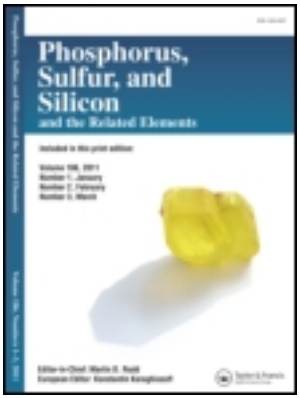

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Pyridazine Derivatives and Related Compounds, Part 12: Synthesis of Some Pyridazino [4′,3′:4,5]thieno[3,2-d]1,2,3-triazines

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Published online: 21 Dec 2010.

To cite this article: Ali Deeb , Mahmoud Kotb & Mohamed El-Abbasy (2005) Pyridazine Derivatives and Related Compounds, Part 12: Synthesis of Some Pyridazino [4′,3′:4,5]thieno[3,2-d]1,2,3-triazines, Phosphorus, Sulfur, and Silicon and the Related Elements, 180:2, 591-599, DOI: 10.1080/104265090517398

To link to this article: http://dx.doi.org/10.1080/104265090517398

Phosphorus, Sulfur, and Silicon, 180:591–599, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090517398

Pyridazine Derivatives and Related Compounds, Part 12: Synthesis of Some Pyridazino [*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazines

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The syntheses of pyridazino[4′,3′:4, 5]*thieno*[3, 2-d]-*1,2,3-triazinones 2, 3, 6, derivatives of the ring system thieno[2,3-c]pyridazine, have been accomplished by a diazotization reaction. Reaction of triazine* ***3*** *with phosphorous oxychloride led to 4-chloro derivative* ***7*** *which, on further displacement reactions, gives 4-substituted derivatives. All new compounds were characterized by elemental analyses and spectral data.*

Keywords Pyridazino[4′,3′:4,5]thieno[3,2-d]-1,2,3-triazines; synthesis; thieno[2,3-c]-pyridazine

INTRODUCTION

Heterocyclic annulated pyridazines continue to attract considerable attention, which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives.[1] On the other hand 1,2,3-triazine systems condensed with carbocycles or heterocycles are known[2] and exhibit antiallergic activity.[3] In connection with these facts and in continuation of our efforts directed toward the synthesis of tricyclic systems containing a pyridazine subunit,[4] we report on the utility of 5-amino-3,4-diphenylthieno[*2,3-c*]pyridazine-6-carbohydrazide (**1**) as a synthon for the preparation of pyridazino[*4′,3′:4,5*]thieno[3, 2-*d*]-1,2,3-triazines with potential biological activity.

Our synthesis began with the preparation of 5-amino-3,4-diphenylthieno-[2,3-*c*]pyridazine-6-carbohydrazide (**1**), which was obtained in good yield from the reaction of ethyl 5-amino-3,4-diphenylthieno[*3,4-c*]pyridazine-6-carboxylate[5] with hydrazine hydrate. This

Received June 1, 2004.
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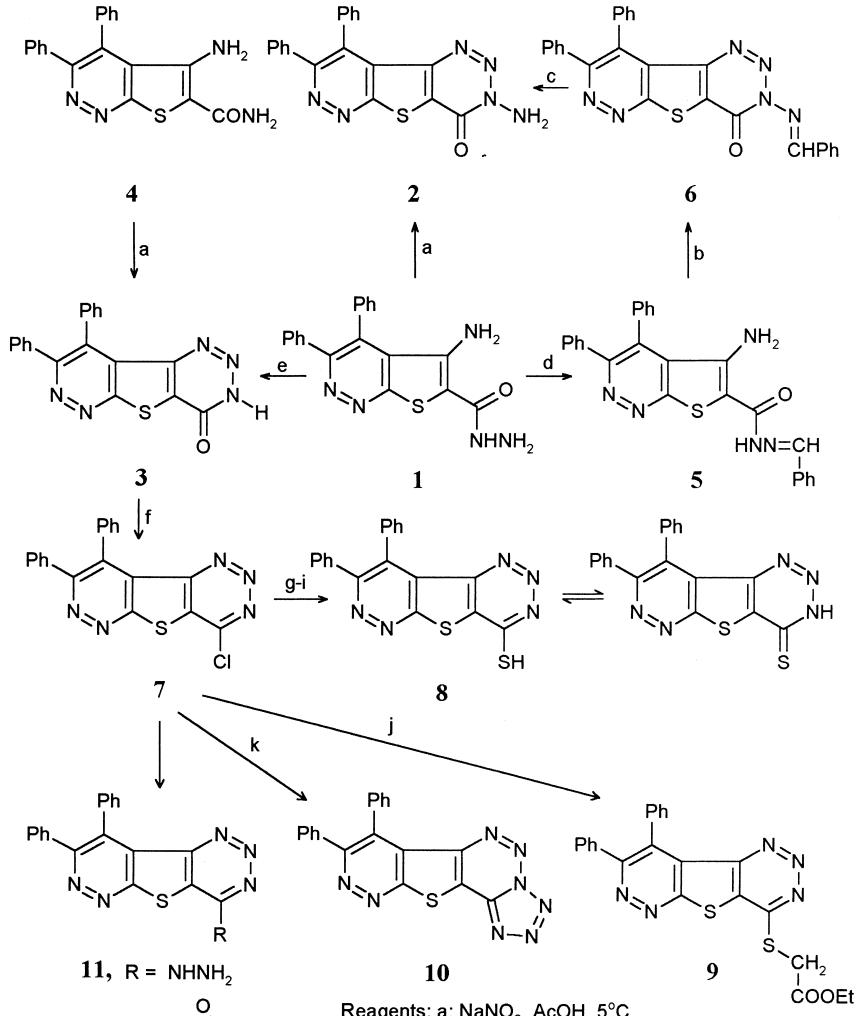
hydrazide, and compounds derived from it, underwent the transformation illustrated in Scheme 1. Diazonium ion condensation with an adjacent function to form a five- or six-membered rings has proved useful for synthesizing various nitrogen heterocycles including a number of 1,2,3-triazines[6] that are formed via intramolecular attack of an electrophilic nitrogen function. Thus, the reaction of **1** with one equivalent of sodium nitrite in acetic acid at 5°C resulted in the formation of a compound which was assigned the structure 3-amino-8,9-diphenylpyridazino[*4′,3′:4,5*]-thieno[*3,2-d*]-1,2,3-triazin-4(3*H*)-one (**2**), rather than either an amino-carbonylazide or a tetrazepin, on the basis of spectral data. Their spectrum did not show any characteristic band for the azido group at about 2000–2200 cm^{-1}. In the ^{1}H-NMR was observed a peak at 6.7 which was assigned to the exocyclic amino group at position three and would not have been observed if a seven membered ring had been formed in the diazotization reaction. When 5-amino-6-carbohydrazide derivative **1** was treated with an excess of sodium nitrite, there was observed a smooth conversion of **1** to 8,9-diphenylpyridazino-[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazin-4(3*H*)-one (**3**). This reaction presumably proceeds via **2** with the excess sodium nitrite, then removing the exocyclic amino group. However, a new and facile preparation of **3** by diazotization of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboxamide (**4**)[7] with sodium nitrite in acetic acid at 5°C was accomplished in the present investigation for comparison with the product obtained from **1**. The 3-aminotriazinone **2** was also obtained following another procedure, by converting the carbohydrazide **1** into the corresponding 6-benzylidenecarbohydrazide derivative **5** followed by treatment with nitrous acid. The 3-benzylideneaminopyridazinothienotriazinone **6** was readily hydrolysed in presence of ethanolic hydrazine hydrate boiling solution to **2**.

The final part of this study was an examination of the reaction of parent pyridazinothienotriazinone **3** with phosphoryl chloride which yielded 4-chloro-8,9-diphenylpyridazino[*4′,3:4,5*]thieno[*3,2-d*]-1,2,3-triazine **7** (42%). The chlorine atom of **7** showed the expected reactivity towards nucleophilic reagents. Treatment of 4-chloro derivative **7** with thiourea provided the 4-mercapto system **8**. Their spectrum of **8** indicated bands at 2550 cm^{-1} and 1470 cm^{-1}, suggesting that it existed as a tautomeric mixture of **8** and the corresponding thioamide. The chlorine atom was also displaced by a thioglycolate and gave the corresponding thioacetate **9**, while with sodium azide **7** gave the tetrazole **10**. Their spectrum of **10** showed no bands near 2100 cm^{-1} which excludes the azidotriazine structure in the solid state. When compound **7** was treated with hydrazine hydrate, 4-hydrazino **11** was obtained.



SCHEME 1

Compound **11** in turn could be transformed to other heterocyclic systems. When reacted with phthalic anhydride, the N-phthalimide **12** was obtained. The reaction of **11** with phenyl isothiocyanate afforded N-phenylthio(carbamoyl)hydrazine **13**, while the condensation with *p*-nitrobenzaldehyde afforded the corresponding hydrazone **14**. The tetrazole **10** was also obtained from **11** via the diazonium process involving sodium nitrite in acetic acid. Finally the interaction of **11** with acetylacetone afforded a compound whose ir spectrum lacked both C=O and NH bands, indicating that both the two carbonyl groups of acetylacetone were condensed with the hydrazine group of **11** giving compound **15**. The most salient features of ir and ^{1}H-NMR spectra are given under experimental.

In view of the wide range of pharmacological properties reported for various thienopyridazines and several other related compounds, the various pyridazino-thienotriazines prepared now should be screened for their biological activity. The results will be published elsewhere.

EXPERIMENTAL

Melting points were determined in open-glass capillaries and were uncorrected. Their spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer, model 1310, as potassium bromide pellets, and frequencies are reported in cm^{-1}. The ^{1}H-NMR spectra were observed on a Perkin-Elmer R12 B spectrometer, and chemical shifts (δ) are in ppm relative to internal TMS. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental analyzer. Reactions were routinely followed by thin layer chromatography (tlc) on silica gel F_{254} aluminium sheets (Merck). The spots were detected by uv irradiation at 254–365 nm.

5-Amino-3,4-diphenylthieno[2,3-*c*] pyridazine-6-carbohydrazide (1)

A solution of ethyl 5-amino-3,4-diphenylthieno[*2,3-c*]pyridazine-6-carboxylate (0.75 g, 2 mmol) and hydrazine hydrate (0.7 mL, 85%) in ethanol (20 mL) was boiled under reflux for 2 hours. The crystals that separated on cooling were filtered off and dried to give the hydrazide derivative **1** (0.89 g, 92%), m.p. 245–246°C (ethanol); ir: 3450, 3320, 3260 (NH groups), 1640 (C=O), 1600 (C=N), 1530 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 9.4 (s, 1H, NH), 7.80 (s, 2H, NH_2), 7.4–7.0 (s, 10H, 2Ph), 4.2 (s, 2H, 5-NH_2).

Anal. Calcd for $C_{19}H_{15}N_5OS$: C, 63.14; H, 4.18; N, 19.38. Found: C, 63.00; H, 4.10; N, 19.20.

3-Amino-8,9-diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazin-4(*3H*)-one (2)

Carbohydrazide **1** (11.7 g, 32.3 mmol) was dissolved in water (45 mL) containing 10 ml of acetic acid with rapid stirring. This solution was cooled to 5°C, and then sodium nitrite (2.3 g, 33.3 mmol) dissolved in water (10 mL) was added dropwise over a period of 15 minutes to the rapidly stirred solution while maintaining the temperature at 5–10°C. After the addition was complete, the solution was stirred an additional 15 minutes, and the temperature was then allowed to rise to 15°C. The solution was maintained at this temperature for 30 minutes at which time a solid began to separate. The reaction mixture was allowed to stand at 5°C for 16 hours. The solid was removed by filtration, washed with ether, and dried at room temperature to yield 7.6 g 63.4% of **2**, m.p. 196–197°C (ethanol); ir: 3500, 3310, 3180 (NH groups), 1670 (C=O), 1640 (C=N), 1530 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 7.6–7.4 (m, 10H, 2Ph), 6.7 (s, 2H, NH_2).

Anal. Calcd. for $C_{19}H_{12}N_6OS$: C, 61.27; H, 3.25; N, 22.57. Found: C, 61.00; H, 3.00; N, 22.10.

8,9-Diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazin-4(*3H*)-one (3)

Method A

Carbohydrazide **1** (3.5 g, 9.69 mmol) was dissolved in water (25 mL) and acetic acid (5 mL). Sodium nitrite (3.4 g, 50 mmol) was dissolved in water (10 mL) and added in the same manner as for compound **2**. The solid that formed was collected by filtration and dried at room temperature to yield 2.97 g, (86%) of **3**, m.p. 260–261°C (ethanol); ir: 3210 (NH), 1650 (C=O), 1640 (C=N), 1520 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 7.6–7.4 (m, 10H, 2Ph), 3.35 (br, s, 1H, NH).

Anal. Calcd. for $C_{19}H_{11}N_5OS$: C, 63.85; H, 3.10; N, 19.59. Found: C, 63.60; H, 3.00; N, 19.30.

Method B

3,4-Diphenyl-5-aminothieno[2, 3-*c*]pyridazine-6-carboxamide (**4**) (2.48 g, 7.15 mmol) was dissolved in a mixture of water (15 mL) and acetic acid (3 mL). Sodium nitrite (1.5 g, 21.7 mmol) was dissolved in water (3 mL) and then added in the same manner as that described for the preparation and isolation of compound **2**. The solid that formed was

collected by filtration and dried at room temperature to yield 2.13 g, (83.5%) of **3** which was identical in all respects with the compound from Method A.

5-Amino-3,4-diphenylthieno[*2,3-c*]pyridazine-6-benzylidene carbohydrazide (5)

A solution of the benzaldehyde (0.5 g, 4.7 mmol) and compound **1** (1.5 g, 4.15 mmol) in ethanol (30 mL) containing a few drops of glacial acetic acid was boiled under reflux for 2 hours. The precipitated product was collected by filtration upon cooling and was recrystallized for analysis, m.p. 155–156°C (ethanol), 1.6, (87%); ir: 3500, 3370, 3176 (NH groups), 1671 (C=C), 1605 (C=N), 1542 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 8.40 (s, 1H, NH), 7.90 (s, 1H, CH), 7.8 (s, 2H, NH_2), 7.60–7.40 (m, 15H, 3Ph).

Anal. Calcd. for $C_{26}H_{19}N_5OS$: C, 69.46; H, 4.26; N, 15.58. Found: C, 69.20; H, 4.00; N, 15.30.

3-Benzylideneamino-8,9-diphenylpyridazino[*4′,3′:4,5*]thieno [*3,2-d*]-1,2,3-triazin-4(*3H*)-one (6)

A suspension of finely ground compound **5** (1 g) in 2*M* hydrochloric acid (20 mL) was diazotized in the usual way with sodium nitrite (0.3 g) in water (4 mL), the temperature being kept below 5°C throughout. The bright yellow suspension was stirred at room temperature for 1.5 hours after the addition had been completed. The solid was then collected by filtration, washed with cold water, and dried to give the title **6** (0.9 g, 94%), m.p. 280–281°C (ethanol); ir: 1705 (C=O), 1620 (C=N), 1540 (C=C) cm^{-1},^{1}H-NMR (DMSO-d_6): 8.10 (s, 1H, CH), 7.70–7.40 (m, 15 H, 3Ph).

Anal. Calcd. for $C_{26}H_{16}N_6OS$: C, 67.80; H, 3.50; N, 18.25. Found: C, 67.60; H, 3.30; N, 18.00.

Hydrolysis of 6

Compound **6** (0.7 g, 1.52 mmol) was suspended in ethanol (25 mL), 95% hydrazine hydrate (3 mL) was added, and the reaction mixture was refluxed for 5 hours. When it cooled to room teperature, a solid precipitated, which was washed with water and dried to give **2**, 0.38 g, 68%, m.p. 196–197°C, that was not depressed when mixed with an authentic sample of **2**.

4-Chloro-8,9-diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazine (7)

A mixture of compound **3** (5 g, 13.95 mmol) and phosphorous oxychloride (15 mL) was heated at reflux temperature for 3 hours. The reaction

mixture was cooled in an ice bath and then hydrolyzed by addition of crushed ice. The precipitate was filtered and wash with water and dried, (2.18 g,, 42%), m.p. 116–117°C; ir: 1660 (C=N), 1540 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{10}ClN_5S$: C, 60.72; H, 2.68; N, 18.64. Found: C, 60.60; H, 2.60; N, 18.60.

4-Mercapto-8,9-diphenylpyridazino[*4′,3:4,5*]thieno[*3,2-d*]-1,2,3-triazine (8)

A solution of **7** (3.38 g, 9.0 mmol) and thiourea (1 g, 13.0 mmol) in ethanol (60 mL) was refluxed for 1 hour. The solvent was evaporated in vacuo, and the residue was refluxed in sodium hydroxide solution (50 mL, 2.5 N) for 30 minutes and then filtered on hot. The filtrate was cooled and acidified with hydrochloric acid (pH 2). The yellow crystals obtained were filtered, washed with water, and dried to give **8** (3 g, 90%), m.p. 245–246°C (ethanol); ir: 2550 (SH), 1635 (C=N), 1570 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 13.5 (s, ^{1}H, NH), 7.9–7.6 (m, 10H, 2Ph).

Anal. Calcd. for $C_{19}H_{11}N_5S_2$: C, 61.10; H, 2.97; N, 18.75. Found: C, 61.00; H, 2.90; N, 18.60.

Ethyl 9,10-Diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazin-4-ylthio-acetate (9)

To a solution of **7** (0.76 g, 2 mmol) in acetone (30 mL) containing anhydrous potassium carbonate (0.5 g) and ethyl mercaptoacetate (0.72 g, 6 mmol) was added. The reaction mixture was refluxed for 4 hours and the insoluble solid was removed by filtration and washed with acetone. The filtrate and the washings were combined and evaporated. The residue was recrystallized to give **9** (0.74 g, 79%), m.p. 166–167°C (pet. ether 40/60); ir: 1738 (C=O), 1650 (C=N) and 1530 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 7.6–7.2 (m, 10H, 2Ph), 5.6 (br, s, 2H, SCH_2), 4.6-4.2 (q, 2H $J = 6.5$ Hz, $\underline{CH_2}CH_3$), 1.4 (t, 3H$J = 6.5$ Hz, $CH_2\underline{CH_3}$).

Anal. Calcd. for $C_{23}H_{17}N_5S_2O_2$: C, 60.11; H, 3.73; N, 15.24. Found: C, 60.00; H, 3.60; N, 15.10.

7,8-Diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]tetrazolo[*1,5-f*]-1,2,3-triazine (10)

Method A

A solution of **7** (0.78 g, 2 mmol) and sodium azide (0.26 g, 4 mmol) in ethanol (25 mL) was refluxed for 2 hours. The solvent was evaporated in vacuo and the residue was washed with water, filtered, and dried to

give **10** (076 g, 96%), m.p. 187–188°C (ethanol); ir: 1650 (C=N), 1540 (C=C) cm^{-1}.

Anal. Calcd. for $C_{19}H_{10}N_8S$: C, 59.67; H, 2.64; N, 29.30. Found: C, 59.60; H, 2.50; N, 29.20.

Method B

To a suspension of **11** (0.74 g, 2 mmol) in acetic acid (1N, 25 mL) at 45° was added sodium nitrite 0.3 g (4.0 mmol). Effervescence occurred immediately. After 1.5 hours, the solution was cooled, and the product was filtered to give **10** (0.3 g, 40%) which, upon recrystallization, was identical to that described in method A.

4-Hydrazino-8,9-diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazine (11)

A solution consisting of **7** (0.76 g, 2 mmol) and hydrazine hydrate (1 mL, 85%) in ethanol (30 mL) was refluxed for 2 hours, and upon cooling, the product precipitated was filtered and recrystallized to give **11** (0.73 g, 97%; m.p. 232-233°C (ethanol); ir: 3427, 3325 (NH_2), 1610 (C=N), 1535 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 8.81 (br s, 1H, NH), 7.90-7.40 (m, 10H, 2Ph), 4.40 (s, 2H, NH_2).

Anal. Calcd. for $C_{19}H_{13}N_7S$: C, 61.44; H, 3.53; N, 26.40. Found: C, 61.30; H, 3.40; N, 26.30.

N-(4-Amino-8,9-diphenylpyridazino[*4′,3′:4,5*]thieno[*3,2-d*]-1,2,3-triazine)-phthalimide (12)

A mixture of **11** (0.38 g, 1 mmol) and phthalic anhydride (0.15 g, 1 mmol) in absolute ethanol (30 mL) was refluxed for 3 hours. The pale yellow crystals separated upon cooling and were filtered and dried to give **12** (0.4 g, 77%), m.p. 299-300°C (ethanol); ir: 3310 (NH), 1720 (C=O), 1640 (C=N), 1520 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 7.6-7.2 (m, 14H, aromatic phenyl protons), 3.0 (br, s, 1H, NH).

Anal. Calcd. for $C_{27}H_{15}N_7O_2S$: C, 64.66; H, 3.01; N, 19.55. Found: C, 64.60; H, 2.90; N, 19.40.

N-(8,9-Diphenylpyridazino[*4′,3:4,5*]thieno[*3,2-d*]-1,2,3-triazin-4-yl)-N′-[phenylthio(carbamoyl)]hydrazine (13)

A solution of **11** (0.38 g, 1 mmol) and phenyl isothiocyanate (0.14 g, 1 mmol) in absolute ethanol (30 mL) was refluxed for 1.5 hours. Upon cooling the product precipitated was filtered and dried to give **13** (0.34 g, 65%), m.p. 270–271°C (ethanol); ir: 3460, 3300, 3100 (NH groups), 1620

(C=N), 1550 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 13.10 (br s, 1H, NH), 11.35 (br s, 1H, NH), 9.5 (br s, 1H, NH), 7.8-7.5 (m, 15H, 3Ph).

Anal. Calcd. for $C_{26}H_{18}N_8S_2$: C, 61.64; H, 3.58; N, 22.12. Found: C, 61.50; H, 3.50; N, 22.00.

4-(*p*-Nitrobenzaldehydehydrazone)-8,9-diphenylpyridazino [*4′,3:4,5*]thieno-[*3,2-d*]-1,2,3-triazine (14)

A mixture of **11** (0.38 g, 1 mmol) and *p*-nitrobenzaldehyde (0.16 g, 1 mmol) in ethanol (30 mL) was refluxed for 2 hours. Pale yellow crystals deposited during the refluxing time. The separated product was filtered and dried to give **14** (0.31 g, 61%); m.p. 275–276°C; ir: 3500, 3300 (NH), 1640 (C=N), 1550 (C=O) 1510, 1475 (NO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 8.95 (s, 1H, −CH=N−), 8.2–8.0 (m, 5H, aromatic protons and NH), 7.8–7.2 (d, 10H, 2Ph).

Anal. Calcd. for $C_{26}H_{16}N_8O_2S$: C, 61.89; H, 3.20; N, 22.21. Found: C, 61.80; H, 3.00; N, 22.10.

8,9-Diphenyl-4-(3,5-dimethyl-1-pyrazolyl)pyridazino[*4′,3′:4,5*] thieno[*3,2-d*]-1,2,3-triazine (15)

To a solution of **11** (0.38 g, 1 mmol) in absolute ethanol (30 mL) was added acetylacetone (0.1 g, 1 mmol). The reaction mixture was refluxed for 6 hours. Upon cooling, the precipitated product was filtered and dried to give **15** (0.38 g, 85%); m.p. 245–246°C (ethanol); ir: 1620 (C=N), 1530 (C=C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): 7.65 (s, 1H, 4′-H), 7.6-7.2 (m, 10H, 2Ph), 2.95 (s, 3H, CH_3), 2.45 (s, 3H, CH_3).

Anal. Calcd. for $C_{24}H_{17}N_7S$: C, 66.19; H, 3.93; N, 22.51. Found: C, 66.00; H, 3.80; N, 22.40.

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