Fused Pyridines by a Tandem Aza-Wittig / Heterocyclization Strategy: Synthesis of 1,2,4-Triazolo[1,5-*a*]pyridines and Pyrido[1,2-*b*][1,2,4]triazines

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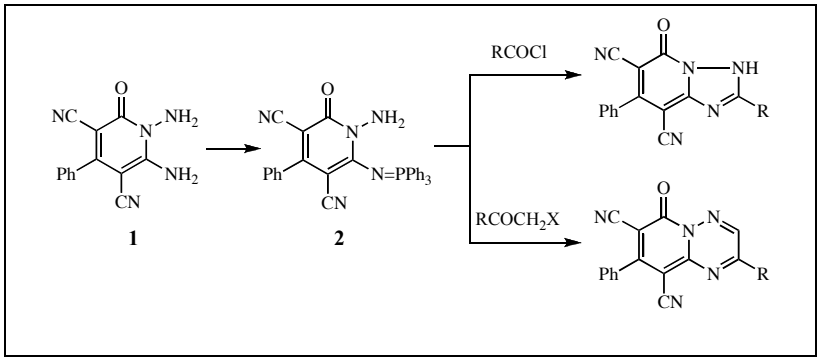

The iminophosphorane 1-amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **2** prepared from 1,6-diaminopyridine **1** reacts with heterocumulenes such as carbon disulfide and phenylisocyanate, and with acid chlorides, acid anhydrides and haloketones to give directly the title compounds in an one-pot aza-Wittig / heterocyclic-ring closure process with good yields.

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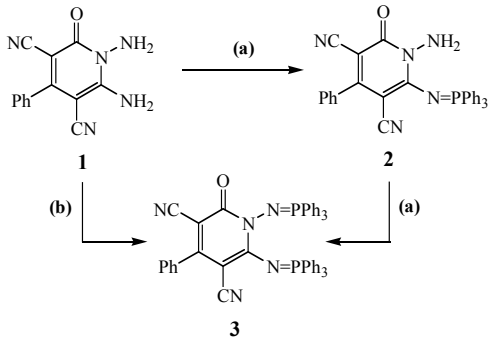
INTRODUCTION

Triazoles and 1,2,4-triazines are important classes of heterocyclic compounds. In particular, fused 1,2,4-triazoles express antifungal [1], bactericidal [1,2], anxiolytic [3,4], anticonvulsant [5] or herbicidal [6] activities and can act as antidepressants [7]. Therefore, versatile and widely applicable methods for their synthesis are of considerable interest. Most methods for the preparation of fused 1,2,4-triazoles are mainly based on hydrazones as precursors. However, these methods have some restrictions regarding their applicability and the use of toxic reagents like lead tetracetate [8,9] and bromine [9,10], also the products were formed in low yield and isolated as salts [11,12]. Many 1,2,4-triazine derivatives are well known to possess biological activities, thus they have found use as herbicides [13,14]. In the last decade they have been screened in vitro supporting their anti-HIV and anti-cancer activities [15-18]. However the aza-Wittig reaction is a powerful tool for the synthesis of five- to seven-membered nitrogen heterocycles [19-26]. Annulation of ring systems with *N*-heterocycles by means of an aza-Wittig reaction has recently been widely utilized because of the availability of functionalized iminophosphoranes [27-31]. Many important fused nitrogen heterocycles such as indole, pyridine, pyrimidine and isoquinoline derivatives have been synthesized *via* the intramolecular aza-Wittig reaction [19-22], as well as by the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocyclization [23-26]. We have previously published the synthesis of fused pyrimidines based on the tandem aza-Wittig annulation strategy [32], and as a part of our ongoing studies we now describe a novel one-pot synthesis of 1,2,4-triazolo[1,5-*a*]pyridine and pyrido[1,2-*b*][1,2,4]triazines derivatives in good yield.

RESULTS AND DISCUSSION

The key iminophosphorane **2** is easily prepared in 95 % yield from the readily available 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **1** by reaction with triphenylphosphine/hexachloroethane and triethylamine reagent system (the Appel method, *i.e.* the modified Kirsanov reaction) [33] (Scheme 1). It is plausible that the amino group in the 6-position is more reactive than that attached to the ring nitrogen in the 1-position. However, the X-ray crystallographic analysis of the product unequivocally confirms its structure. All bond distances present the expected values, bond angle analysis indicated that the pyridine ring is planar, and the 4-phenyl is quite perpendicular to it, while the phenyl rings of triphenylphosphine group are almost coplanar with the pyridine ring and the two others are perpendicular to it (Figure). Attempted preparation of bis(iminophosphorane) **3** by reaction of **1** with two equivalents of the triphenylphosphine/hexachloroethane/triethylamine reagent system was less efficient and resulted in formation of the same iminohosphorane **2**. Preparation of **3** then was achieved by treatment of **2** with an additional equivalent triphenyl phosphine/hexachloroethane/triethylamine reagent system.

Scheme 1



(a) : 1 eq. PPh_3, C_2Cl_6 / TEA, toluene / reflux 2h.
(b) : 2 eq. PPh_3, C_2Cl_6 / TEA, toluene / reflux 2h.

Iminophosphorane **2** reacted with acetyl-, and benzoyl chloride in refluxing toluene to afford the triazole-pyridinone derivatives **5a,b**, the structures of which were confirmed on the basis of spectral and analytical data. The IR spectra of **5a** showed bands at 1651, 2220, and 3120 cm^{-1} assigned to C=O, CN and NH groups, respectively. The ^1H NMR spectrum of **5a** showed two singlet signals for the methyl and NH protons of triazole at δ 1.9 and 10.1, in addition to a multiplet for the aromatic protons at δ 7.1-7.6 ppm. Formation of **5** is assumed to proceed *via* aza-Wittig reaction between **2** and acid chloride yielding an imidoyl chloride intermediate **4**. The new generated electrophilic center is then attacked by the 1-amino group with release of hydrogen chloride and rearrangement to the final product **5**, (Scheme 2).

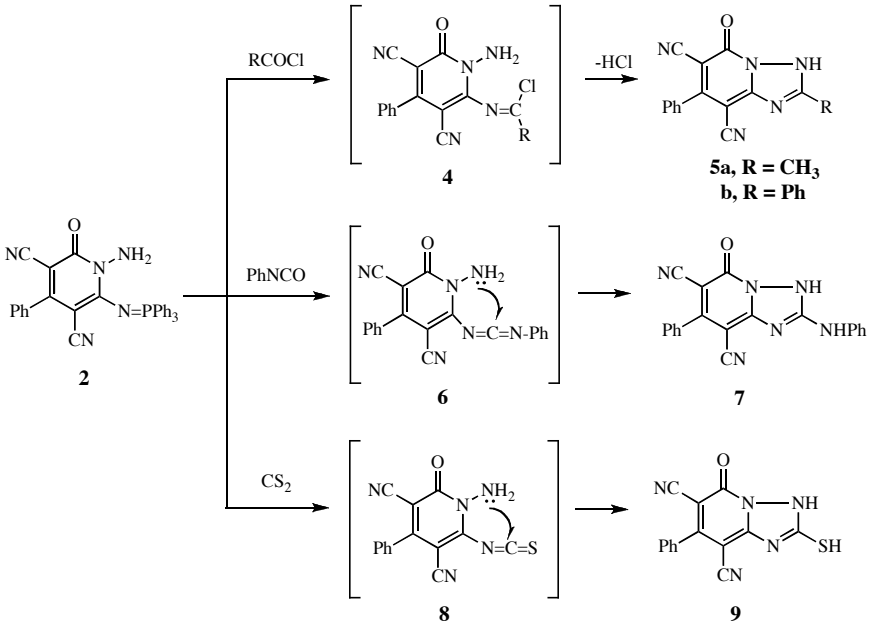
Also, the reaction of **2** with phenylisocyanate in dry toluene at reflux temperature lead directly to the formation of triazolopyridine **7**. Presumably, the conversion here involves an initial aza-Wittig reaction between the iminophosphorane and the isocyanate to give a carbodiimide **6** as highly reactive intermediate, which readily undergoes heterocyclization to afford the final triazolopyridine **7**. The structure of **7** was determined based on microanalysis and spectral data. In its ^1H-NMR spectrum the characteristic chemical shifts of the aromatic protons and NH groups are found at δ 7.1-7.8, 8.2 and 10.2, respectively.

Heating iminophosphorane **2** with excess carbon disulfide in presence of toluene in a sealed tube at 100 ºC gave the 2-thiol derivative **9** through formation of the presumed intermediate **8**, which contains a cumulated double bond at one end. An intramolecular cycloaddition takes place to afford the 2-sulfanyl-triazolopyridine **9**. Structure of **9** was determined from its spectral data. The mass spectrum showed the expected molecular ion peak at m/z = 293 (35 %), the IR spectrum exhibited characteristic bands at 1200, 1655, 2210 and at 3120 cm^{-1} due to the thiol, carbonyl, nitrile and imino groups, respectively.

Compound **2** reacts with each of maleic anhydride and phthalic anhydride in dry toluene to yield the corresponding pyrrolo[1,2:2,3][1,2,4]triazolo[1,2-*a*]pyridine **11** and indolo[1,2:2,3][1,2,4]triazolo[1,2-*a*]pyridine **13**, respectively. Attack of the primary amino group of **2** on one carbonyl group of the anhydride leading to malimido and phthalimido intermediates **10** and **12** followed by intramolecular aza-Wittig reaction can account for the formation of the final products **11** and **13** (Scheme 3).

Also compound **2** reacts with phenacylbromide and chloroacetyl chloride in refluxing toluene to yield

Scheme 2



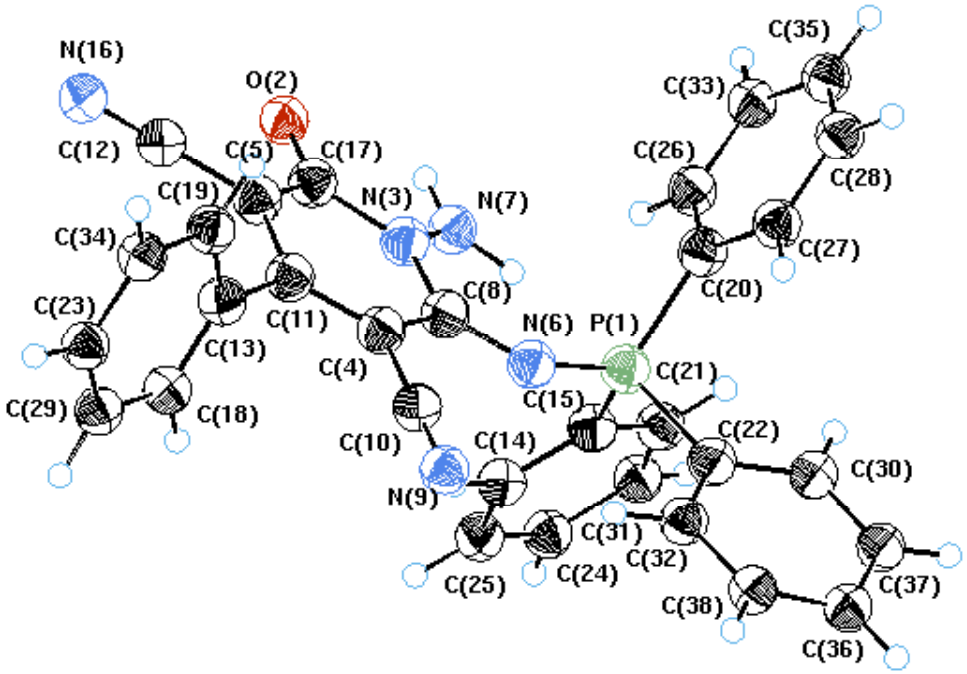
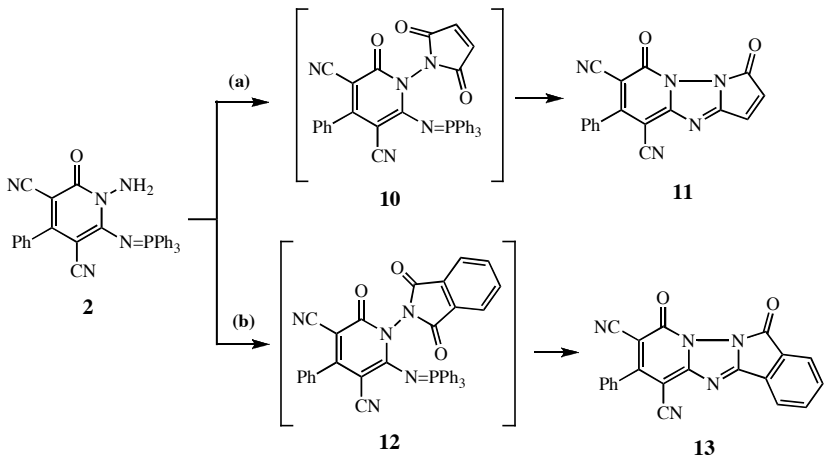


Figure. ORTEP Diagram of 1-amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl-1,2-dihydro-pyridine-3,5-dicarbonitrile **(2)**.

Scheme 3



(a) maleic anhydride, toluene / TEA, reflux 3h.
(b) phthalic anhydride, toluene / TEA, reflux 3h.

pyrido[1,2-*b*][1,2,4]triazines **15**, and **17**. The pathway to the products was explained by the formation of intermediates **14** and **16** resulting from aza-Wittig reaction followed by release of hydrogen halide and air-oxidation. The structure of the products was also established by their spectral and analytical data. Likewise, sequential treatment of iminophosphorane **2** with benzil under the same reaction conditions afforded pyridotriazine **19** through loss of water from the intermediate **18**. Pyridotriazine **19** could also be obtained by reaction of benzil and bis(iminophosphorane) **3** under the same conditions (Scheme 4). In order to prepar new derivatives of pyrido-triazepine, the bis(iminophosphorane) **3** was allowed to react with each of acetyl acetone and/or dibenzoylmethane under otherwise identical reaction conditions, but the reaction was found unsuccessful.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets on a Pye-

Scheme 4

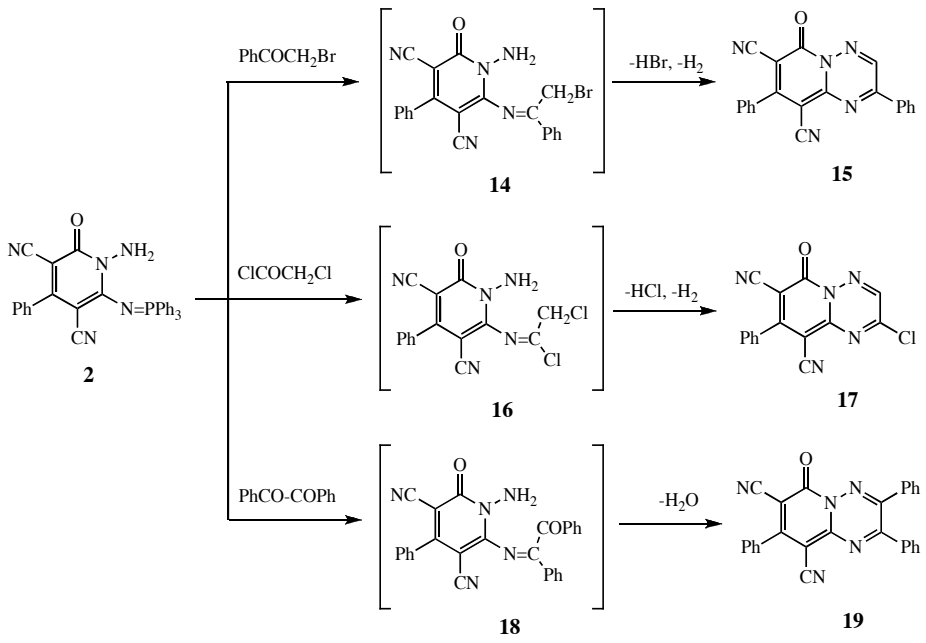


Table 1

Crystal and Refinement Parameters for Compound **2**

Molecular Formula	$C_{31}H_{22}N_5OP$
Molecular weight	511.525
Color	White
Crystal system	Prismatic
Symmetry	Orthorhombic
a, Å	8.880 (3)
b Å	18.405 (5)
c, Å	34.43 (2)
α, deg	90.00
β, deg	90.00
γ, deg	90.00
v, Å	5500.0 (4)
Z	8
Density calculated, mg/mm-1	1.236
Reflections collected	6178
Independent reflections	3887 [R (int) = 0.030
Data/restraints/parameters	3887/0/338
Final R[I>2 σ(1)]	0.066
R (all data)	0.196

Unicam SP-1100 Spectrophotometer. ^{1}H NMR spectra were obtained in deuterated dimethyl sulfoxide on a Varian EM-390 spectrometer using tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer. The single crystal X-ray structural analysis was performed using a maXus diffractometer with a monochromator at (λ = 0.71073, T = 298 K). Elemental analysis was carried out at the Microanalytical Center of Cairo University, Egypt.

Preparation of 1-amino-6-(triphenylphosphoranylidene-amino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (2). To a stirred mixture of 1,6-diamino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **1**, (0.5 g, 2.0 mmol), hexachloroethane (0.473 g, 2.0 mmol, 1.0 equiv.) and triphenylphosphine (0.52 g, 2.0 mmol, 1.0 equiv.) in anhydrous benzene (50.0 mL) triethylamine (0.4 mL, 4.0 mmol, 2.0 equiv.) was added dropwise. The resultant solution was heated at reflux for 2 h. The mixture was filtered while still hot in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid product which was crystallized from ethanol as colorless crystals; yield: 950 mg (95 %); mp 170 °C, ir: ν 1656 (CO), 2210 (CN), 3229, 3259 (NH_2); ^{1}H nmr (DMSO) δ: 7.1-7.8 (*m*, 20H, Ar-H), 8.9 (*s*, 2H, NH_2); ms: *m/z* = 511 (M^+, 85 %). *Anal.* Calcd. for $C_{31}H_{22}N_5OP$ (511.53): C, 72.79; H, 4.34; N,13.69; Found: C, 72.65; H, 4.25; N, 13.57.

Preparation of 1,6-bis(triphenylphosphoranylidene-amino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbo-nitrile (3). To a stirred mixture of 1-amino-6-(triphenylphos-phoranylideneamino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile **2**, (0.771 g, 2.0 mmol), hexachloroethane (0.473 g, 2.0 mmol, 1.0 equiv.) and triphenylphosphine (0.52 g, 2.0 mmol, 1.0 equiv.) in anhydrous benzene (50.0 mL) triethylamine (0.4 mL, 4.0 mmol, 2.0 equiv.) was added dropwise. The resultant solution was heated at reflux for 1.5 h. The mixture was filtered while still hot in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid product which was crystallized from ethanol as colorless crystals; yield: 750 mg (75 %); mp 315 °C, ir: ν 1656 (CO), 2210 (CN); ^{1}H nmr (DMSO) δ: 6.9-7.9 (*m*, 35H, Ar-H); ms: *m/z* = 772 (M^+, 90 %). *Anal.* Calcd. for $C_{49}H_{35}N_5OP_2$ (771.79): C, 76.26; H, 4.57; N,9.07; Found: C, 76.35; H, 4.35; N, 9.12.

General procedure for the reaction of iminophosphorane (2) with acid chlorides. To a solution of iminophosphorane 2 (0.51 g, 1.0 mmol) in 20 mL of dry toluene the appropriate acid chloride (2.0 mmol) and triethylamine (0.2 mL, 2 mmol) were added, and the reaction mixture was heated under reflux for 1.5 h. The solid that formed while the mixture was still hot was separated by filtration, and the filtrate was then evaporated under reduced pressure to give colorless crystals.

Table 2

Selected Bond Lengths, Bond Angles and Torsion Angles of **2**

Bond Angles (°)[a]		Bond lengths (Å)		Torsion Angles (°)	
O2-C7-N3	116.8(4)	P1-N6	1.583(3)	N7-N3-C8-C4	-71.3(13)
O2-C17-C5	24.3(5)	P1-C15	1.787(4)	N7-N3-C8-N6	8.4(9)
N7-N3-C17	117.1(4)	P1-C20	1.811(4)	N7-N3-C17-O2	-4.5(9)
N7-N3-C8	118.9(3)	P1-C22	1.797(4)	N7-N3-C17-C5	174.3(14)
N3-C8-N6	125.2(4)	O2-C17	1.267(4)	C11-C4-C8-N3	-2.1(9)
C4-C8-N6	120.9(4)	N3-C8	1.368(4)	C10-C4-C8-N3	177.0(113)
C4-C10-N9	178.2(4)	N3-C17	1.468(5)	O2-C17-C5-C11	175.(2)
P1-N6-C8	138.6(3)	N3-N7	1.389(4)	O2-C17-C5-C12	1.4(10)
N6-P1-C20	119.5(2)	C4-C8	1.447(4)		
N6-P1-C22	102.1(2)	C4-C10	1.416(5)		
N6-P1-C15	114.1(2)	C4-C11	1.367(4)		
C20-P1-C22	106.1(2)	C5-C11	1.372(5)		
C15-P1-C22	104.5(2)	C5-C12	1.438(5)		
C5-C11-C13	17.9(4)	C5-C17	1.404(5)		
C11-C13-C19	121.9(4)	N6-C8	1.289(4)		
C15-P-C20	109.0(2)0	N9-C10	1.148(4)		
C8-N3-C17	123.8(4)	C11-C13	1.483(5)		
		C12-N16	1.156(5)		
		C13-C18	1.344(5)		
		C13-C19	1.381(5)		
		C14-C15	1.359(5)		

2-Methyl-5-oxo-7-phenyl-3, 5-dihydro[1,2,4]triazole[1,5-*a*]-pyridine-6,8-dicarbonitrile (5a). Yield: 220 mg (81 %), mp 175 °C (dioxane), ir: ν 1650 (CO), 2220 (CN), 3120 (NH); ^{1}H nmr (DMSO) δ: 1.9 (*s*, 3H, CH_3), 7.1-7.6 (*m*, 5H, Ar-H), 10.1 (*s*,1H, NH); ms: *m*/*z* = 275 (M^+, 67 %). *Anal.* Calcd. for $C_{15}H_9N_5O$ (275.27): C, 65.45; H, 3.30; N, 25.44; Found: C, 65.35; H, 3.15; N, 25.37.

2,7-Diphenyl-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (5b). Yield : 300 mg (81 %) (dioxane); mp 280 °C, ir: ν 1651 (CO), 2211 (CN), 3120 (NH); ^{1}H nmr (DMSO) δ: 6.9-7.5 (*m*, 10H, Ar-H), 10.2 (*s*, 1H, NH); ms: *m*/*z* = 339 (M+2, 90 %). *Anal.* Calcd. for $C_{20}H_{11}N_5O$ (337.34): C, 71.21; H, 3.29; N, 20.76; Found: C, 71.35; H, 3.15; N, 20.37.

Preparation of 5-oxo-7-phenyl-2-phenylamino-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (7). To a solution of iminophosphorane **2** (0.51 g, 1.0 mmol) in 30 mL of dry toluene phenylisocyanate (0.23 g, 2.0 mmol) was added. The reaction mixture was heated under reflux for 1 h. The yellow precipitate formed during reflux was collected by filtration and crystallized from methanol, yield: 260 mg (76 %); mp >300 °C, ir: ν 1650 (CO), 2222 (CN), 3130 (NH); ^{1}H nmr (DMSO) δ: 7.1-7.8 (*m*, 10 H, Ar-H), 8.2 (*s*, 1H, NH), 10.2 (*s*, 1H, NH); ms: *m*/*z* = 352 (M^+, 40 %). *Anal.* Calcd. for $C_{20}H_{12}N_6O$ (352.36): C, 68.17; H, 3.43; N, 23.85; Found: C, 68.31; H, 3.55; N, 23.57.

Preparation of 5-oxo-7-phenyl-2-thiol-3,5-dihydro[1,2,4]-triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (9). To a solution of iminophosphorane **2** (0.5 g, 1.0 mmol) in 15 mL of dry toluene an excess of carbon disulfide (7 mL) was added. The reaction mixture was heated in a sealed tube at 100 °C for 3 h. The crystals that formed were collected and crystallized from a mixture of DMF and H_2O (1:1) as yellow crystals, yield: 240 mg (83 %); mp 215 °C, ir: ν 1200 (SH), 1655 (CO), 2210 (CN), 3120 (NH); ^{1}H nmr (DMSO) δ: 2.5 (*s*, 1H, SH), 6.9-7.3 (*m*,5H, Ar-H), 10.3 (*s*, H, NH); ms: *m*/*z* = 293 (M^+, 35 %). *Anal.* Calcd. for $C_{14}H_7N_5OS$ (293.3): C, 57.33; H, 2.41; N, 23.88; Found: C, 57.11; H, 2.55; N, 23.57.

General procedure for the reaction of iminophosphorane 2 with maleic and phthalic anhydride. A mixture of iminophosphorane **2** (0.5 g, 1.0 mmol) and the appropriate acid anhydride (1.0 mmol) in dry toluene (20 mL), was heated at reflux for 3 h. After cooling the solvent was evaporated, the crude residue was suspended in methanol and the solid formed was collected by filtration to give a colorless product.

Pyrrolo[1,2:2,3]triazolo[1,2-*a*]pyridine (11). Crystallized from ethyl alcohol/acetic acid mixture (3:1) to yield: 220 mg (73 %); mp 240 °C, ir: ν 1618, 1659 (CO), 2222 (CN); ^{1}H nmr (DMSO) δ: 5.1 (*d*, 1H, H-3), 5.7 (*d*, 1H, H-4), 7.1-7.8 (m, 5H, ArH); ms: *m*/ *z* = 315 (M+2, 89 %). *Anal.* Calcd. for $C_{17}H_7N_5O_2$ (313.27): C, 65.18; H, 2.25; N, 22.36; Found: C, 65.37; H, 2.41; N, 22.47.

Indolo[1,2:2,3]triazolo[1,2-*a*]pyridine (13). Crystallized from dioxane/H_2O mixture (3:1) to yield: 240 mg (80 %); mp 305 °C, ir: ν 1630, 1650 (CO), 2220 (CN); ^{1}H nmr (DMSO) δ: 7.0-7.6 (m, 9H, Ar-H); ms: *m*/*z* = 365 (M+2, 25 %). *Anal.* Calcd. for $C_{21}H_7N_5O_2$ (363.34) C, 69.42; H, 2.50; N, 19.28; Found: C, 69.23; H, 2.38; N, 19.13.

Preparation of 2,8-diphenyl-6-oxo-pyrido[1,2-*b*][1,2,4]-triazine-7,9-dicarbonitrile (15). To a solution of iminophosphorane **2** (0.51 g, 1.0 mmol) in 20 mL of dry toluene, phenacylbromide (0.38 g, 2.0 mmol) and triethylamine (0.2 mL, 2 mmol) were added, and the reaction mixture was heated under reflux for 2 h. The solid that formed in the hot mixture was separated by filtration, and the filtrate was evaporated under reduced pressure to give yellow crystals, which were recrystallized from ethanol. Yield: 240 mg (71 %); mp 250 °C, ir: ν 1650 (CO), 2211 (CN); ^{1}H nmr (DMSO) δ: 7.0-7.4 (m, 11H, Ar-H); ms: *m*/*z* = 349 (M^+, 82 %). *Anal.* Calcd. for $C_{21}H_{11}N_5O$ (349.35): C, 72.20; H, 3.17; N, 20.05; Found: C, 72.11; H, 3.25; N, 20.32.

Preparation of 2-chloro-6-oxo-8-phenyl-pyrido[1,2-*b*][1,2,4]-triazine-7,9-dicarbonitrile (17). The preparation was carried out by the same method used for the preparation of compound **15** using chloro acetyl chloride to give a colorless product and crystallized from ethyl acetate / toluene (3:1) to yield: 220 mg (71 %); mp 240 °C, ir: ν 1649 (CO), 2210 (CN); ^{1}H nmr

(DMSO) δ: 6.9-7.8 (*m*, 6H, Ar-H); ms: *m/z* = 309 (M+2, 65%). *Anal*. Calcd. for $C_{15}H_6N_5OCl$ (307.70): C, 58.55; H, 1.96; N, 22.76; Found: C, 58.32; H, 1.89; N, 22.52.

Preparation of 6-oxo-2,3,8-triphenyl-pyrido[1,2-*b*][1,2,4]-triazine-7,9-dicarbonitrile (19). A mixture of iminophosphorane **2** (0.51 g, 1.0 mmol), benzil (0.2 g, 1.0 mmol) and triethylamine (0.2 mL, 2 mmol) in 30 mL of dry toluene was heated at reflux for 3h. The solution was evaporated under reduced pressure and the residue was collected and crystallized from ethyl acetate as orange crystals, yield: 320 mg (76 %); mp > 330 °C, ir: ν 1653 (CO), 2222 (CN); ^{1}H nmr (DMSO) δ: 7.3-7.8(*m*, 15H, Ar-H); ms: *m/z* = 425 (M^+, 35 %). *Anal*. Calcd. for $C_{27}H_{15}N_5O$ (425.45): C, 76.22; H, 3.55; N, 16.46; Found: C, 76.11; H, 3.35; N, 16.72.

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