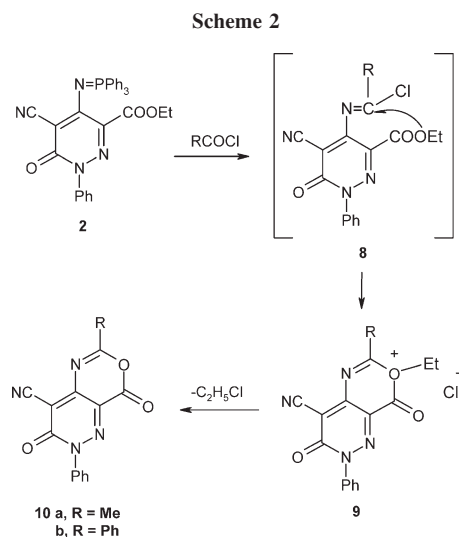
Similarly, the aza-Wittig reaction of iminophosphorane **2** with benzoyl chloride under the same reaction conditions furnished pyridazino[4,3-*d*]oxazine **10b**.

Formation of **10** proceeds *via* aza-Wittig reaction between iminophosphorane **2** with acid chloride to yield imidoyl chloride intermediate **8** [51–53]. The newly generated amidoyl carbon atom of the later is then attacked by ester ethoxy group forming the thermodynamically favored six-membered ring intermediate **9**. Elimination of alkyl halide afforded the stable pyridazino[4,3-*d*]oxazine **10** (Scheme 2).

The β-enamino ester (6-amino-5-ethoxycarbonyl-3-phenyl thiinthione) (**11**) [54] was converted to the iminophosphorane **12** on reaction with the triphenylphosphine/triethylamine/hexachloroethane reagent system [48,49], this phosphazine was isolated as stable compound in good yield (83%) and can be used as synthetic intermediate of new substituted thiinopyrimidines **15** by a domino processes involving an aza-Wittig reaction/heterocyclization.

Structure of **12** was confirmed based on spectral data and elemental analysis. For example, its mass spectrum revealed a molecular ion peak at *m/z* 551. Moreover, its IR spectrum showed the absence of absorption band corresponding to amino group. The reaction pattern of compound **12** is indicated in Scheme 3. The first step in the reaction sequence was the aza-Wittig-type reaction between iminophosphorane and phenylisocyanate to provide triphenylphosphine oxide and carbodiimide moiety **13** as a highly reactive intermediate. This reactive cumulene in turn reacts with primary amines in presence of catalytic amounts NaOEt to give the guanidine **14** followed by heterocyclization to afford the thiino[2,3-*d*]pyrimidine **15**.

The mass spectra of compounds **15** showed the expected molecular ion peaks and the IR spectra showed a strong bands at ν = 3320–3129 cm$^{-1}$, attributed to the NH group, and a C=O absorption band at 1682–1695 cm$^{-1}$.

The reaction of iminophosphorane **12** with phenylisocyanate and dimethylamine at room temperature resulted in the formation of triphenylphosphine oxide and the corresponding guanidine-type intermediate **16**, and in the presence of NaOEt, **16** underwent intramolecular heterocyclization across the electrophilic ester functionality to give the fused pyrimidine **15f** (Scheme 3).

The next step of this study was the preparation of thiino[2,3-*d*]oxazine by an initial aza-Wittig reaction between the phosphazine **12** and alkanoyl or aroyl chlorides and subsequent heterocyclization. Chloroimidoyl derivatives **17** are assumed to be the key intermediates in the consecutive reactions even though they could not be detected due to its high reactivity, these reactive intermediates were cyclized to give **18** then **19** through elimination of ethyl chloride (Scheme 4).

**EXPERIMENTAL**

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected, IR spectra were recorded as potassium bromide pellets using a FTIR unit Bruker-vector 22 spectrophotometer, $^{1}$H- and $^{13}$C-NMR spectra were obtained in deuterated dimethyl sulfoxide as solvent at 300 MHz and 75 MHz, respectively, on a Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Microanalytical Center of Cairo University, Egypt.

**Ethyl-5-cyano-4-(triphenylphosphoranylideneamino)-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2).** To a stirred mixture of **1** (0.284 g, 1.0 mmol), hexachloroethane (0.473 g, 2.0 mmol, 1.0 eq.) and triphenylphosphine (0.52 g, 2.0 mmol, 1.0 eq.) in benzene (50.0 mL) triethylamine (0.4 mL, 4.0 mmol, 2.0 eq.) was added dropwise. The resultant

**Scheme 3**



15a, R =Ethyl
b, R =n-Butyl
c, R =n-Hexyl
d, R =n-Octyl
e, R =Benzyl

**Scheme 4**
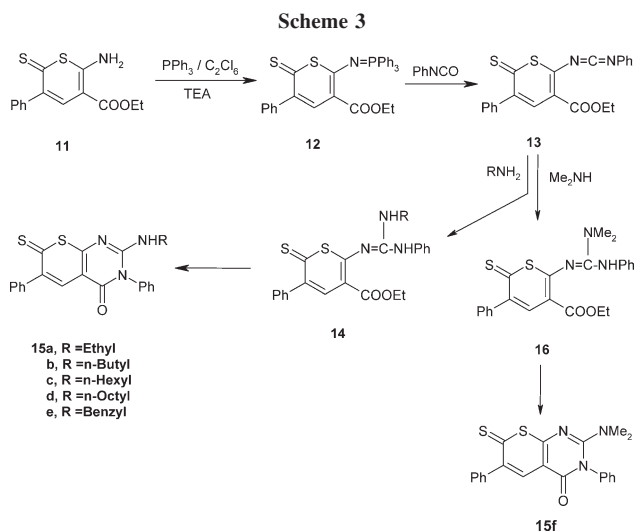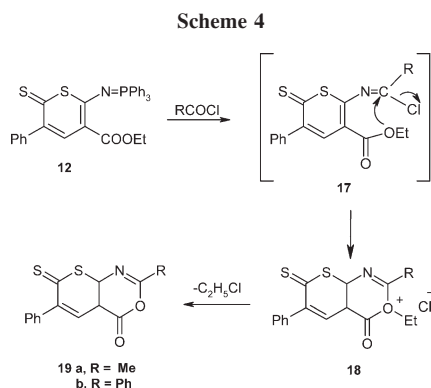


solution was heated at reflux for 1.5 h. The mixture was filtered while still hot to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid product which was crystallized from ethanol as white crystals; yield: 528 mg (97%); mp: 189–91°C, ir: ν 2221 (CN), 1657 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.35 (t, 3H, CH$_3$), 4.45 (q, 2H, CH$_2$), 7.30–7.81 (m, 20H, Ar-H); $^{13}$C-NMR: δ = 165.9, 164, 163, 155, 137, 129, 124, 121, 61.5, 13.9; ms: $m/z$ = 544 (M$^+$, 31%). Anal Calcd for C$_{32}$H$_{25}$N$_4$O$_3$P (544.55): C, 70.58; H, 4.63; N, 10.29; Found: C, 70.64; H, 4.33; N, 10.17.

**6-Alkylamino-4-cyano-2,7-diphenylpyrimido[5,4-*c*]pyridazine-3,8-diones 5a–e.** General procedure: To a solution of iminophosphorane **2** (1.6 g, 3 mmol) in dry methylene dichloride (20 mL) was added phenyl isocyanate (0.36 g, 3 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 24 h at 0–5°C, alkylamine was added to the reaction solution and stirred for 1 h. Then the solvent was removed off under reduced pressure and 25 mL of anhydrous ethanol and 1.5 mL of sodium ethoxide in ethanol (3*M*) were added to the mixture. After stirring for 3–4 h, the solid formed was removed off. Concentrating the residue under reduced pressure, and cooling, furnishing a white solid which was purified by crystallization.

**4-Cyano-2,7-diphenyl-6-ethylamino-pyrimido[5,4-c]pyridazine-3,8-dione 5a.** White crystals from ethanol; yield: 288 mg (75%); mp: 232–34°C, ir: ν 3220 (NH), 2217 (CN), 1703, 1690 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.10 (t, $J$ = 7.2 Hz, 3H, CH$_3$), 3.33–3.40 (m, 2H, NCH$_2$), 4.14 (br, 1H, NH), 7.26–7.74 (m, 10H, Ar-H); ms: $m/z$ = 384 (M$^+$, 70%). Anal Calcd for C$_{21}$H$_{16}$N$_6$O$_2$ (384.40): C, 65.62; H, 4.20; N, 21.86; Found: C, 65.41; H, 4.07; N, 21.73.

**4-Cyano-6-(n-butylamino)-2,7-diphenyl-pyrimido[5,4-c]pyridazine-3,8-dione 5b.** White crystals from ethanol; yield: 301 mg (73%); mp: 130–32°C, ir: ν 3320 (NH), 2210 (CN), 1707, 1695 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 0.98 (t, $J$ = 7.7 Hz, 3H, CH$_3$), 1.30–1.53 (m, 4H, 2CH$_2$), 3.33 (m, 2H, NCH$_2$), 4.14 (br, 1H, NH), 7.26–7.74 (m, 10H, Ar-H); ms: $m/z$ = 412 (M$^+$, 55%). Anal Calcd for C$_{23}$H$_{20}$N$_6$O$_2$ (412.45): C, 66.98; H, 4.89; N, 20.38; Found: C, 66.84; H, 4.76; N, 20.23.

**4-Cyano-2,7-diphenyl-6-(n-hexylamino)-pyrimido[5,4-c]pyridazine-3,8-dione 5c.** White crystals from ethanol; yield: 308 mg (70%); mp: 197–99°C, ir: ν 3230 (NH), 2217 (CN), 1710, 1697 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.32 (t, 3H, CH$_3$), 2.10–2.40 (m, 8H, 4 CH$_2$), 3.33–3.43 (m, 2H, NCH$_2$), 4.26 (br, 1H, NH), 7.28–7.94 (m, 10H, Ar-H); ms: $m/z$ = 440 (M$^+$,

35%). Anal Calcd for C$_{25}$H$_{24}$N$_6$O$_2$ (440.51): C, 68.17; H, 5.49; N, 19.08; Found: C, 67.76; H, 5.37; N, 18.94.

**4-Cyano-2,7-diphenyl-6-(n-octylamino)-pyrimido[5,4-c]pyridazine-3,8-dione 5d.** White crystals from ethanol; yield: 318 mg (68%); mp: 251–53°C, ir: ν 3280 (NH), 2215 (CN), 1707, 1699 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.10 (t, 3H, CH$_3$), 3.20–3.45 (m, 2H, NCH$_2$), 4.18 (br, 1H, NH), 4.30–4.61 (m, 12H, 6CH$_2$), 7.26–7.79 (m, 10H, Ar-H); ms: $m/z$ = 468 (M$^+$, 15%). Anal Calcd for C$_{27}$H$_{28}$N$_6$O$_2$ (468.56): C, 69.21; H, 6.02; N, 17.94; Found: C, 69.07; H, 5.87; N, 17.82.

**4-Cyano-2,7-diphenyl-6-(phenylmethylamino)-pyrimido[5,4-c]-pyridazine-3,8-dione 5e.** White crystals from ethanol; yield: 307 mg (68%); mp: 160–62°C, ir: ν 3270 (NH), 2215 (CN), 1710, 1698 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 4.50 (d, $J$ = 5.7 Hz, 2H, NCH$_2$), 4.70 (br, 1H, NH), 7.19–7.58 (m, 15H, Ar-H); ms: $m/z$ = 446 (M$^+$, 55%). Anal Calcd for C$_{26}$H$_{18}$N$_6$O$_2$ (446.47): C, 69.95; H, 4.06; N, 18.82; Found: C, 69.83; H, 3.96; N, 18.72.

**4-Cyano-2,7-diphenyl-6-(dimethylamino)-pyrimido[5,4-c]-pyridazine-3,8-dione 5f.** White crystals from ethanol; yield: 272 mg (71%); mp: 175–77°C, ir: ν 2217 (CN), 1720, 1715 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.61 (s, 6H, 2CH$_3$), 7.19–7.58 (m, 10H, Ar-H); ms: $m/z$ = 384 (M$^+$, 65%). Anal Calcd for C$_{21}$H$_{16}$N$_6$O$_2$ (384.40): C, 65.62; H, 4.20; N, 21.86; Found: C, 65.86; H, 4.47; N, 21.55.

**Preparation of the pyridazino[4,3-*d*]oxazinones 10 a,b.** To a solution of iminophosphorane **2** (10 mmol) in acetonitrile (15 mL) was added acid chloride (12 mmol) and triethylamine (0.29 g, 20 mmol) under nitrogen. The resultant solution was heated at reflux for 3 h. After cooling, the white precipitate ammonium salt was separated by filtration. The filtrate was concentrated, the residue was recrystallized from ethanol.

**4-Cyano-6-methyl-2-phenyl-2H-pyridazino[4,3-d][1,3]oxazine-3,8-dione 10a.** White crystals from ethanol; yield: 193 mg (69%); mp: 220–22°C, ir: ν 2220 (CN), 1692, 1638 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 2.11 (s, 3H, CH$_3$), 7.17–7.89 (m, 5H, Ar-H); ms: $m/z$ = 282 (M + 2, 69%). Anal Calcd for C$_{14}$H$_8$N$_4$O$_3$ (280.24): C, 60.00; H, 2.88; N, 19.99; Found: C, 60.26; H, 2.77; N, 19.78.

**4-Cyano-2,6-diphenyl-2H-pyridazino[4,3-d][1,3]oxazine-3,8-dione 10b.** White crystals from ethanol; yield: 214 mg (67%); mp: 234–36°C, ir: ν 2219 (CN), 1697, 1649 (CO) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 7.17–7.88 (m, 10H, Ar-H); ms: $m/z$ = 344 (M + 2, 67%). Anal Calcd for C$_{19}$H$_{10}$N$_4$O$_3$ (342.31): C, 66.67; H, 2.94; N, 16.37; Found: C, 66.29; H, 2.67; N, 15.98.

**5-Ethoxycarbonyl-3-phenyl-6-(triphenylphosphoranylideneamino)-thiin-2-thione 12.** To a stirred mixture of **11** (0.291 g, 1.0 mmol), hexachloroethane (0.473 g, 2.0 mmol, 1.0 eq.) and triphenylphosphine (0.52 g, 2.0 mmol, 1.0 eq.) in anhydrous benzene (50.0 mL) triethylamine (0.4 mL, 4.0 mmol, 2.0 eq.) was added dropwise. The resultant solution was heated at reflux for 2 h. The mixture was filtered while still hot to remove the precipitates and the filtrate was evaporated under reduced pressure to give crystals which was recrystallized from ethanol as white crystals; yield: 457 mg (83%); mp: 173–75°C, ir: ν 1699 (CO), 1159 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.34 (t, 3H, CH$_3$), 4.19 (q, 2H, CH$_2$), 7.26–7.82 (m, 21H, Ar-H and thiin-γ-proton); ms: $m/z$ = 551 (M$^+$, 89%). Anal Calcd for C$_{32}$H$_{26}$NO$_2$S$_2$P (551.66): C, 69.68; H, 4.75; N, 2.54; Found: C, 69.32; H, 4.49; N, 2.39.

**2-Alkylamino-3,6-diphenyl-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15a–e.** General procedure: To a solution of iminophosphorane **12** (3 mmol) in dry methylene dichloride (20 mL) was added phenyl isocyanate (0.36 g, 3 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 24 h at 0–5°C, alkyl amine was added to the reaction solution and stirred for 1 h. Then the solvent was removed off under reduced pressure and 25 mL of anhydrous ethanol and 1.5 mL of sodium ethoxide in ethanol (3*M*) were added to the mixture. After stirring for 3–4 h, the solid formed was removed off. Concentrating the residue under reduced pressure, and cooling, furnishing an orange solid which was purified by crystallization.

**2-Ethylamino-3,6-diphenyl-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15a.** Orange crystals from ethanol; yield: 264 mg (67%); mp: 157–59°C, ir: ν 3320 (NH), 1682 (CO), 1148 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.23 (t, 3H, CH$_3$), 4.14 (m, 2H, NCH$_2$), 4.32 (br, 1H, NH), 7.30–7.81 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 392 (M + 1, 43%). Anal Calcd for C$_{21}$H$_{17}$N$_3$OS$_2$ (391.51): C, 64.43; H, 4.38; N, 10.73; S 16.29; Found: C, 64.22; H, 4.37; N, 10.37; S 16.55.

**2-N-Butylamino-3,6-diphenyl-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15b.** Orange crystals from ethanol; yield: 293 mg (70%); mp: 160–161°C, ir: ν 3225 (NH), 1690 (CO), 1159 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.08 (t, $J$ = 7.7 Hz, 3H, CH$_3$), 1.61–1.66 (m, 4H, 2CH$_2$), 3.11 (m, 2H, NCH$_2$), 4.16 (br, 1H, NH), 7.27–7.76 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 419 (M$^+$, 59%). Anal Calcd for C$_{23}$H$_{21}$N$_3$OS$_2$ (419.56): C, 65.84; H, 5.05; N, 10.02; Found: C, 65.61; H, 5.32; N, 10.15.

**2-N-Hexylamino-3,6-diphenyl-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15c.** Orange crystals from ethanol; yield: 332 mg (74%); mp: 135–136°C, ir: ν 3230 (NH), 1695 (CO), 1160 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.10 (t, 3H, CH$_3$), 2.15–2.55 (m, 8H, 4 CH$_2$), 3.41–3.52 (m, 2H, NCH$_2$), 4.27 (br, 1H, NH), 7.17–7.95 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 449 (M + 2, 5%). Anal Calcd for C$_{25}$H$_{25}$N$_3$OS$_2$ (447.62): C, 67.08; H, 5.63; N, 9.39; S 14.33; Found: C, 67.26; H, 5.47; N, 9.12; S 14.25.

**2-N-Octylamino-3,6-diphenyl-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15d.** Orange crystals from ethanol; yield: 334 mg (70%); mp: 160–62°C, ir: ν 3129 (NH), 1695 (CO), 1150 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.32 (t, 3H, CH$_3$), 3.12–3.55 (m, 2H, NCH$_2$), 4.11 (br, 1H, NH), 4.35–4.57 (m, 12H, 6CH$_2$), 7.16–7.89 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 476 (M + 1, 11%). Anal Calcd for C$_{27}$H$_{29}$N$_3$OS$_2$ (475.67): C, 68.18; H, 6.15; N, 8.83; S 13.48; Found: C, 68.28; H, 6.33; N, 8.37; S 13.25.

**3,6-Diphenyl-2-phenylmethylamino-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15e.** Orange crystals from ethanol; yield: 299 mg (66%); mp: 153–55°C; ir: ν 3266 (NH), 1694 (CO), 1160 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 4.10 (d, $J$ = 5.7 Hz, 2H, NCH$_2$), 4.55 (br, 1H, NH), 7.19–7.58 (m, 16H, Ar-H and thiin-γ-proton); ms: $m/z$ = 454 (M + 1, 12%). Anal Calcd for C$_{26}$H$_{19}$N$_3$OS$_2$ (453.58): C, 68.85; H, 4.22; N, 9.26; S 14.14; Found: C, 68.23; H, 4.15; N, 9.45; S 14.39.

**3,6-Diphenyl-2-(dimethylamino)-7-thioxo-3*H*-thiino[2,3-*d*]pyrimidine-4-one 15f.** Orange crystals from ethanol; yield: 262 mg (67%); mp: 163–55°C; ir: ν 3223 (NH), 1688 (CO), 1158 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 1.56 (s, 6H, 2CH$_3$), 7.19–7.77 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 392 (M + 1, 12%). Anal Calcd for C$_{21}$H$_{17}$N$_3$OS$_2$ (391.51): C, 64.42; H, 4.38; N, 10.73; S 16.38; Found: C, 64.23; H, 4.15; N, 10.93; S 16.49.

**Preparation of thiino[4,3-*d*]oxazinones 19 a,b.** To a solution of iminophosphorane **12** (10 mmol) in acetonitrile (15 mL) was added acid chloride (12 mmol) and triethylamine (0.29 g, 20 mmol) under nitrogen. The resultant solution was heated at reflux for 2 h. After cooling, the white precipitate ammonium salt was separated by filtration. The filtrate was concentrated, the residue was recrystallized from ethanol/methylene chloride (1:1) mixture.

**2-Methyl-6-phenyl-7-thioxo-7*H*-thiino[2,3-*d*[1,3]oxazin-4-one 19a.** Deep red crystals from ethanol; yield: 192 mg (67%); mp: 136–38°C; ir: ν 1699, 1648 (CO), 1158 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 2.12 (s, 3H, CH$_3$), 7.19–7.90 (m, 6H, Ar-H and thiin-γ-proton); ms: $m/z$ = 287 (M$^+$, 35%). Anal Calcd for C$_{14}$H$_9$NO$_2$S$_2$ (287.35): C, 58.52; H, 3.16; N, 4.87; S 22.31; Found: C, 58.26; H, 3.17; N, 4.76; S 22.42.

**2,6-Diphenyl-7-thioxo-7*H*-thiino[2,3-*d*[1,3]oxazin-4-one 19b.** Deep red crystals from ethanol; yield: 231 mg (66%); mp: 140–42°C; ir: ν 1699, 1658 (CO), 1155 (C=S) cm$^{-1}$; $^1$H-NMR (DMSO) δ: 7.12–7.79 (m, 11H, Ar-H and thiin-γ-proton); ms: $m/z$ = 349 (M$^+$, 18%). Anal Calcd for C$_{19}$H$_{11}$NO$_2$S$_2$ (349.42): C, 65.31; H, 3.17; N, 4.01; S 18.35; Found: C, 65.44; H, 3.28; N, 4.36; S 18.27.

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