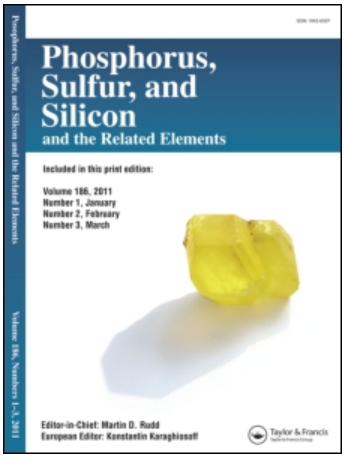

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Pyridazine Derivatives and Related Compounds, Part 17:[1] The Synthesis of Some 3-Substituted Pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazines and Their Antimicrobial Activity

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*The reaction of the hydrazide of pyridazino[3′,4′:3,4]pyrazolo[5,1-c]-1,2,4-triazine-3-carboxylic acid **3** with carbon disulfide in the presence of potassium hydroxide gave the 1,3,4-oxadiazole-2-thione derivative **4**. The methylation of this product in an alkaline medium proceeds at the sulfur atom. The reaction of **3** with KOH and carbon disulfide followed by addition of hydrazine hydrate afforded the 4-amino-1,2,4-triazole derivative **6**. Compound **3**, when heated either with ammonium thiocyanate or with potassium thiocyanate, afforded the same product **7**, which underwent cyclodehydration in the presence of acetyl chloride, which led to the 2-acetylamino-1,3,4-thiadiazole derivative **8**. In a basic medium, the product was 1,2,4-triazole-3-thione derivative **9**. The reaction of **3** with phenyl isothiocyanate provided thiosemicarbazide derivative **10**, which underwent cyclodehydration in a basic medium and gave the 1,2,4-triazole derivative **11**. The reaction of **3** with formic acid yielded the 3-carboxyl-2′-(formyl)hydrazine derivative **12**. The refluxing of the latter with phosphorus pentasulfide in xylene yielded compound **14** (65%). The reaction of compound **12** with phosphorus pentoxide afforded compound **15**. Some representative examples were screened for antimicrobial activity.*

Keywords 1,2,4-triazole-3-thion; 1,3,4-oxadiazole-2-thione; 1,3,4-thiadiazole; antimicrobial activity

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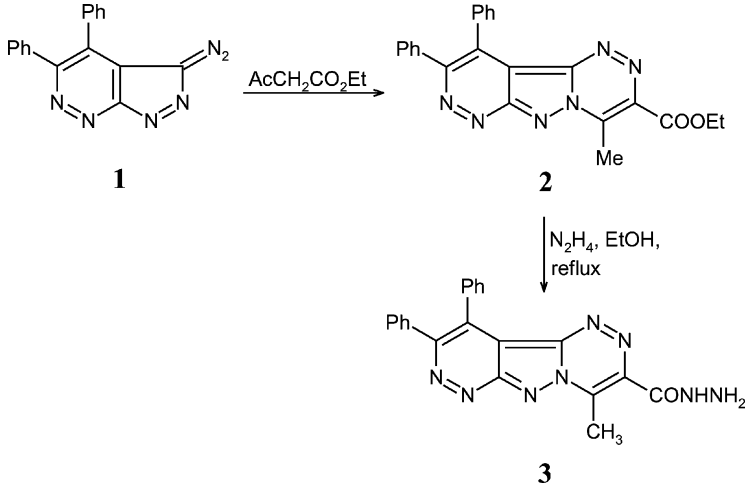
INTRODUCTION

Pyrazolopyridazines and pyrazolotriazines are well known for diverse biological activities.[2] Sometimes the fusion of heterocyclic nucli enhances the pharmacological activities much more than its parent nucleus. On the other hand, several 1,3,4-thiadiazole[3] derivatives and their bioisosteres 1,3,4-oxadiazoles[4] and 1,2,4-triazoles[5] have antibacterial and antifungal activity. Hence, it was thought that the incorporation of the latter hetero-cyclic moieties into a pyridazine condensed system might modify their biological activities. The present investigation is in continuation of our previous work[6] on the synthesis and antimicrobial activity of other pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*] -1,2,4-triazine derivatives.

RESULTS AND DISCUSSION

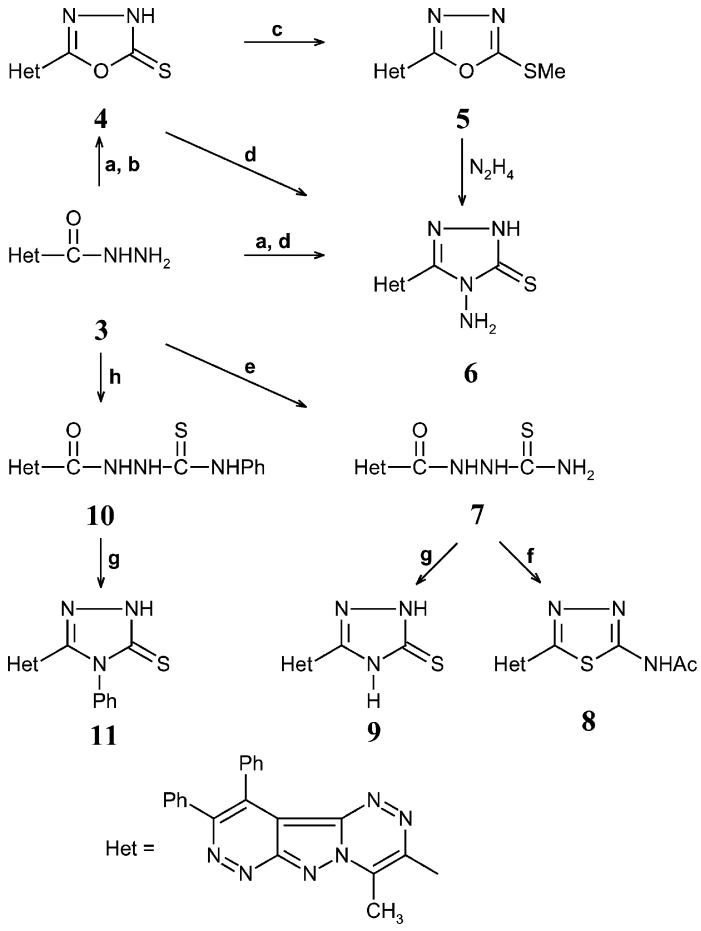
The required ethyl 4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*] -1,2,4-triazine-3-carboxylate (**2**) was prepared (92.6%) as yellow crystals (m.p. 248–250°C) by the coupling of 3-diazo-4,5-diphenylpyrazolo[3,4-*c*]pyridazine (**1**) with ethyl acetoacetate (Scheme 1). This carboxylate **2** on refluxing with hydrazine hydrate gave the acid hydrazide **3**[6] in a high yield.



SCHEME 1

Compound **4** was prepared from the reaction of the corresponding acid hydrazide **3** and carbon disulfide in the presence of potassium

hydroxide followed by the treatment of the resulting anionic form with hydrochloric acid (Scheme 2). Product **4** in the solid state exists as the



SCHEME 2 **a**, CS_2/KOH; **b**, HCl; **c**, MeI; **d**, N_2H_4; **e**, NH_4SCN or KSCN; **f**, AcCl; **g**, NaOH; and **h**, PhNCS.

thione form as indicated by its IR spectrum, displaying bands for NH (3192 cm^{-1}) and C=S group (1332 cm^{-1}) but lacking a band at 2600–2500 cm^{-1} (SH stretching vibrations). The finding of these bands is in accord with the data of Ainsworth[7] for various 5-substituited 1,3,4-oxadiazole-2-thiones. Oxadiazolethion **4** undergoes methylation upon reaction with methyl iodide in boiling ethanol with sodium hydroxide and led to the SMe derivative **5**. The structure of compound **5** was

established from analytical and spectral data. The mass spectra showed the expected molecular ion peaks. The most salient features of the IR, ^{1}H-NMR, and mass spectra are given in the Experimental section.

On the other hand, the reaction of the acid hydrazide **3** with KOH and carbon disulfide followed by the addition of hydrazine hydrate afforded 4-amino-1,2,4-triazole derivative **6** in a moderate yield. In the infrared spectrum compound **6** absorbs strongly at 3445, 3320, 3151, 1613, and 1423 cm^{-1}. The 3445 cm^{-1} and 3320 cm^{-1} bands were assigned to NH_2, the band at 1613 cm^{-1} to endocyclic C=N, and the band at 1423 cm^{-1}, referred to C=S. Moreover, the mass spectra recorded a molecular ion peak at m/z 452. Compound **6** was also prepared unequivocally by the ring transformation of oxadiazolethione derivative **5** when it reacted with hydrazine hydrate.

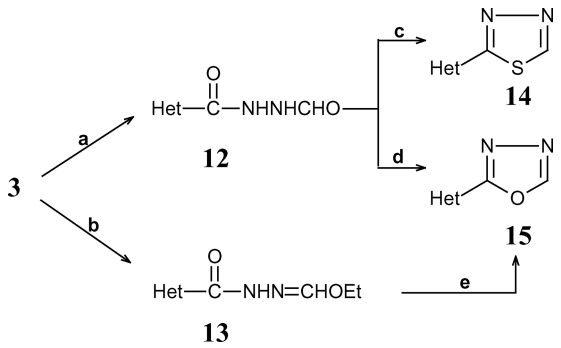
Compound **3**, when heated either with ammonium thiocyanate in absolute ethanol or with potassium thiocyanate, afforded the same product. The isolated product was proven to be 4-methyl-9,10-diphenylpyridaz-ino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine-3-carbothiosemicarbazide (**7**).

The cyclodehydration of **7** in the presence of acetyl chloride led to 2-acetylamino-1,3,4-thiadiazole derivative **8**. When the thiosemicarbazide **7** was cyclized under a basic condition (NaOH), the 1,2,4-triazole-3-thione derivative **9** was obtained.

The treatment of the acid hydrazide **3** with phenyl isothiocyanate provided the 3-(1′-phenylthiocarbamyl)hydrazino carbonyl derivative **10** in a 64% yield (Scheme 2). The IR spectra of **10** showed vibrational bands due to NH, C=O, and CNS amide. The thiosemicabazide **10** was then cyclo-dehydrated with 4% aqueous NaOH to produce the 1*H*-4-phenyl-5-thio-1,2,4-triazole derivative **11**. The IR, ^{1}H-NMR, and mass spectra of **11** were consistent with the assigned structure. The IR spectrum showed absorption due to the C=N and NCS amide function indicating that they exist in the triazolinethione rather than in the mercaptotriazole form. The ^{1}H-NMR spectra showed a highly deshielded signal at 14.08–14.25 ppm assigned for the NH proton of the triazoline ring

The refluxing compound **3** with formic acid for 5 h gave 3-carboxyl-2′-(formyl)hydrazine derivative **12** in a high yield (Scheme 3). Refluxing compound **12** with phosphorus pentasulfide gave 1,3,4-thiadiazole derivative **14** (65%).

The usual reaction for the formation of 1,3,4-oxadiazole, namely the reaction of compound **3** with ethyl orthoformate, did not give the desired compound **15**. In the latter reaction, ethoxyformaldehyde 3-carboxyhydrazone **13** was formed. Heating compound **13** to its melting point gave compound **15** (66%). Compound **15** also could be obtained in a



SCHEME 3 **a**, HCOOH; **b**, $CH(OEt)_3$; **c**, P_2S_5; **d**, P_2O_5; and **e**, heat.

yield of 58% by refluxing compound **12** with phosphorus pentoxide in xylene.

Antimicrobial Activity

Representative compounds were screened for their antibacterial activity against gram-negative bacteria *E. coli*, *K. pneumoniae*, and *P. aeruginosa* and gram positive bacteria *S. aureus* at 500, 1,000, 5,000, and 10,000 ppm concentration; the antifungal activity against *C. albicans* and *A. fumogitus* also was determined. The compounds were screened for their biological activity using the inhibition zone technique.[6] The results obtained for antibacteria are given in Table I. No significant inhibition was shown by any of the tested compounds against *A. fumigatus* and *C. albicans*.

TABLE I Mean Value of Area of Inhibition in mm. A, *P. aeruginosa*; B, *S. aureus*; (–) = no inhibition zones

	Organism							
	A				B			
Compounds[a]	500	1000	5000	10000	500	1000	5000	10000
4	–	–	2	4	2	5	6	8
5	–	–	–	–	–	1	4	6
6	2	3	4	6	1	4	5	15
7	1	3	5	7	–	–	–	–
8	–	–	3	6	1	3	6	7
10	–	–	–	–	–	–	3	5
12	–	–	–	–	1	2	3	4

[a]No significant inhibition was shown against: *E. coli* and *K. pneumoniae*.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1430 as potassium bromide pellets, and frequencies are reported in cm^{-1}. The ^1H-NMR spectra were observed on a Perkin-Elmer R12B spectrometer, and chemical shifts (δ) are in ppm relative to internal TMS; mass spectra were recorded on a Mass Spectrometer HP model MS 5988 E1 70 eV. Reactions were routinely followed by thin layer chromatography on silica gel F_{254} aluminium sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

5-(4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)-2,3-dihydro-1,3,4-oxadiazole-2-thion 4

To a solution of compound **3** (1.5 g, 3.87 mmol) in ethanol (10 mL) at 0°C carbon disulfide (0.7 g, 9.2 mmol) and potassium hydroxide (0.22 g, 3.9 mmol) were added. The mixture was refluxed for 7 h. The solvent was evaporated. The residue was dissolved in water (100 mL) and acidified with conc. HCl (pH = 6). The precipitate was filtered and recrystallized from ethanol to give 1.5 g (90%) of **4**, m.p. 232–234°C; IR: 3192 (NH), 3090 (CH aromatic), 1635 (C=N), 1332 (C=S) cm^{-1}. Anal. calcd. for $C_{22}H_{14}N_8OS$: C, 60.26; H, 3.22; N, 25.56. Found: C, 60.00; H, 3.10; N, 25.30.

5-(4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)-2-methylthio-1,3,4-oxadiazole 5

To a stirred solution of compound **4** (1.0 g, 2.28 mmol) in ethanol (15 mL) and sodium hydroxide (1 *N*, 1 mL), methyl iodide (0.32 g, 2.28 mmol) was added. After half an hour, the precipitate was filtered and recrystallized from ethyl acetate to give 0.8 g (77.6%) of **5**, m.p. 130–131°C; IR: 3135 (CH aromatic), 1615 (C=N) cm^{-1}; ms: *m/z* (%) 452 (M^+, 0.4), 407 (0.43), 366 (1.0), 315 (11), 301 (100). Anal. calcd. for $C_{23}H_{16}N_8OS$: C, 61.05; H, 3.56; N, 24.77. Found: C, 60.90; H, 3.40; N, 24.50.

4-Amino-5-(4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)-2,3-dihydro-1,2,4-triazole-3-thione 6

To a solution of potassium hydroxide (0.2 g, 3.56 mmol) in absolute ethanol (10 mL), compound **3** (1.0 g, 2.52 mmol) was added with stirring. After a few minutes, a slight excess of carbon disulfide

(0.3 g, 3.94 mmol) was added, and the mixture was held at reflux for 10 h. A solid product appeared occasionally during the addition of carbon disulfide but was usually dissolved upon heating. Evaporation of the solvent by distillation in vacuo left a residue that was washed with cold absolute ethanol and ether. A mixture of the potassium salt and hydrazine hydrate 85% (5 mL) in absolute ethanol (20 mL) was refluxed for 1 h. The reaction mixture then was diluted with cold water (100 mL) and acidified by dropwise concentrated hydrochloric acid. The precipitate, separated by filtration, was dried and recrystallized (ethanol) to give 0.65 g (65%) of **6**, m.p. 178–180°C; IR: 3445, 3320, 3151, 1613, 1423 cm^{-1}; ms: *m/z* (%) 451 (M^+-1, 0.09), 443 (0.1), 433 (0.12), 423 (0.13), 420 (0.25), 286 (100). Anal. calcd. for $C_{22}H_{16}N_{10}S$: C, 58.39; H, 3.56; N, 30.96. Found: C, 58.10; H, 3.40; N, 30.70.

4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine-3-carbothiosemicarbazide 7

Method A

Compound **3** (1.0 g, 2.52 mmol) was suspended in 12 mL of alcoholic hydrogen chloride solution and then was evaporated under reduced pressure. The residue was dried by evaporation using small amounts of alcohol. The product was heated under reflux for 18 h with a solution of dry ammonium thiocyanate (0.2 g, 2.62 mmol) in absolute ethanol (10 mL). The solid was filtered, washed several times with water, and recrystallized (ethanol) to give **7** (0.8 g, 69.6%), m.p. 248–249°C; IR: 3433, 3333, 3271, 3163, 1617, 1590 cm^{-1}; ms: *m/z* (%) 450 (M^+-5, 0.07), 449 (1.13), 435 (2.02), 420 (1.51), 411 (1.1), 206 (100). Anal. calcd. for $C_{22}H_{17}N_9OS$: C, 58.01; H, 3.76; N, 27.68. Found C, 57.80; H, 3.80; N, 27.90.

Method B

A mixture of compound **3** (1.0 g, 2.52 mmol), potassium thiocyanate (0.5 g, 5.14 mmol), water (50 mL) and concentrated hydrochloric acid (2.5 mL) was refluxed for 3 h. After cooling, the precipitate was filtered off and recrystallized (ethanol) to give 0.9 g, 78.3% of compound **7**, m.p. 248–250°C. It was identical in every respect with that prepared by Method A.

2-Acetylamino-5-(4-methyl-9,10-diphenylpyridazino-[3′,4′:3,4]pyr-azolo[5,1]-1,2,4-triazin-3-yl)-1,3,4-thiadiazole 8

Compound **7** (0.5 g, 1.09 mmol) and acetyl chloride (2 mL, 25.48 mmol) were mixed in an ice bath and afterwards were gently heated under

reflux for 3 h. After the vigorous reactions subsided, heating was continued for 15 min. To the cold reaction mixture water (100 mL) was added. The insoluble material was collected, washed several times with water, and recrystallized (ethanol) to give **8** (0.3 g, 57.03%), m.p. 268–270°C; IR: 3447, 3263, 3180, 3056, 1612 cm^{-1}. Anal. calcd. for $C_{24}H_{17}N_9OS$: C, 60.11; H, 3.57; N, 26.29. Found: C, 59.90; H, 3.20; N, 26.40.

5-(4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]- pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)-2,3-dihydro-1,2,4- triazole-3-thione 9

A solution of **7** (1.0 g, 2.19 mmol) in 2 *N* NaOH (10 mL) was refluxed for 3 h. The mixture was cooled and acidified with dil. HCl (pH 5.6), and the separated solid was filtered, dried, and recrystallized (ethanol) to give **9** (0.8 g, 83%), m.p. 238–240°C; IR: 3445, 3326, 3153, 3058, 1612, 1564, 1423 cm^{-1}. Anal. calcd. for $C_{22}H_{15}N_9S$: C, 60.40; H, 3.46; N, 28.82. Found: C, 60.30; H, 3.30; N, 28.60.

4-Methyl-9,10-diphenyl-3-(1′-phenylthiocarbomyl)-hydrazinocarbonylpyridazino[3′,4′:3,4]pyrazolo-[5,1-*c*]-1,2,4-triazine 10

To a solution of **3** (1.5 g, 3.78 mmol) in hot absolute ethanol (10 mL) phenyl isothiocyanate (1.0 ml, 7.29 mmol) was added. The mixture was refluxed while stirring for 3 h. The separated solid was washed with ethanol and recrystallized (ethyl acetate/pet. ether 40–60°C) to give **10** (1.3 g, 64.67%), m.p. 162–163°C; IR: 3445, 3378, 3155, 3057, 1598 cm^{-1}. Anal. calcd. For $C_{28}H_{21}N_9OS$: C, 63.26; H, 3.98; N, 23.71. Found: C, 63.00; H, 3.80; N, 23.50.

1H-4-Phenyl-3-(4-methyl-9,10-diphenylpyidazino[3′,4′:3,4]-pyrazolo-[5,1-*c*]-1,2,4-triazin-3-yl)-1,2,4-triazole-5-thione 11

A solution of **10** (0.4 g, 0.75 mmol) in 2 *N* NaOH (10 mL) was refluxed for 3 h. The mixture was cooled and acidified with dil. HCl (pH = 6), and the separated solid was recrystallized (ethanol) to give **11** (0.25 g, 64.7%), m.p. 198–200°C; IR: 3400–3250 (NH), 1600 (C=N), 1590, 1510–1490 (C=C), 1550–1520, 1380–1360, 1270–1250, 980–970 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm: 14.25–14.08 (br s, 1H, NH), 7.6–7.2 (m, 10H, 2Ph), 1.4 (s, 3H, CH_3); ms: *m/z* (%) 509 ($M^+ - 4$, 0.4), 495 (0.3), 481 (0.2), 368 (3.5), 313 (3.1). Anal. calcd. for $C_{28}H_{19}N_9S$: C, 65.48; H, 3.73; N, 24.55. Found: C, 65.20; H, 3.80; N, 24.70.

3-Carboxyl-2′-(formyl)hydrazino-4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine 12

A solution of compound **3** (1.5 g, 3.78 mmol) in formic acid (10 mL) was refluxed for 5 h. After cooling, the precipitate was filtered and recrystallized (ethanol) to give **12** (1.2 g, 75%), m.p. 268–270°C; IR: 3439, 3384, 3148, 1702, 1562 cm^{-1}. Anal. calcd. for $C_{22}H_{16}N_8O_2$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.00; H, 3.50; N, 26.10.

2-(4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazin-3-Yl)-1,3,4-thiadiazole 14

To a solution of compound **12** (1.0 g, 2.35 mmol) in xylene (50 mL) was added phosphorus pentasulfide (1.0 g). The mixture was refluxed for 45 min and filtered. The solvent was evaporated. To the residue was added dimethyl sulfoxide (10 mL), and the mixture was filtered. The precipitate was collected, dried, and recrystallized (ethanol) to give **14** (0.65 g, 65.65%), m.p. 210–212°C; IR: 3125, 1610, 1560, 1500, 1350; ^{1}H-NMR ($CDCl_3$) ppm: 8.8 (s, 1H, oxadiazole), 7.8–7.2 (m, 10H, 2Ph), 2.4 (s, 3H, CH_3); ms: *m/z* (%) 422 (M^+, 0.2), 365 (0.3), 351 (0.2), 315 (37). Anal. calcd. for $C_{22}H_{14}N_8S$: C, 62.54; H, 3.34; N, 26.53. Found: C, 62.30; H, 3.10; N, 26.20.

Ethoxyformaldehyde 3-Carboxyhydrazone-4-methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-c]-1,2,4-triazine 13

A mixture of compound **3** (0.4 g, 1.0 mmol) and ethyl orthoformate (5 mL) was heated under reflux for 3 h. After cooling, the precipitate was filtered and recrystallized (methylene chloride/diethyl ether) to give (0.3 g, 65.78%) of compound **13**, m.p. 126–127°C; IR: 3055, 2979, 1624, 1562, 1428 cm^{-1}. Anal. calcd. for $C_{24}H_{20}N_8O_2$: C, 63.71; H, 4.46; N, 24.77. Found: C, 63.50; H, 4.20; N, 24.50.

2-(4-Methyl-9,10-diphenylpyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazin-3-yl)-1,3,4-oxadiazole 15

Method A

Compound **13** (0.5 g, 1.1 mmol) was heated at 125–130°C for 30 min. The residue was triturated with diethyl ether to give (0.3 g, 66.8%) of compound **15**, recrystallized (ethanol), m.p. 270–272°C; IR: 3055, 1631, 1558, 1490 cm^{-1}; ms: *m/z* (%) 406 (M^+, 5.2), 286 (100), 257 (11.4), 243 (18.2), 189 (48.8). Anal. calcd. for $C_{22}H_{14}N_8O$: C, 65.02; H, 3.47; N, 27.57. Found: C, 65.10; H, 3.20; N, 27.30.

Method B

To a solution of compound **12** (0.4 g, 0.94 mmol) in xylene (10 mL), phosphorus pentoxide (0.5 g) was added. The mixture was refluxed for 3 h. The solvent was evaporated and the residue was recrystallized (ethanol) to give (0.2 g, 52.6%) of compound **15**, m.p. 270–272°C. It was identical in every respect with that prepared by Method A.

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