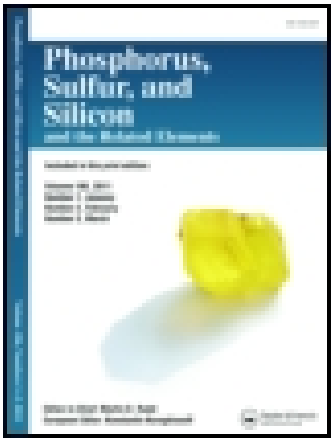

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthetic Approaches Towards 1,2,4-Triazines Utilizing Wittig and Wittig-Horner Reagents

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Published online: 12 Aug 2008.

To cite this article: Mona H. N. Arsanious & Maysa E. Moharam (2008) Synthetic Approaches Towards 1,2,4-Triazines Utilizing Wittig and Wittig-Horner Reagents, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:9, 2344-2359, DOI: 10.1080/10426500802077606

To link to this article: http://dx.doi.org/10.1080/10426500802077606

Phosphorus, Sulfur, and Silicon, 183:2344–2359, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802077606

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Synthetic Approaches Towards 1,2,4-Triazines Utilizing Wittig and Wittig-Horner Reagents

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*The reaction of 5-aroyl-1,2,4-triazin-6(1H)-ones **2a, 2b** with methoxycarbonyl-, ethoxycarbonyl-, methylenetriphenylphosphorane (**1a,1b**) gave olefinic adducts **4a-4d**, pyranotriazine products **5a-5d**, and triphenylphosphine oxide. Moreover, benzoylmethylenetriphenylphosphorane (**1c**) reacts with 5-[(4-methoxyphenyl) carbonyl]-3-phenyl-1,2,4-triazin-6(1H)-one (**2b**) to yield **4e** and triphenylphosphine oxide. On the other hand, the application of phosphorus ylides on 5-[(hydroxyimino) (4-methoxyphenyl)methyl]-3-phenyl-1,2,4-triazin-6(1H)-one (**3b**) render the new product tetraazabenzocyclohepten-8-one oxide **6**, and triphenylphosphine oxide. Trimethylphosphonoacatate **7** reacts with 5-aroyl-1,2,4-triazin-6(1H)-ones **2a, 2b** to afford 5,6-dihydro-5-hydroxy-3,5-diarylpyrano[3,2-e][1,2, 4]-triazin-7-ones **8a, 8b** and alkylated adducts **9a, 9b**. Moreover, 5-[(hydroxyimino)aryl methyl]-3- phenyl-1,2,4-triazin-6(1H)-ones **3a, 3b** react with Wittig-Horner reagent to give alkylated products **10a, 10b** and isoxazolo [4,5-e]-1,2,4-triazines **11a, 11b**. The biological activity of the new synthesized compounds was also examined. Possible reaction mechanisms are considered and the structural assignments are based on analytical and spectroscopic results.*

Keywords 5-Aroyl-1,2,4-triazinones; 5-[(hydroxyimino)arylmethyl]-3-phenyl-1,2,4-triazin-6(1*H*)-ones; phosphonium ylides; Wittig-Horner reagent

INTRODUCTION

Microorganisms of the genus *Pseudomonas* produce a wide spectrum of heterocyclic antibiotics, including phenazine, quinoline, and pyrrole derivatives.[1] Many of these substances are synthesized by strains of *P. fluorescens*, one of the most prolific producers of antibiotic in the genus.[2] Triazine derivatives represent one of these substances, which exhibits

Received 19 December 2007; 8 February 2008.
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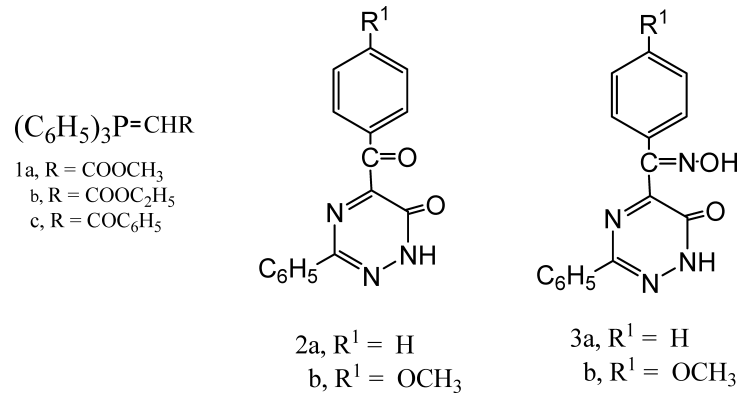


FIGURE 1

biological activities.[3–6] This, together with our interest in organophosphorus chemistry,[7–13] triggered the synthesis of new organophosphorus compounds incorporating such important nuclei that may possibly lead to biological activity. The present study deals with the reaction of stabilized phosphonium ylides **1a**–**1c** with 5-aroyl-1,2,4-triazinones **2a, 2b** and 5-[(hydroxyimino)arylmethyl]-3-phenyl-1,2,4-triazinones **3a, 3b** (Figure 1).

RESULTS AND DISCUSSION

When 3-phenyl-5-benzoyl-1,2,4-triazin-6(1*H*)-one (**2a**) was treated with one mol equivalent of methoxycarbonylmethylene triphenylphosphorane (**1a**) in boiling toluene for 4 h, adduct **4a**, triphenylphosphine oxide, and the starting triazinone, **2a**, were isolated.

Compound **4a** was chromatographically pure and exhibited a sharp melting point. The IR spectrum of **4a,** in KBr, revealed the presence of strong absorption bands at $\nu = 3230$ (NH), 1736 (C=O ester) and 1617 (C=C, Ar) cm^{-1}.[14] The ^1H NMR spectrum of **4a** exhibits signals centered at 3.61 (s, 3H, $COOCH_3$), 6.50 (s,1H, =CH), and 10.62 (s,1H, NH). The mass spectrum of **4a** yielded a prominent peak for M^+ at $m/z = 333$, which corroborates the structure **4a** . The ^{13}C NMR spectrum of **4a** supports the established structure (see Experimental section). Carrying out the reaction using 2 mol of the phosphonium ylide **1a** instead of 1 mol led to the formation of **4a**, **5a**, and triphenylphosphine oxide.

It is worth mentioning that when compounds **4a–4d** were allowed to react with 1 mol equivalent of phosphorus ylides, **1a–1b**, **5a–5d**, and triphenylphosphine oxide were obtained.

Compound **5a** was chromatographically pure and exhibited a sharp melting point. The ^{1}H NMR spectrum of **5a** consisted of signals at 3.79 as singlet for methyl ester. The exocyclic methine proton appeared as singlet at 5.91, whereas the cyclic CH proton exhibits a singlet at 8.57. Moreover, the ^{13}C NMR spectrum of **5a** shows signals at 101.2 ppm, corresponding to exocylic methine carbon, 166.5 ppm to carbonyl ester, and at 127.9 for cyclic =CH carbone.[14]Actually, the mass spectrum of **5a** contains a prominent peak for M^+ at $m/z = 357$, which supports structure **5a**.

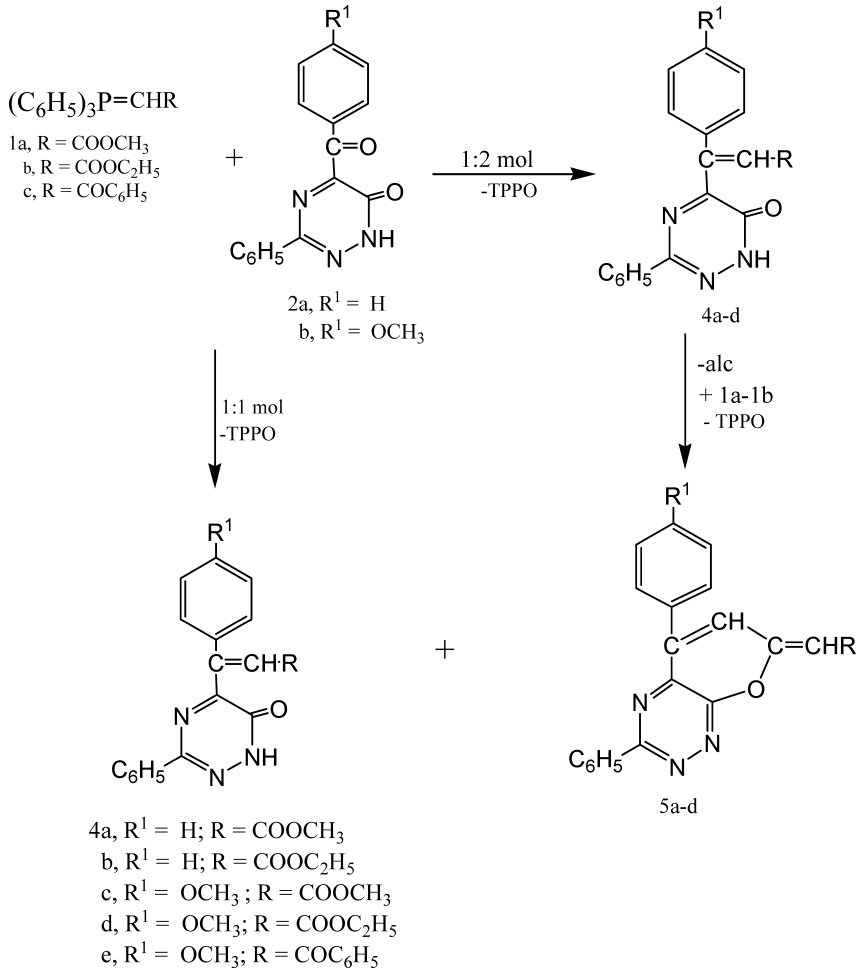
Next, the reaction of **2b** with methoxycarbonyl-(**1a**) and ethoxycarbonyl-, methylenetriphenylphosphorane (**1b**) was also investigated. We have found that when **2b** reacts with 1 mol equivalent of **1a** and/or **1b**, adducts **4c** and **4d** were obtained together with triphenylphosphine oxide.

Moreover, when **2b** reacts with 2 mol equivalents of **1a** and/or **1b**, in boiling toluene, products **4c, 4d, 5c,** and **5d** were isolated. Triphenylphosphine oxide is also obtained from each reaction and identified. Structure of products **4c, 4d, 5c,** and **5d** from correct microanalysis, IR,^{1}H NMR, ^{13}C NMR, and MS spectral data (see Experimental section).

When **2b** was treated with benzoylmethylenetriphenylphosphorane (**1c**) in boiling toluene for 10–12 h, compound **4e** was isolated. 5-(1-(4-methoxyphenyl) -3-oxo-3-phenylprop-1-enyl)-3-phenyl-1,2,4-triazin-6 (1*H*)-one (**4a**) was obtained irrespective where 1 or 2 mol equivalents of **1c** were used (Scheme 1). Its elemental analysis and spectroscopic results were consistent with the assigned structure **4e**. The IR spectrum of **4e** revealed the presence of strong absorption band at 1721 cm^{-1} (COPh), 3180 (NH), and 1611cm^{-1}(C=C,Ar).[14] The mass spectrum of **4e** contains a prominent peak for M^+at m/z = 409, which corroborates the structure **4e**.

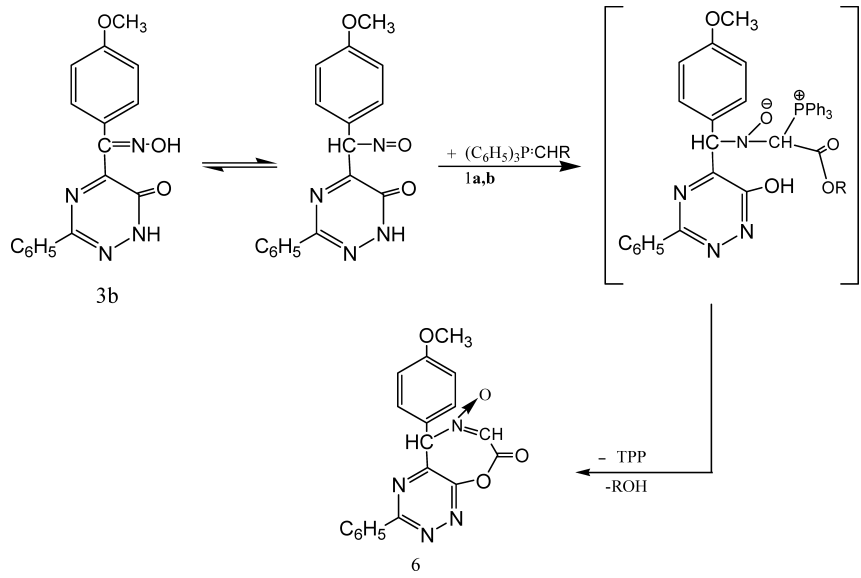
A possible explanation for the course of the reaction of the phosphonium ylides **1a–1c** with **2a** and **2b** is shown in Scheme 1. Formation of adducts **4a–4e** can be explained in terms of carbonyl olefination[15] of **2a** and **2b** by the Wittig reagents **1a–1c** with expulsion of triphenylphosphine oxide.The olefinic compounds **4a–4d** reacted with another molecule of phosphorus ylides **1a** and **1b** to give products **5a–5d** presumably through loss of one mol alcohol and expulsion of triphenylphosphine oxide (Scheme 1).[16]

Furthermore, this study was extended to include the behavior of **3b** toward phosphonium ylides **1a** and **1b**. We found that 5-[(hydroxyimino)(4-methoxyphenyl)methyl]-3-phenyl-1,2,4-triazin-6(1*H*)-one (**3b**) reacts with 2 mol equivalents methoxycarbonyl- (**1a**), and ethoxycarbonyl-, methylenetriphenylphosphorane (**1b**) in refluxing



SCHEME 1

xylene, to give yellowish green crystalline product assigned structure **6**. Triphenylphosphine was isolated from the reaction medium (Scheme 2). Structural support for 5-(4-methoxyphenyl)-3-phenyl-5*H*-9-oxa-1,2,4,6-tetraazabenzocyclohepten-8-one-6-oxide (**6**) was based upon correct elemental analysis spectroscopic data. The IR spectrum of **6** revealed the presence of strong absorption bands at 1565 cm^{-1} (N $\rightarrow$ O), 1740 (C=O, lactone).[14] Its ^{1}H NMR spectrum aromatic protons at δ = 7.47–8.14 ppm (m, 9H, Ar), 7.28 (s,1H,N=CH). The ^{1}H NMR spectrum of compound **6** disclosed the presence of signal at



SCHEME 2

$\delta =$ 12.25 (s, 1H, N═OH) ppm. The mass spectrum of **6** showed prominent peak for M^+ at $m/z = 362$, which supports the nitrogen oxide structure **6**. A possible explanation of the course of the reaction of the ylides **1a** and **1b** with **3b** is shown in Scheme 2.[17]

Moreover, we have also studied the reactions of Wittig-Horner reagent **7** with 5-aroyl-1,2,4-triazinones **2a** and **2b**. We have found that reaction of **2a** and **2b** with 2 mol equivalents of trimethylphosphonoacetate **7** in the presence of *DMF*/ *NaH* suspension with stirring at room temperature gave 5,6-dihydro-5-hydroxy-3,5-diarylphenylpyrano[3,2-e][1,2,4] triazin-7-ones **8a–8b** and alkylated products **9a–9b** (Figure 2).[18]

The possible explanation for the course of the reaction of Wittig-Horner reagent **7** with **2a** and **2b** is show in Scheme 3. Formation of adducts **8a, 8b** can be explained in terms of nucleophilic attack of the carbanion Wittig-Horner reagent **7** at the carbonyl group with the formation of intermediate (**A**), followed by hydrolysis with molecule of water to give intermediate (**B**).[19] 5,6-Dihydro-5-hydroxy-3,5-diarylphenyl-pyrano[3, 2-e][1,2,4]triazin-7-ones **8a, 8b** were derived by loss a methanol moity Scheme 3.[19]

The reaction of trimethylphosphonoacetate (**7**) with 5-[(hydroxylimino) arylmethyl]-3-phenyl-1,2,4-triazin-6(1*H*)-ones **3a**, **3b** was also investigated. We have found that reaction with **3a, 3b**, in the

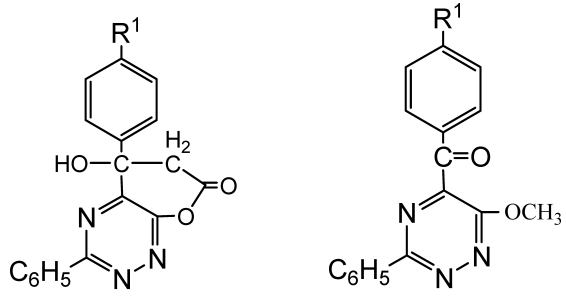
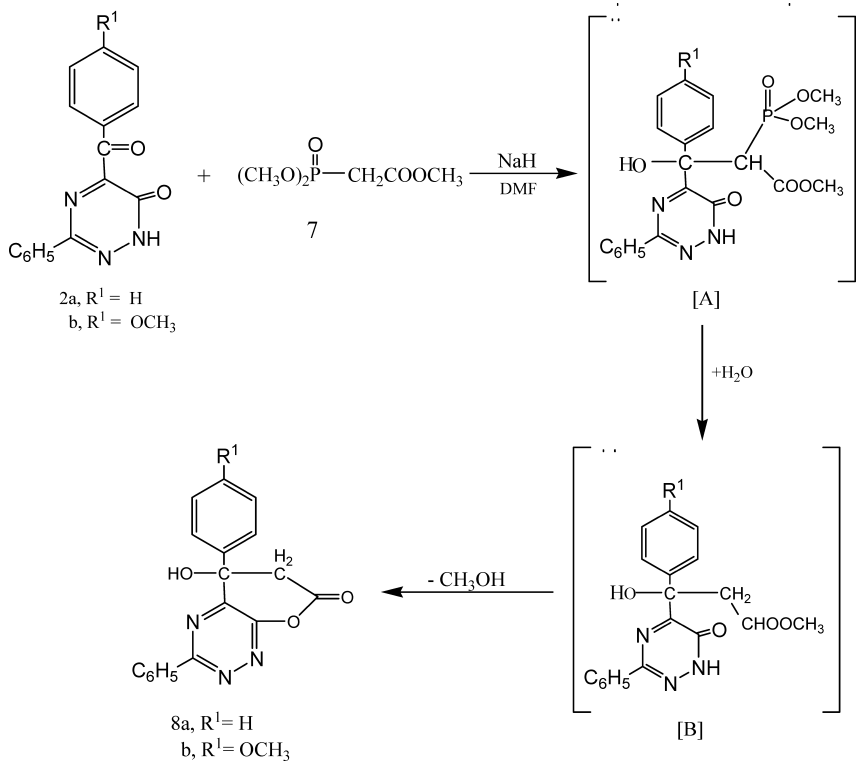
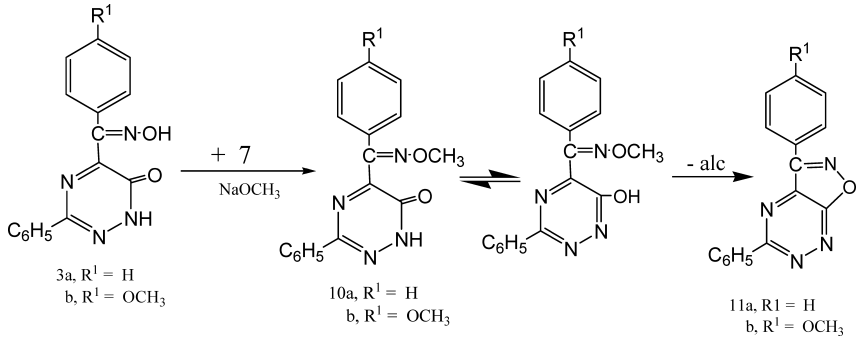


FIGURE 2



SCHEME 3



SCHEME 4

presence of alcoholic sodium methoxide, at refluxing temperature gave products **10a, 10b,** and **11a, 11b** (Scheme 4). The structure of the new compounds is confirmed through elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data (see Experimental section).

A possible explanation for the course of the reaction of **3a, 3b** with trimethylphosphonoacetate **7** is shown in (Scheme 4).

CONCLUSIONS

From the results of the present investigation it could be concluded that 5-aroyl-1,2,4-triazin-6(1*H*)-ones **2a** and **2b** react with one mol of phosphonium ylides **1a** and **1b** to give the corresponding olefinic products **4a–4d** and triphenylphosphine oxide. Moreover, when **2a** and **2b** react with two mol equivalents of ylides, the olefinic compounds,**5a–5d** and triphenylphosphine oxide were isolated.[16] On the other hand, benzoylmethylenetriphenylphosphorane (**1c**) reacts with **2b** to yield the olefinic adduct **4e**. Moreover, the behavior of 5-[(hydroxyimino)(4-methoxyphenyl)methyl]-3-phenyl-1,2,4-triazin-6(1*H*)-one **3b** towards phosphorans ylide **1a** and or **1b** leading to 5-(4-methoxyphenyl)-3-phenyl-5*H*-9-oxa-1,2,4,6-tetraazabenzocyclohepten-8-one-6-oxide (**6**). Trimethylphosphonoacetate (**7**) reacts with **2a** and **2b** to give adducts **8a**, **8b** and **9a**,**9b.** Moreover,5-[(hydroxyimino)(aryl) methyl]-3-phenyl-1,2,4-triazin-6 (1*H*)-ones **3a, 3b** react with **7** to yield products **10a, 10b** and **11a, 11b,** respectively.

EXPERIMENTAL

All melting points are uncorrected. 5-aroyl-1,2,4-triazin-6(1*H*)-ones **2a–2b** were prepared according to Nalepa et al.[20] The IR spectra were measured in KBr pellets with a Perkin-Elmer Infrared Spectrophotometer

Model 157 (Grating). The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$/and DMSO as solvent, with a Varian Spectrometer at 270 and 67.5MHz using *TMS* as internal reference. The mass spectra were performed at 70 eV on a Shimadzu GCS-OP 1000 Ex Spectrometer provided with a data system. Elemental analyses were performed using the Elmentar Varu EL Germany Instrument. Their value agreed favorably with the calculated ones.

Reaction of 3-phenyl-5-benzoyl-1,2,4-triazin-6(1*H*)-one (2*α*) with pho-sphonium ylides 1a and 1b.

A mixture of **2a** (0.27g; 0.001 mol), and 0.002 mol phosphonium ylide **1a** and **1b** in 30 cm^3dry toluene was refluxed for 6 h. After evaporation of the volatile materials under reduced pressure, the residue was applied to silica gel column chromatography. The eluent, yield, and m.p. are given below for adducts **4a**,**5a, 4b,** and **5b**.

Methyl-3-(6-oxo-3-phenyl-1,6-dihydro-1,2,4-triazin-5-yl)3-phenyl acrylate 4a

Eluent: petroleum ether/ethyl acetate (80/20, v/v). Product **4a** was separated as pale yellow crystals, m.p. 222–223°C, yield (35%). Anal. calcd. for $C_{19}H_{15}N_3O_3$(333.34):C,68.46;H,4.54;N,12.61. Found: C, 68.52; H, 4.64; N, 12.54%. IR (KBr): 1736 (C=O ester) 3230 (NH), and 1617(C=C, Ar.), cm^{-1}; ^{1}H–NMR ($CDCl_3$): δ = 3.61 (s, 3H, COOC*H*$_3$), 6.50 (s,1H, = C*H*), 6.90–6.93 (d, 2H, J = 7.4 Hz, Ar), 7.37–7.40 (m, 3H, Ar), 8.13–8.16 (m, 5H, Ar), 10.62 (b, 1H, NH) ppm;^{13}C NMR($CDCl_3$): δ = 55.1 (COO$\underline{C}$H$_3$), 167.8 ($\underline{C}$OO–CH$_3$), 140.2 ($\underline{C}$=CH), 100.6 (C=$\underline{C}$H), 161.8 ($\underline{C}$=O–NH), 161.3, 158.6 ($\underline{C}$=N), 124.6, 126.7, 127.8, 129.2, 128.8, 131.2, 130.83, 134.2 ($\underline{C}$–Ar) ppm; MS *m/z* (%) 333 (100) [M^+].

Methyl(3,5-diphenyl-7H-pyrano[3,2-e][1,2,4]triazin-7-ylidene) acetate 5a

Eluent: petroleum ether/ethyl acetate (80/20, v/v). Product **5a** was separated as yellow crystals, m.p. 209–211°C, yield (55%). Anal. calcd. for C_{21} $H_{15}N_3O_3$(357.36): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.67; H, 4.34; N, 11.84%. IR (KBr): 1670 (C=O ester) cm^{-1};^{1}H NMR($CDCl_3$): δ = 3.79 (s, 3H, COOC*H*$_3$), 5.91 (s, 1H, exo=CH), 7.84–7.65 (2H, d, J = 7.8Hz, Ar), 7.83–7.86 (m, 3H, Ar), 8.37–8.41 (m, 5H, Ar), 8.57 (s, 1H, pyrano C=C*H*) ppm; ^{13}C NMR($CDCl_3$): δ = 51.6 (COO$\underline{C}$H$_3$), 166.5 ($\underline{C}$OOCH$_3$), 140.3 ($\underline{C}$=CH), 127.9 (C=$\underline{C}$H), 101.2 (C=$\underline{C}$H, exo), 160.8 ($\underline{C}$=CH), 158.6 ($\underline{C}$O, pyrano), 161.3, 158.3 ($\underline{C}$=N), 139.8, 126.4, 128.7, 128.0, 130.7, 129.3, 127.5, 132.1 (C–Ar) ppm; MS: *m/z* (%) 357 (70) [M^+].

Ethyl-3-(6-oxo-3-phenyl-1,6-dihydro-1,2,4-triazin-5-yl)-3-phenyl acrylate 4b

Eluent: petroleum ether/ethyl acetate (88/12, v/v). Product **4b** was separated as pale yellow crystals, m.p. 189–190°C, yield (35%). Anal. calcd. for $C_{20}H_{17}N_3O_3$ (347.37): C,69.15; H, 4.93; N, 12.10. Found: C, 69.28; H, 4.89; N, 12.25%. IR (KBr): 3230 (NH), 1700 (C=O ester) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.20 (t, 3H, J = 7.1Hz, CH_2CH_3), 4.25 (q, 2H, J = 7.1Hz, CH_2CH_3), 6.50 (s, 1H, =CH), 6.90–6.93 (d, 2H, Ar), 7.37–7.42 (m, 5H, Ar), 8.13–8.18 (m, 3H, Ar), 11.30 (b, 1H, NH) ppm; ^{13}C NMR($CDCl_3$): δ = 14.2 ($\underline{C}H_3$), 64.2 ($\underline{C}H_2$), 167.8 ($\underline{C}O$), 140.8 ($\underline{C}$=CH), 100.3 (C=$\underline{C}$H), 161.7 ($\underline{C}$=O–NH), 161.3, 158.6 ($\underline{C}$=N), 129.6, 126.7, 127.4, 114.8, 131.0, 130.0, 132.2, 126.4 ($\underline{C}$–Ar) ppm; MS: *m/z* (%) 347 (48) [M^+].

Ethyl(3,5-diphenyl-7H-pyrano[3,2-e][1,2,4]triazin-7-ylidene) acetate 5b

Eluent: petroleum ether/ethyl acetate (92/8, v/v). Product **5b** was separated as yellow crystals, m.p.173–174°C, yield (35%). Anal. calcd. for $C_{22}H_{17}N_3O_3$(371.39): C, 71.15; H, 4.61; N, 11.31. Found: C, 71.01; H, 4.68; N, 11.20%. IR (KBr): 1710 (C=Oester)cm^{-1}; ^1H–NMR($CDCl_3$): δ = 1.30 (t, 3H, J = 7.3Hz, CH_2CH_3), 4.19 (q, 2H, J = 7.3Hz, CH_2CH_3), 5.06 (s, 1H, exo=CH), 7.80–7.75 (d, 2H, Ar), 7.83–7.86 (m, 3H, Ar), 8.37–8.41 (m, 5H, Ar), 8.51 (s, 1H, pyrano C=CH) ppm; ^{13}C NMR($CDCl_3$): δ = 14.2 ($OCH_2\underline{C}H_3$), 61.4 (OCH_2–CH_3), 167.5 ($\underline{C}$O-ester), 139.0 ($\underline{C}$=CH), 124.6 (C=$\underline{C}$H,pyrano), 161.2 (O–$\underline{C}$=CH), 100.9 (=$\underline{C}$H, exo), 161.3, 161.6, 158.7 ($\underline{C}$-triazine), 140.0, 125.6, 128.4, 127.8, 131.4, 129.3, 128.5, 127.5 ($\underline{C}$–Ar) ppm; MS: *m/z* (%) 371 (80) [M^+].

Reaction of 5-(4-methoxybenzoyl)-3-phenyl-1,2,4-triazin-6(1*H*) one (2b) with phosphonium ylides 1a and 1b

A mixture of 0.001 mol **2b** and 0.002 mol phosphonium ylide**1a** and **1b** in 30 cm^3dry toluene was refluxed for 6 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give **4c, 5c, 4d** and **5d.**

Methyl-3-(4-methoxyphenyl)-3-(6-oxo-3-phenyl-1,6-dihydro-1,2,4-triazin-5-yl) acrylate 4c

Eluent: petroleum ether/ethyl acetate (75/25, v/v). Product **4c** was separated as yellow crystals, m.p. 197–198°C, yield (25%). Anal. calcd. for $C_{20}H_{17}N_3O_4$(363.37): C, 66.11; H, 4.72; N, 11.56. Found: C, 66.23; H, 4.80; N, 11.50%. IR (KBr): 1664 (CO–NH), 3230 (NH), 1670 (C=O ester) cm^{-1}; ^1H NMR($CDCl_3$): δ = 3.67 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3),

6.56 (s, 1H, =C*H*), 6.89–6.94 (d, 2H, J = 6.90 Hz, Ar), 7.37–7.45 (m, 5H, Ar), 8.13–8.16 (m, 2H, Ar), 10.60 (b, 1H, NH) ppm;^{13}C NMR($CDCl_3$): δ = 55.1 (COO$\underline{C}H_3$), 55.4 (O$\underline{C}H_3$), 167.8 ($\underline{C}OOCH_3$), 140.2 ($\underline{C}$=CH), 100.6 (C=$\underline{C}$H), 161.8 ($\underline{C}$O–NH), 161.3, 158.6 ($\underline{C}$=N), 159.0, 124.6, 126.7, 127.8, 113.8, 129.6, 130.8, 128.2 ($\underline{C}$–Ar) ppm; MS: *m/z* (%) 363 (100) [M^+].

Methyl-(5-(4-methoxyphenyl)-3-phenyl-7H-pyrano[3,2-e][1,2,4] triazin-7-ylidene acetate 5c

Eluent: petroleum ether/acetone (96/4, v/v). Product **5c** was separated as yellow crystals, m.p. 214–215°C, yield (65%). Anal. calcd. for C_{22} $H_{17}N_3O_4$ (387.39): C, 68.21; H, 4.42; N, 10.85. Found: C, 68.07; H, 4.56; N, 10.76%. IR (KBr): 1730 (C=Oester) cm^{-1}; ^{1}H NMR($CDCl_3$): δ = 3.92 (s, 3H, COOC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 5.87 (s, 1H, =C*H*COOCH$_3$), 7.05–7.08 (d, 2H, J = 9.0 Hz, Ar), 7.51–7.53 (m, 3H, Ar), 7.88–7.85 (d, 2H, J = 9.0 Hz, Ar), 8.39–8.42 (m, 2H, Ar), 8.54 (s, 1H, N=CH) ppm;^{13}C NMR ($CDCl_3$): δ = 51.5 (COO$\underline{C}$H$_3$), 55.4 (O$\underline{C}$H$_3$), 166.7 ($\underline{C}$OOCH$_3$), 139.0 ($\underline{C}$=CH, pyrano), 124.6 (C=$\underline{C}$*H*), 161.2 (–O–$\underline{C}$=CH), 100.4 (=CH, exo), 157.5 (N=$\underline{C}$-O), 161.3, 158.6 (C=N), 158.5, 128.0, 126.7, 127.4, 114.5, 129.2, 130.8, 133.2 ($\underline{C}$–Ar) ppm; MS: *m/z* (%) 387 (100) [M^+].

Ethyl-3-(4-methoxyphenyl)-3-(6-oxo-3-phenyl-1,6-dihydro-1,2,4-triazin-5-yl)acrylate 4d

Eluent: petroleum ether/ethyl acetate (85/15, v/v). Product **4d** was separated as pale yellow crystals, m.p. 190–191°C, yield (30%). Anal. calcd. for $C_{21}H_{19}N_3O_4$(377.39): C, 66.83; H, 5.07; N, 11.13. Found: C, 66.75; H, 5.16; N, 11.24%. IR(KBr): 2930 (NH), 1748 (C=O ester) cm^{-1};^{1}H NMR($CDCl_3$):δ = 1.24 (t, 3H, J = 7.0 Hz, CH_2C*H*$_3$), 4.24 (q, 2H, J = 7.0 Hz, C*H*$_2$CH$_3$), 3.85 (s, 3H, OC*H*$_3$), 6.59 (s, 1H, =C*H*), 6.89–6.93 (m, 3H, Ar), 7.42–7.48 (m, 4H, Ar), 8.16–8.12 (m, 2H, Ar), 11.38 (b, 1H, NH) ppm;^{13}C NMR ($CDCl_3$): δ = 55.4 (O$\underline{C}$H$_3$), 14.2 ($\underline{C}$H$_3$), 60.3 ($\underline{C}$H$_2$), 166.5 ($\underline{C}$O–ester), 139.2 ($\underline{C}$=CH), 100.1 (C=$\underline{C}$H), 161.8 ($\underline{C}$ONH), 161.3, 158.6 (*C*=N), 129.6, 124.6, 126.7, 127.8, 113.8, 130.8, 134.2, 158.4 (C–Ar) ppm; MS *m/z* (%) 377 (90) [M^+].

Ethyl-(5-(4-methoxyphenyl)-3-phenyl-7H-pyrano[3,2-e] [1,2,4]triazin-7-ylidene) acetate 5d

Eluent: petroleum ether/acetone (96/4, v/v). Product **5d** was separated as yellow crystals, m.p. 177–179°C, yield (55%). Anal. calcd. $C_{23}H_{19}N_3O_4$(401.41): C, 68.82; H, 4.77; N, 10.47. Found: C, 68.74; H, 4.86; N, 10.34%. IR (KBr): 1700 (C=O ester) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=1.35 (t, 3H, J = 7.2 Hz, CH_2C*H*$_3$), 4.24 (q, 2H, J=7.2Hz, C*H*$_2$CH$_3$), 3.92 (s, 3H, OC*H*$_3$), 5.85 (s, 1H, exo=CH), 7.05–7.07 (d, 2H, J = 7.2 Hz, Ar), 7.50–7.52 (m, 3H, Ar), 7.85–7.88 (m, 2H, J = 7.2 Hz, Ar),

8.40–8.43 (m, 2H, Ar), 8.54 (s,1H, pyrano C=CH),^{13}C NMR($CDCl_3$): δ = 14.2 ($OCH_2\underline{C}H_3$), 60.4 ($O\underline{C}H_2CH_3$), 55.4 ($O\underline{C}H_3$), 166.2 (<u>C</u>O—ester), 141.3 (<u>C</u>=CH, pyrano), 121.6 (C=<u>C</u>H, pyrano), 161.2 (O—<u>C</u>=CH), 100.9 (exo, = <u>C</u>H), 161.3, 162.7 (<u>C</u>=N—azine), 158.7 (N=<u>C</u>-O), 158.4, 114.2, 127.4, 132.9, 127.5, 129.3, 130.7, 128.8 (<u>C</u>—Ar) ppm; MS: *m/z* (%) 401 (80) [M^+].

Reaction of 2b with benzoylmethylenetriphenylphosphorane (1c)

To a solution of triazinone **2b** (0.30g; 0.001 mol) in dry xylene, was added ylide **1c** (0.001 mol) and the reaction mixture was refluxed for 10 h. The solution was evaporated under reduced pressure and the residue subjected to silica gel column chromatography to give **4e**.

5-[1-(4-Methoxyphenyl)-3-oxo-3-phenylprop-1-en-1-yl]-3-phenyl-1,2,4-triazin-6(1H)-one 4e

Eluent: petroleum ether/ethyl acetate (25/75, v/v). Product **4e** was separated as colorless crystals, m.p. 202–203°C, yield 80%. Anal. calcd. C_{25} $H_{19}N_3O_3$(409.44): C, 73.34; H, 4.68; N, 10.26. Found: C, 73.25; H, 4.73; N, 10.12%. IR (KBr): 1721 (COPh), 3180 (NH), 1611 (C=C, Ar) cm^{-1}; ^{1}H NMR($CDCl_3$):δ = 3.89 (s, 3H, OCH_3), 6.85 (s,1H, =C*H*), 6.72–7.19 (m, 5H, Ar), 7.81–7.54 (m, 5H), 7.3–7.42 (m, 4H, Ar), 8.57 (b, 1H, NH); ^{13}C NMR($CDCl_3$): δ = 54.2($O\underline{C}H_3$), 186.3 (<u>C</u>O—Ph), 143.0 (<u>C</u>=CH), 123.6 (C=<u>C</u>H), 161.3, 161.6, 158.7 (<u>C</u>-triazinon), 165.1 (<u>C</u>ONH), 164.0, 155.0 (<u>C</u>=N), 159.9, 114.2, 127.4, 124.9 ($\underline{C}_6H_4$), 137.9, 129.9, 128.7, 134.6 ($CO\underline{C}_6H_5$), 127.9, 131.9, 128.7, 129.2 ($\underline{C}_6H_5$) ppm; MS: *m/z* (%) 409 (100) [M^+].

Reaction of triphenylphosphorane 1a-1 b with 3b

A mixture of 0.002 mol of **1a** or **1b** and 0.001 mol of **3b** in 30 cm^3 xylene was refluxed for 3–4 h. The reaction mixture was evaporated under reduced pressure and then applied to silica gel column chromatography to give adduct **6**.

5-(4-Methoxyphenyl)-3-phenyl-5H-9-oxa-1,2,4,6-tetraaza-benzocyclohepten-8-one-6-oxide 6

Eluent: petroleum ether/acetone (85/15, v/v). Product **6** was separated as yellow crystals, m.p. 220–221°C, yield 80%. Anal. calcd. C_{19} $H_{14}N_4O_4$(362.34):C, 62.98; H, 3.89; N, 15.46. Found: C, 62.87; H, 3.94; N, 15.50%. IR (KBr): 1565 (O←N=CH), 1740 (CO—lactone)

cm^{-1}; ^1H NMR($CDCl_3$): δ = 3.92 (s, 3H, OCH_3), 6.89 (s, 1H, C*H*), 7.28 (s, 1H, N=C*H*), 7.42–7.43 (d, 2H, J = 8.7 Hz, Ar), 7.47–7.45 (m, 3H, Ar), 8.02–7.99 (d, 2H, J = 8.7 Hz, Ar), 8.14–8.11 (m, 2H, Ar) ppm; ^{13}C NMR($CDCl_3$): δ = 55.49 (O$\underline{C}H_3$), 103.9 (H$\underline{C}$—N→O), 163.0 (O←N = $\underline{C}$H), 158.9 (O—$\underline{C}$O), 159.4, 162.4 ($\underline{C}$=N), 153.2 (= $\underline{C}$—O—), 156.8, 119.5, 125.6, 126.7, 127.8, 123.8, 132.7, 114.3 ($\underline{C}$—Ar) ppm; MS: *m/z* (%) 362 (80) [M^+].

Reaction of Trimethylphosphonoacetate 7 with 2a and 2b

A suspension of NaH (0.048 g; 0.002mol) in 15 ml of anhydrous *DMF* was added slowly to a stirred solution of reagent **7** (0.36g, 0.002 mol) in anhydrous *DMF* at 0°C. After the addition was completed (15 min), a solution of **2a** or **2b** (0.001 mol) in anhydrous *DMF* (10 ml) was added and the resulting mixture was allowed to warm at r.t., and then stirred for additional 10–15 h (TLC). To the reaction mixture, few drops of water was added, and extracted with $CHCl_3$ and the combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the resulting residue was applied to silica gel column chromatography to give products **8a, 8b, 9a** and **9b**.

5-Hydroxy-3,5-diphenyl-5,6-dihydro-7H-pyrano[3,2-e][1,2,4]triazin-7-one 8a

Eluent: petroleum ether/ethyl acetate (15/85, v/v). Product **8a** was separated as colorless crystals, m.p. 272–273°C, yield (35%). Anal.calcd. $C_{18}H_{13}N_3O_3$(319.31): C, 67.71; H, 4.10; N, 13.16. Found: C, 67.82; H, 4.18; N, 13.29%. IR(KBr): 3540 (OH), 1720 (CO, lactone) cm^{-1};^1H NMR(DMSO): δ = 3.50 (s, 2H, CH_2), 7.82–7.81 (m, 5H, Ar), 7.49–7.48 (m, 5H, Ar), 12.5 (b, 1H, OH) ppm. ^{13}C NMR(DMSO): δ = 55.0 (*C*H_2), 78.1 (*C*—OH), 168.0 (*C*O—lactone), 155.5, 154.7, 146.9 (*C*=N), 143.8, 129.1, 126.9, 127.8, 123.8, 132.7, 129.9, 128.9 (*C*—Ar) ppm; MS : *m/z* (%) 319 (25) [M^+].

(6-Methoxy-3-phenyl-1,2,4-triazin-5-yl)(phenyl)methanone 9a

Eluent: petroleum ether/ethyl acetate (92/8, v/v). Product **9a** was separated as pale yellow crystals, m.p. 178–180°C, yield 55%. Anal.calcd. $C_{17}H_{13}N_3O_2$(291.30): C, 70.09; H, 4.50; N, 14.42. Found: C, 70.16; H, 4.62; N, 14.34%. IR(KBr): 1730 (CO) cm^{-1}; ^1H NMR(DMSO): δ = 3.92 (s, 3H, OCH_3), 7.45–7.68 (m, 6H, Ar), 7.79–8.01 (d, 2H, J = 7.8 Hz, Ar), 8.01–8.16 (d, 2H, J = 7.8 Hz, Ar) ppm; ^{13}C NMR(DMSO): δ = 52.4 (O$\underline{C}H_3$), 176.8 ($\underline{C}$O), 155.1, 154.7, 164.9 (*C*=N), 134.8, 129.1, 126.9,

127.8, 123.8, 132.7, 129.4, 128.1 (*C*—Ar) ppm; MS: *m/z* (%) 291 (85) [M^+].

5-Hydroxy-5-(4-methoxyphenyl)-3-phenyl-5,6-dihydro-7H-pyrano [3,2-e][1,2,4]triazin-7-one 8b

Eluent: petroleum ether/ethyl acetate (20/80,v/v). Product **8b** was separated as colorless crystals, m.p. 234–235°C, yield (40%). Anal.calcd. $C_{19}H_{15}N_3O_4$ (349.34): C, 65.32; H, 4.33; N, 12.03. Found: C, 65.16; H, 4.46; N, 12.12%. IR(KBr): 3530 (OH), 1724 (CO, lactone) cm^{-1};^{1}H NMR(DMSO):δ = 3.91 (s, 3H, OCH_3), 3.16 (s, 2H, CH_2), 6.97–7.00 (d, 2H, J = 9.0 Hz, Ar), 7.44–7.47 (m, 3H, Ar), 7.95–7.98 (d, 2H, J = 9.0 Hz, Ar), 8.12–8.16 (m, 2H, Ar), 2.50 (b, 1H, OH) ppm; ^{13}C NMR(DMSO): δ = 53.4 (O<u>C</u>H$_3$), 55.0 (<u>C</u>H$_2$), 78.5 (<u>C</u>—OH), 158.8 (<u>C</u>O—lactone), 156.5, 155.7, 147.9 (<u>C</u>=N), 159.6, 134.8, 129.1, 126.9, 127.8, 132.7, 129.6, 114.6 (C—Ar) ppm; MS: *m/z* (%) 349 (25) [M^+].

(6-Methoxy-3-phenyl-1,2,4-triazin-5-yl)(4-methoxyphenyl)methanone 9b

Eluent: petroleum ether/ethyl acetate (95/5, v/v). Product **9b** was separated as pale yellow crystals, m.p. 200–201°C yield (45%). Anal. calcd. $C_{18}H_{15}N_3O_3$ (321.33): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.16; H, 4.82; N, 13.22%. IR(KBr): 1730 (CO) cm^{-1}; ^{1}H NMR(DMSO): δ = 3.91 (s, 6H, OCH_3), 6.97–7.00 (d, 2H, J = 7.2 Hz, Ar), 7.46–7.47 (m, 3H, Ar), 7.95–7.98 (d, 2H, J = 7.2 Hz, Ar), 8.12–8.16 (m, 2H, Ar) ppm;^{13}C NMR(DMSO): δ = 53.6 (O—<u>C</u>H$_3$), 54.4 (p-O<u>C</u>H$_3$), 179.4 (<u>C</u>O), 155.5, 154.7, 149.9 (<u>C</u>=N), 160.2, 134.8, 129.1, 126.9, 127.8, 127.0, 132.7, 114.3 (<u>C</u>—Ar) ppm; MS: *m/z* (%) = 321 (90) [M^+].

Reaction of Trimethylphosphonoacetate (7) with 3a and 3b

A solution of 0.002 mol of sodium methoxide in absolute methanol was treated with an equimolar amount of the phosphonate **7** (0.36g; 0.002 mol), after 5 min, **3a** or **3b** (0.001 mol) was added, the reaction mixture was boiling under reflux for 4 h. To the reaction mixture, a few drops of water were added, and extracted with ethyl acetate. The extract was evaporated under reduced pressure and the residue subjected to silica gel column chromatography to give products **10a, 11a, 10b,** and **11b**.

5-[Methoxyimino(phenyl)methyl]-3-phenyl-1,2,4-triazin-6(1H)-one 10a

Eluent: petroleum ether/ethyl acetate (82/18, v/v). Product **10a** was separated as pale yellow crystals, m.p.230–231°C, yield (60%). Anal.

calcd. $C_{17}H_{14}N_4O_2$(306.32): C, 66.66; H, 4.61; N, 18.29. Found: C, 66.58; H, 4.70; N, 18.35%. IR(KBr): 1730 (CO), 3240 (NH) cm^{-1}; ^1H NMR (DMSO): $\delta = 3.92$ (s, 3H, N—OCH_3), 7.20(s, 1H, NH), 7.37–7.64 (m, 5H, Ar), 7.93–8.20 (m, 5H, Ar) ppm;^{13}C NMR(DMSO): $\delta = 160.5$ (C=N), 61.6 (N—OCH$_3$), 164.3 (CO), 155.5, 154.7 (C=N), 134.8, 129.1, 126.9, 127.8, 125.8, 130.7, 114.9, 128.9 (C—Ar) ppm; MS: *m/z* (%) 306 (75) [M^+].

3,5-Diphenylisoxazolo[4,5-e]-1,2,4-triazine 11a

Eluent: petroleum ether/ethyl acetate (95/5, v/v). Product **11a** was separated as yellow crystals, m.p. 180–183°C, yield (30%). Anal. calcd. $C_{16}H_{10}N_4O$(274.28): C, 70.06; H, 3.67; N, 20.43. Found: C, 70.15; H, 3.60; N, 20.35%. IR(KBr): 1570 (C=NO) cm^{-1}; ^1H NMR($CDCl_3$): $\delta =$ 7.37–7.60 (m, 5H, Ar), 7.83–8.02 (m, 5H, Ar) ppm;^{13}C NMR(DMSO): δ = 156.4 (C—O—N), 152.2 (C=N), 151.5, 161.7 (C=N), 131.0, 134.8, 128.1, 125.9, 127.8, 123.8, 132.7, 126.9 (*C*—Ar)ppm; MS: *m/z* (%) 274 (75) [M^+].

5-[Methoxyimino(4-methoxyphenyl)methyl]-3-phenyl-12,4-triazin-6(1H)-one 10b

Eluent: petroleum ether/acetone (82/18, v/v). Product **10b** was separated as pale yellow crystals, m.p. 214–215°C, yield (65%). Anal. calcd. $C_{18}H_{16}N_4O_3$(336.34): C, 64.28; H, 4.79; N, 16.66. Found: C, 64.34; H, 4.84; N, 16.71%. IR (KBr): 1730 (CO), 3240 (NH) cm^{-1};^1H NMR($CDCl_3$): $\delta = 3.91$ (s, 3H, OCH_3), 3.86 (s, 3H, N—OCH_3), 7.16 (s, 1H, NH), 6.88–7.03 (m, 3H, Ar), 7.42–7.57 (m, 3H, Ar) 8.17–8.19 (m, 3H, Ar) ppm; ^{13}C NMR(DMSO):$\delta = 55.7$ (OCH$_3$), 162.5 (C=N), 61.6 (N—OCH$_3$), 165.1 (CO), 160.5, 154.7 (C=N), 161.2, 134.8, 129.1, 126.9, 127.8, 125.8, 130.7, 114.9 (C—Ar) ppm; MS: *m/z* (%) 336 (75) [M^+].

3(4-Methoxyphenyl)-5-phenylisoxazolo[4,5-e]-1,2, 4-triazine 11b

Eluent: petroleum ether/acetone (95/5, v/v). Product **11b** was separated as yellow crystals, m.p. 220–222°C, yield 30%. Anal. calcd. $C_{17}H_{12}N_4O_2$(304.30): C, 67.10; H, 3.97; N, 18.41. Found: C, 67.24; H, 3.86; N, 18.52%. IR (KBr): 1568 (C=NO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta =$ 3.95 (s, 3H, OCH_3), 7.13–7.62 (m, 2H, Ar), 7.60–7.62 (m, 3H, Ar) 8.53–8.56 (m, 2H, Ar) 8.65–8.68 (m, 2H, Ar) ppm; ^{13}C NMR(DMSO): $\delta = 55.4$ (OCH$_3$), 158.4 (N—O—C), 152.5 (C=N), 160.1, 154.7(C=N), 159.2, 134.8, 129.1, 126.9, 127.8, 123.8, 132.7, 114.9 (C—Ar) ppm; MS: *m/z* (%) 304 (25) [M^+].

Biological Activity

The antibacterial and antifungal activities were carried out in the Microbial Department, National Research Centre, using the diffusion

TABLE I The Antibacterial and Antifungal Activities of the Synthesized Compounds

Micro-organism	Gram Strain reaction	*Inhibition zone diameter mm / mg sampl*					
		Control Chloroform	Compound No 5c	2b	5d	11b	Reference antibiotic
Bacillus subtilis	+ve	0.0	0.0	0.0	0.0	30	40
Bacillus cereus	+ve	0.0	0.0	0.0	0.0	0.0	30
Escherichia coli	−ve	0.0	16	11	11	11	20
Pseudomonas aeruginose	−ve	0.0	0.0	0.0	0.0	0.0	35
Staphylococcus aureus	+ve	0.0	16	0.0	0.0	0.0	50
Candida albicans	fungus	0.0	15	12	10	10	44

plate method.[21–24] A filter paper sterilized disc saturated with measured quantity (1ml, mg/ml) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37°C for 24 h for bacteria (in case of fungi, at 25°C for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in chloroform as a solvent which has zero inhibition activity. The antimicrobial activity of the tested compounds were examined with gram positive bacteria *Bacillus subtilis, Bacillus cereus* and *Staphylococcus aureus* and gram negative bacteria *Escherichia coli, Pseudomonas aeruginose* and fungus *Candida albicans*. The obtained results are compared with reference antibiotics that were purchased from Egyptian markets.

As shown in (Table 1), the compounds **5c, 2b**,**5d, 11b** were found be active against gram negative bacteria *Escherichia* and *Candida albicans*. Compound **11b** was found to be active against gram positive bacteria *Bacillus subtilis*, while the other derivatives have inhibitory effect against the same microorganism.

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