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Reactivity of Pyridazin-3(*2H*) Thiones

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ABSTRACT: *4,6-Disubstituted pyridazin-3(2H)-thiones* **3a–f** *were prepared by thiation of 4,6-disubstituted pyridazin-3(2H)-one* **1a–f** *either with thiourea or phosphorus pentasulphide. The reactivity of* **3a-f** *towards nucleophilic and electrophilic species under different conditions was studied successively. The structure of the products was confirmed by NMR and mass spectral data. Mechanisms for their formation are also proposed.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:334–341, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10157

INTRODUCTION

Divers biological and pharmacological activities have been reported for diazines and related compounds, for instance, many pyridazines are in preclinical use [1,2]. While many diazinethiones exhibit antiprotozoal, antiviral, bactericidal, and fungicidal properties, probably by virtue of the toxopheric —N=C—S goup [3,4]. Usually, pyridazin-3(*2H*)-ones are prepared from β-oxoalkanoic acid derivatives and hydrazines [5]. Pyridazin-3(*2H*)-one rings are of chemical and biological interest for a long time. Nannini et al. [6] have established that the pyridazin-3(*2H*)-one ring displays analgesic and antiinflammatory activities beside antihypertensive activity [7–9].

RESULTS AND DISCUSSION

In a previous study, we reported the synthesis of 4,6-disubstituted pyridazin-3(*2H*)-one **1a–f** [10–11]. Using a new method for their thiation we now obtained the corresponding thiones **3a–f**.

Reaction of **1a–f** with phosphorus oxychloride gave 3-chloropyridazines **2a–f**, which by treatment with thiourea in refluxing ethanol gave **3a–f** in low yield. These compounds were also obtained in a similar yield from the reaction of **1a–f** with phosphorus pentasulphide in boiling xylene (Scheme 1).

The pyridazin-3(*2H*)thiones **3d–f** react with ethyl chloroacetate in the presence of anhydrous K_2CO_3 in refluxing acetone to yield the corresponding thioethers **4d–f** in moderate to good (56–78%) yields (Scheme 2). The ^{1}H NMR spectrum of **4d–f** exhibits two singlets at δ 4.26 and 3.97 of methylene protons CH_2Ar and SCH_2 respectively. These spectral data are consistent with the data described by Yang et al. [12].

3b reacted with acrylonitrile in refluxing ethanol in the presence of alkaline medium (10%) to give thioethers **5b** in 65% yield. The ^{1}H NMR spectrum of **5b** exhibits three singlets of methylene protons at δ 4.12, 3.4, and 2.24 for CH_2Ar, SCH_2, and $—CH_2C{\equiv}N$ respectively. These spectral data are consistent with the data of the related compound [13]. The reaction of **3d–f** with dimethylsulphate was also examined

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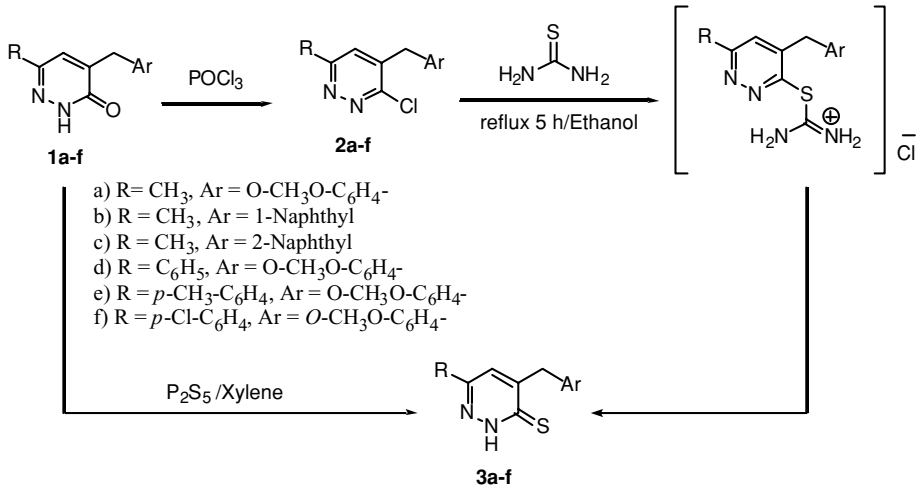
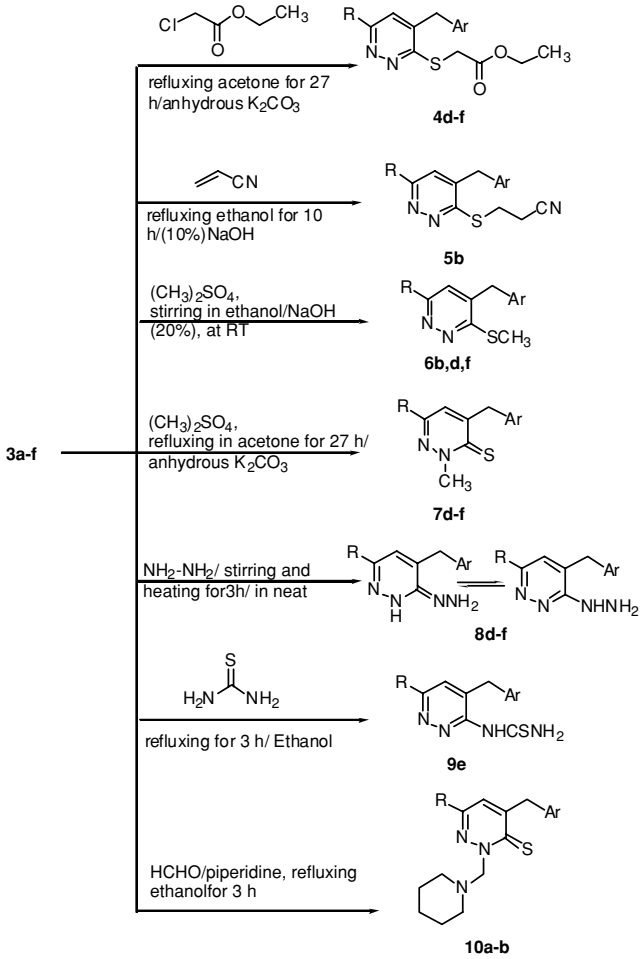


SCHEME 1

under different condition. When the reaction took place in ethanol at room temperature in presence of NaOH (20%), *S*-alkylation occured to yield thioethers **6b,d,f** in moderate (25–60%) yield. But when the reaction was heated under reflux in acetone in presence of K_2CO_3, *N*-alkylation occured to yield *N*-methylpyridazin-3(*2H*) thiones **7d–f** in good (60–83%) yields.



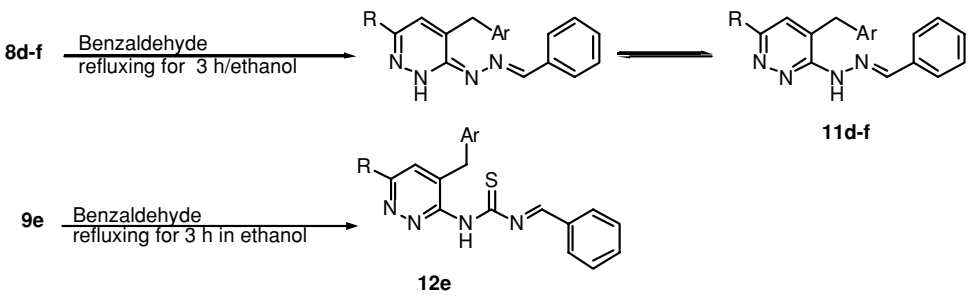
SCHEME 2

Hydrazones formed by condensation with thioketones are not only important for identification purposes and occasionally as protecting groups but the classical application is in the synthesis of heterocyclic compounds [14–16]. Treatment of **3d–f** with hydrazine in neat at boiling point afforded hydrazones **8d–f** in good (60–70%) yield.

In this sequence, the urea derivatives have recently found applications [16]. **9e** was prepared in moderate (60%) yield by the reaction of **3e** with thiourea in refluxing ethanol. The reaction of **3a–b** with a mixture of formaldehyde and piperidine, that is the condition of Mannich reaction, yielded **10a–b** for biological importance. The ^{1}H NMR spectrum of **10a–b** exhibits two doublet signals at δ 3.6 and 5.2 of the same coupling constant ($J = 15$ Hz) for N—CH_2—. Condensation of **8d–f** and **9e** with benzaldehyde in refluxing ethanol gave hydrazones **11d–f** and phenylmethylenethiourea **12e** in good (40–65%) yield (Scheme 3). The synthesis of these meet biological interest of thiacarbamide derivatives [17]. All unknown structural products were completely characterized by spectroscopic (IR, NMR, mass spectrometry, and analytical measurements).

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. Products were characterized by comparison of their physical data with those of known samples. IR spectra were recorded on a Perkin-Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were recorded in



SCHEME 3

$CDCl_3$ as solvent on a Bruker AC-200 spectrometer with reference to the deuterium signal $CDCl_3$ and the data obtained using an IBM NR-200. TLC accomplished the purity determination of the substrates and reaction monitoring on silica gel SILG/UV 254 plates. MS were recorded at 70 eV on a Varian MAT-313 spectrometer. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) at Microanalytical Center of Cairo and Ain Shams Universities.

4-Aryl-6-alkyl-3-chloropyridazines **2a–f**

General Procedure A. A suspension of **1a–f** (0.01 mol) in phosphorus oxychloride (5 ml) was heated under reflux for 3 h and then poured into crushed ice containing sodium hydroxide 10%. The solid product formed in each case was washed with water, collected by filtration, and recrystallized from benzene to give the title compounds.

4-(2-Methoxybenzyl)-6-methyl-3-chloropyridazine **2a**. Colourless crystals 1.37 g, 55% yield, mp 110–112°C; IR (KBr pellet): 1544.5 (s) and 1457.9 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.2–7.71(m, 4H, Ar-H), 6.91 (s, 1H, 5-H) 4.2 (s, 2H, Ar-C$\underline{H}_2$), 3.89 (s, 3H, $-OCH_3$), 2.67 (s, 3H, 6-CH_3) ppm; Anal. calcd for $C_{13}H_{13}ClN_2O$ (248.71).; C, 62.78; H, 5.26; Cl, 14.2545; N, 11.26; found: C, 63.00; H, 5.30; N, 11.10; Cl, 14.40; HRMS calcd. for $C_{13}H_{13}ClN_2O$ 248.71; found 248.07.

6-Methyl-4-(1-naphthylmethyl)-3-chloropyridazine **2b**. Colourless crystals 1.35 g, 50% yield, mp 130–132°C; IR (KBr pellet): 1550 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.3–7.69 (m, 7H, Ar-H), 6.85 (s, 1H, 5-H) 4.31 (s, 2H, Ar-C$\underline{H}_2$), 2.68 (s, 3H, 6-CH_3) ppm; Anal. calcd. for $C_{16}H_{13}$ Cl N_2 (268.74); C, 71.50; H, 4.87; Cl, 13.19; N, 10.42; found: C, 71.50; H, 4.90; N, 10.30; Cl, 13.30; HRMS calcd. for $C_{16}H_{13}ClN_2$ 268.74; found 268.07.

6-Methyl-4-(2-naphthylmethyl)-3-chloropyridazine **2c**. Colourless crystals 1.4 g, 52% yield, mp 125–126°C; IR (KBr pellet): 1570 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.1–7.69 (m, 7H, Ar-H), 6.83 (s, 1H, 5-H) 4.25 (s, 2H, Ar-C$\underline{H}_2$), 2.68 (s, 3H, 6-CH_3) ppm; Anal. calcd. for $C_{16}H_{13}ClN_2$ (268.74); C, 71.50; H, 4.87; Cl, 13.19; N, 10.42; found: C, 71.50; H, 4.90; N, 10.30; Cl, 13.30; HRMS calcd. for $C_{16}H_{13}ClN_2$ 268.74; found 268.07.

6-Phenyl-4-(2-methoxybenzyl)-3-chloropyridazine **2d**. Colourless crystal 1.63 g, 52% yield, mp 145–147°C; IR (KBr pellet): 1670 (v) for (C=O), 1570 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.1–7.9 (m, 9H, Ar-H), 6.83 (s, 1H, 5-H) 4.25 (s, 2H, Ar-C$\underline{H}_2$), 3.88 (s, 3H, $-OCH_3$) ppm; Anal. calcd. for $C_{18}H_{15}ClN_2O$ (310.78); C, 69.56; H, 4.86; N, 9.01; Cl: 11.40; found: C, 69.00; H, 4.70; N, 8.80; Cl, 11.00; HRMS calcd. for $C_{18}H_{15}ClN_2O$ 310.78; found 310.08.

6-(4-Methylphenyl)-4-(2-methoxybenzyl)-3-chloropyridazine **2e**. Colourless crystals 1.80 g, 55% yield, mp 145–147°C; IR (KBr pellet): 1670 (v) for (C=O), 1570 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.23–7.82 (m, 8H, Ar-H), 6.69 (bs, 1H, pyridazine-$\underline{H}_4$) 4.22 (s, 2H, Ar-C$\underline{H}_2$), 3.88 (s, 3H, $-OCH_3$) 2.31 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{19}H_{17}ClN_2O$ (324.81); C: 70.25; H: 5.27; N: 8.62; Cl: 10.91; found: C, 69.70; H, 5.00; N, 9.10; Cl, 10.20; HRMS calcd. for $C_{19}H_{17}ClN_2O$ 324.81; found 324.10.

6-(4-Chlorophenyl)-4-(2-methoxybenzyl)-3-chloropyridazine **2f**. Colourless crystals 2.60 g, 75% yield, mp 160–162°C; IR (KBr pellet): 1670 (v) for (C=O), 1570 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.3–7.77 (m, 8H, Ar-H), 6.74 (bs, 1H, 5-H) 4.23 (s, 2H, Ar-C$\underline{H}_2$), 3.87 (s, 3H, OCH_3) 2.31 ppm; Anal. calcd. for $C_{18}H_{14}Cl_2N_2O$ (345.23); C: 62.62; H: 4.08; N: 8.11; Cl: 20.53; found: C, 62.00; H, 4.00; N, 8.60; Cl, 19.98; HRMS calcd. for $C_{18}H_{14}Cl_2N_2O$ 345.23; found 344.05.

6-Aryl-4-(arylmethyl) Pyridazin-3(2H)-Thiones **3a–f**

General Procedure B. To a solution of **2a–f** (0.015 mol) in ethanol (50 mL) and thiourea (0.012 mol) was added. The reaction mixture was heated under reflux for 3 h and then cooled. The solid product, formed in each case, was collected by filtration and recrystallized from benzene for **3a–c** and from ethanol for **3d–f**. Compounds **3a–f** were shown by direct comparison (mp and mixed mp) and also GC/MS to be identical in all aspects with the authentic products obtained by the action of phosphorus pentasulphide in boiling xylene upon 4,6-disubstitutedpyridazin-3(*2H*)-ones **1a–f.**

4-(2-Methoxybenzyl)-6-methyl-pyridazine-3(2H)-thione **3a**. Colourless crystals 2.98 g, 80% yield, mp 206–208°C; IR (KBr pellet): 3000–3150, (br, —NH), 1120–1130 (v) for (C=S), 15580 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.43 (s, 1H, NH), 7.2–7.71 (m, 4H, Ar-H), 6.92 (s, 1H, 5-H) 4.15 (s, 2H, Ar-C$\underline{H_2}$), 3.83 (s, 3H, —OCH_3), 2.64 (s, 3H, 6-CH_3) ppm; Anal. calcd. for $C_{13}H_{14}N_2OS$ (246.32); C: 63.38; H: 5.72; N: 11.3724; S: 13.0151; found: C, 63.00; H, 5.50; N, 11.30; S, 12.80; HRMS calcd. for $C_{13}H_{14}N_2OS$ 246.32; found 246.08.

6-Methyl-4-(1-naphthylmethyl)-pyridazine-3(2H)-thione **3b**. Colourless crystals 3.2 g, 80% yield, mp 222–223°C; IR (KBr pellet): 3005–3140, (br, —NH), 1122–1135 (v) for (C=S), 1560 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.44 (s, 1H, NH), 7.3–7.7 (m, 7H, Ar-H), 6.85 (s, 1H, 5-H) 4.31 (s, 2H, Ar-C$\underline{H_2}$), 2.68 (s, 3H, 6-CH_3) ppm; Anal. calcd. for $C_{16}H_{14}N_2S$ (266.36); C: 72.14; H: 5.29; N: 10.51; S: 12.03; found: C, 72.20; H, 5.10; N, 10.70; S, 12.30; HRMS calcd. for $C_{16}H_{14}N_2S$ 266.36; found 266.09.

6-Methyl-4-(2-naphthylmethyl)-pyridazines-3(2H)-thione **3c**. Colourless crystals 3.4 g, 85% yield, mp 175–176°C; IR (KBr pellet): 3005–3140, (br, —NH), 1122–1135 (v) for (C=S), 1560 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.44 (s, 1H, NH), 7.19–7.71 (m, 7H, Ar-H), 6.85 (s, 1H, 5-H) 4.22 (s, 2H, Ar-C$\underline{H_2}$), 2.68 (s, 3H, 6-CH_3) ppm; Anal. calcd. for $C_{16}H_{14}N_2S$ (266.36); C: 72.14; H: 5.29; N: 10.517; S: 12.03; found: C, 72.20; H, 5.10; N, 10.70; S, 12.30; HRMS calcd. for $C_{16}H_{14}N_2S$ 266.36; found 266.09.

4-(2-Methoxybenzyl)-6-phenylpyridazine-3(2H)-thione **3d**. Colourless crystals 4.10 g, 88% yield, mp 190–191°C; IR (KBr pellet): 3010–3150, (br, —NH), 1124–1135 (v) for (C=S), 1565 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.45 (s, 1H, NH), 7.1–7.82 (m, 9H, Ar-H), 6.81 (s, 1H, 5-H) 4.21 (s, 2H, Ar-C$\underline{H_2}$), 3.85 (s, 3H, —OCH_3) ppm; Anal. calcd. for $C_{18}H_{16}N_2OS$ (308.40); C: 70.10; H: 5.22; N: 9.08; S: 10.39; found: C, 69.50; H, 4.80; N, 8.20; S, 9.80; HRMS calcd. for $C_{18}H_{16}N_2OS$ 308.40; found 308.10.

6-(4-Methylphenyl)-4-(2-methoxybenzyl)-pyridazine-3(2H)-thione **3e**. Colourless crystals 4.15 g, in 85% yield, mp 185–186°C; IR (KBr pellet): 3000–3150, (br, —NH), 1125–1135 (v) for (C=S), 1560 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.41 (s, 1H, NH), 7.23–7.82 (m, 8H, Ar-H), 6.67 (s, 1H, 5-H) 4.21 (s, 2H, Ar-C$\underline{H_2}$), 3.81 (s, 3H, —OCH_3) 2.32 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{19}H_{18}N_2OS$ (322.42); C: 70.77; H: 5.626; N: 8.68; S: 9.94; found: C, 71.40; H, 5.10; N, 9.20; S, 10.10; HRMS calcd. for $C_{19}H_{18}N_2OS$ 322.42; found 322.11.

6-(4-Chlorophenyl)-4-(2-methoxybenzyl)-pyridazine-3(2H)-thione **3f**. Colourless crystals 4.65 g, 90% yield, mp 225–226°C; IR (KBr pellet): 3000–3150, (br, —NH), 1125–1135 (v) for (C=S), 1560 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.41 (s, 1H, NH), 7.3–7.77 (m, 8H, Ar-H), 6.74 (bs, 1H, 5-H) 4.23 (s, 2H, Ar-C$\underline{H_2}$), 3.87 (s, 3H, —OCH_3) ppm; Anal. calcd. for $C_{18}H_{15}ClN_2OS$ (342.84); C: 63.06; H: 4.40; Cl: 10.34; N: 8.17; S: 9.35; found: C, 63.30; H, 4.30; N, 8.40; S, 8.90; HRMS calcd. for $C_{18}H_{15}ClN_2OS$ 342.84; found 342.06.

Ethyl{[4,6-diarylpyridazin-3-yl]thio}acetates **4d–f**

General Procedure C. To a solution of **3d–f** (0.01 mol) in acetone (50 mL), ethyl chloroacetate (0.01 mol) was added in the presence of anhydrous K_2CO_3 (3 mol%). The reaction mixture was heated under reflux for 27 h and then cooled. The solid product formed in each case was collected by filtration and recrystallized from ethanol to yield the title compounds.

Ethyl{[4-(2-methoxybenzyl)-6-phenylpyridazin-3-yl]thio}acetate **4d**. Colourless crystals 3.10 g, 78% yield, mp 115–116°C; IR (KBr pellet): 1735–1760 (v) for (C=O), 670 (v) for (C—S), 1630 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.95–7.66 (m, 9H, Ar-H), 6.78 (s, 1H, 5-H) 4.28 (s, 2H, Ar-C$\underline{H_2}$), 4.12 (q, 2H, $J = 6.4$ Hz, C$\underline{H_2}$$CH_3$), 3.98 (s, 2H, —S—$\underline{CH_2}$—CO), 3.87 (s, 3H, —$OCH_3$), 1.22 (t, 3H, $J =$ 7.3 Hz, $CH_2C\underline{H_3}$) ppm; Anal. calcd. for $C_{22}H_{22}N_2O_3S$ (394.49); C: 66.98; H: 5.62; N: 7.10114; S: 8.12; Found: C, 67.30; H, 5.27; N, 7.50; S, 8.60; HRMS calcd. for $C_{18}H_{16}N_2OS$ 394.49; found 394.136.

Ethyl{[6-(4-methylphenyl)-4-(2-methoxybenzyl)-pyridazin-3-yl]thio}acetate **4e**. Colourless crystals 2.30 g, 56% yield, mp 106–108°C; IR (KBr pellet): 1730–1762 (v) for (C=O), 670 (v) for (C—S), 1630 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.51–8.08 (m, 8H, Ar-H), 6.77 (s, 1H, 5-H) 4.22 (s, 2H, Ar-C$\underline{H}_2$), 4.12 (q, 2H, J = 6.4 Hz, C$\underline{H}_2$CH$_3$), 3.97 (s, 2H, —S—$\underline{CH}_2$—CO), 3.87 (s, 3H, —OCH$_3$), 1.63 (s, 3H, CH$_3$), 1.23 (t, 3H, J = 7.3 Hz, CH$_2$C$\underline{H}_3$) ppm; Anal. calcd. for $C_{23}H_{24}N_2O_3S$ (408.51); C: 67.62; H: 5.92; N: 6.85; S: 7.84; found: C, 68.00; H, 5.60; N, 6.40; S, 7.30; HRMS calcd. for $C_{23}H_{24}N_2O_3S$ 408.51; found 408.15.

Ethyl{[6-(4-chlorophenyl)-4-(2-methoxybenzyl)-pyridazin-3-yl]thio}acetate **4f**. Colourless crystals 3.40 g, 79% yield, mp 110–112°C; IR (KBr pellet): 1736–1762 (v) for (C=O), 675 (v) for (C—S), 1620 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.33–8.14 (m, 8H, Ar-H), 6.78 (s, 1H, 5-H) 4.26 (s, 2H, Ar-C$\underline{H}_2$), 4.12 (q, 2H, J = 6.4 Hz, C$\underline{H}_2$CH$_3$), 3.98 (s, 2H, —S—C$\underline{H}_2$—CO), 3.82 (s, 3H, —OCH$_3$), 1.18 (t, 3H, J = 7.3 Hz, CH$_2$C$\underline{H}_3$) ppm; Anal. calcd. for $C_{22}H_{21}ClN_2O_3S$ (428.93); C: 61.60; H: 4.93; Cl: 8.26; N: 6.53; S: 7.47; found: C, 61.60; H, 4.94; N, 6.50; S, 7.45, Cl, 8.40; HRMS calcd. for $C_{22}H_{21}ClN_2O_3S$ 428.93; found 428.09.

3-{[6-Methyl-4-(1-naphthylmethyl)pyridazin-3-yl]-thio}propanenitrile **5b**. To a solution of **3b** (0.01 mol) in ethanol (20 mL), acrylonitrile (0.012 mol) was added in the presence of 10% sodium hydroxide. The reaction mixture was heated under reflux for 10 h, then cooled. The solid product was collected by filtration and recrystallized from benzene to give the title compounds 2.10 g, 65% yield, mp 193–195°C; IR (KBr pellet): 2260 (v) for (C≡N), 670 (v) for (C—S), 1620 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.55–8.56 (m, 7H, Ar-H), 6.78 (s, 1H, 5-H) 4.12 (s, 2H, Ar-C$\underline{H}_2$), 3.4 (t, 2H, J = 6.4 Hz, —S—$\underline{CH}_2$—CH$_2$—), 2.68 (s, 3H, 6-CH$_3$), 2.23 (t, 2H, J = 6.4 Hz, —S—CH$_2$—C$\underline{H}_2$—CN) ppm; Anal. calcd. for $C_{19}H_{17}N_3S$ (319.42); C: 71.44; H: 5.36; N: 13.15; S: 10.03; found: C, 72.10; H, 5.40; N, 13.30; S, 10.10; HRMS calcd. for $C_{19}H_{17}N_3S$ 319.42; found 319.11.

4,6-Diaryl-3-(methylthio)pyridazines **6b,d,f**

General Procedure D. To a solution of **3b,d,f** (0.01 mol) in ethanol, dimethyl sulphate (0.01 mol) was added in the presence of NaOH 20%. The reaction mixture was warmed for 20 min with continued stirring and cooled to room temperature. The solid product was collected by filtration and recrystallized from benzene for **6b** and from ethanol for **6d,f** to afford the title compounds.

6-Methyl-4-(1-naphthylmethyl)-3-(methylthio)-pyridazine **6b**. Colourless crystals 1.70 g, 60% yield, mp 101–102°C; IR (KBr pellet): 1620 (s) for (C=N), 675 (v) for (C—S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.55–8.66 (m, 7H, Ar-H), 6.73 (s, 1H, 5-H) 4.26 (s, 2H, Ar-C$\underline{H}_2$), 2.68 (s, 3H, 6-CH$_3$), 2.63 (s, 3H, —S—$\underline{CH}_3$) ppm; Anal. calcd. for $C_{17}H_{16}N_2S$ (280.38); C: 72.82; H: 5.75; N: 9.99; S: 11.43; found: C, 72.81; H, 5.60; N, 9.80; S, 11.80; HRMS calcd. for $C_{17}H_{16}N_2S$ 280.38; found 280.10.

4-(2-Methoxybenzyl)-3-(methylthio)-6-phenyl-pyridazine **6d**. Colourless crystals 1.63 g, 50% yield, mp 135–136°C; IR (KBr pellet): 1630 (s) for (C=N), 670 (v) for (C—S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.55–8.66 (m, 9H, Ar-H), 6.73 (s, 1H, 5-H), 4.22 (s, 2H, —C$\underline{H}_2$), 3.87 (s, 3H, —OCH$_3$), 2.63 (s, 3H, —S—C$\underline{H}_3$) ppm; Anal. calcd. for $C_{19}H_{18}N_2OS$ (322.42); C: 70.77; H: 5.62; N: 8.68; S: 9.94; found: C, 71.20; H, 6.06; N, 8.60; S, 9.00; HRMS calcd. for $C_{19}H_{18}N_2OS$ 322.42; found 322.11.

6-(4-Chlorophenyl)-4-(2-methoxybenzyl)-3-(methylthio)pyridazine **6f**. Colourless crystals 0.90 g, 25% yield, mp 150–152°C; IR (KBr pellet): 1736–1762 (v) for (C=O), 675 (v) for (C—S), 1620 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.98–7.56 (m, 8H, Ar-H), 6.78 (s, 1H, 5-H), 4.26 (s, 2H, Ar-C$\underline{H}_2$), 3.87 (s, 3H, —OCH$_3$), 2.63 (s, 3H, —S—C$\underline{H}_3$) ppm; Anal. calcd. for $C_{19}H_{17}ClN_2OS$ (356.87); C: 63.94; H: 4.80; N: 7.84; S: 8.98; found; C, 63.42; H, 4.77; N, 7.54; S, 8.95; HRMS calcd. for $C_{19}H_{17}ClN_2OS$ 356.87; found 356.07.

4,6-Diaryl-2-methylpyridazine-3(2H) Thiones **7d–f**

General Procedure E. To a solution of **3d–f** (0.01 mol) in acetone, dimethyl sulphate (0.01 mol) was added in the presence of anhydrous K_2CO_3 (0.03 mol). The reaction mixture was heated under reflux for 27 h and then cooled to room temperature. The solid product was collected by filtration and recrystallized from ethanol to afford the title compounds.

4-(2-Methoxybenzyl)-2-methyl-6-phenylpyridazine-3(2H)-thione **7d**. Colourless crystals 2.27 g, 70% yield, mp 129–130°C; IR (KBr pellet): 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.66–8.65 (m, 9H, Ar-H), 6.77 (s, 1H, 5-H), 4.26 (s, 2H, —C$\underline{H}_2$), 3.88 (s, 3H, —OCH$_3$), 3.33 (s, 3H, —N—$\underline{CH}_3$) ppm; Anal. calcd.

for $C_{19}H_{18}N_2OS$ (322.42); C: 70.77; H: 5.62; N: 8.68; S: 9.94; found: C, 71.20; H, 6.06; N, 8.60; S, 9.00; HRMS calcd. for $C_{19}H_{18}N_2OS$ 322.42; found 322.11.

4-(2-Methoxybenzyl)-6-(4-methylphenyl)-2-methylpyridazine-3(2H)-thione **7e**. Colourless crystals 2.80 g, 83% yield, mp 127–129°C; IR (KBr pellet): 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26–8.16 (m, 8H, Ar-H), 6.76 (s, 1H, 5-H), 4.22 (s, 2H, $-C\underline{H}_2$), 3.88 (s, 3H, $-OCH_3$), 3.32 (s, 3H, $-N-C\underline{H}_3$), 2,63 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{20}H_{20}N_2OS$ (336.45); C: 71.39; H: 5.99; N: 8.32; S: 9.52; found: C, 70.83; H, 6.28; N, 8.09; S, 9.30; HRMS calcd. for $C_{20}H_{20}N_2OS$ 336.45; found 336.13.

6-(4-Chlorophenyl)-4-(2-methoxybenzyl)-2-methylpyridazine-3(2H)-thione **7f**. Colourless crystals 2.15 g, 60% yield, mp 150–152°C; IR (KBr pellet): 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.66–8.65 (m, 8H, Ar-H), 6.78 (s, 1H, 5-H), 4.27 (s, 2H, $-C\underline{H}_2$), 3.87 (s, 3H, $-OCH_3$), 3.38 (s, 3H, $-N-C\underline{H}_3$) ppm. Anal. Calcd. for $C_{19}H_{17}ClN_2OS$ (356.87); C: 63.94; H: 4.80; N: 7.84; S: 8.98; found; C, 63.42; H, 4.77; N, 7.54; S, 8.95; HRMS calcd. for $C_{19}H_{17}ClN_2OS$ 356.87; found 356.07.

(3E)-4,6-Diarylpyridazin-3(2H)-one Hydrazones **8d–f**

General Procedure F. A mixture of 4,6-diarylpyridazin-3(*2H*)-thiones **3d–f** (0.01 mol) and hydrazine hydrate (0.01 mol) was heated for 3–5 h and then allowed to cool at room temperature. The solid product was collected by filtration and recrystallized from benzene to give the title compounds.

(3E)-4-(-2-Methoxybenzyl)-6-phenylpyridazin-3(2H)-one Hydrazone **8d**. Colourless crystals 1.85 g, 60% yield, mp 174–175°C; IR (KBr pellet): 3100–3150 (br) for (NH), 1630 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.78 (s, 1H, NH), 8.32 (s, 2H, NH), 7.15–7.90 (m, 9H, Ar-H), 6.73 (s, 1H, 5-H), 4.23 (s, 2H, $-C\underline{H}_2$), 3.88 (s, 3H, $-OCH_3$) ppm; Anal. calcd. for $C_{18}H_{18}N_4O$ (306.36); C: 70.56; H: 5.9219; N: 18.28; found: C, 70.95; H, 5.40; N, 18.72; HRMS calcd. for $C_{18}H_{18}N_4O$ (306.36); found 306.14.

(3E)-4-(2-Methoxybenzyl)-6-(4-methylphenyl)-pyridazin-3(2H)-one Hydrazone **8e**. Colourless crystals 2.25 g, 70% yield, mp 165–166°C; IR (KBr pellet): 3100–3250 (br) for (NH), 1630 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.67 (s, 1H, NH), 8.30 (s, 2H, NH), 7.14–7.90 (m, 8H, Ar-H), 6.90 (s, 1H, 5-H), 4.22 (s, 2H, $-C\underline{H}_2$), 3.81 (s, 3H, $-OCH_3$), 2.41 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{19}H_{20}N_4O$ (320.39); C: 71.22; H: 6.29; N: 17.48; found: C, 69.96; H, 6.31; N, 17.33; HRMS calcd. for $C_{19}H_{20}N_4O$ 320.39; found 320.1.

(3E)-6-(4-Chlorophenyl)-4-(-2-Methoxybenzyl)-pyridazin-3(2H)-one Hydrazone **8f**. Colourless crystals 2.4 g, 70% yield, mp 146–148°C; IR (KBr pellet): 3100–3350 (br) for (NH), 1635 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.60 (s, 1H, NH), 8.37 (s, 2H, NH), 6.96–7.65 (m, 8H, Ar-H), 6.77 (s, 1H, 5-H), 4.27 (s, 2H, $-C\underline{H}_2$), 3.87 (s, 3H, $-OCH_3$) ppm; Anal. calcd. for $C_{18}H_{17}ClN_4O$ (340.81); C: 63.43; H: 5.027; N: 16.43; found; C, 63.30; H, 5.10; N, 16.02; S, 8.40; HRMS calcd. for $C_{18}H_{17}ClN_4O$ 340.81; found 340.10.

N[4-(2-Methoxybenzyl)-6-(4-methylphenyl)-pyridazin-3-yl]thiourea **9e**

To a solution of **3e** (0.01) in ethanol (50 ml), thiourea (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and then cooled. The solid product was collected by filtration and recrystallized from benzene to give 2.2 g, 60% yield, mp 130–132 °C; IR (KBr pellet): 3100–3250 (br) for (NH), 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.55 (s, 1H, NH), 8.36 (s, 2H, NH), 7.16–7.92 (m, 8H, Ar-H), 6.76 (s, 1H, 5-H), 4.22 (s, 2H, $-C\underline{H}_2$), 3.88 (s, 3H, $-OCH_3$), 2,63 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{20}H_{20}N_4OS$ (364.46); C: 65.91; H: 5.53; N: 15.37; S: 8.79; found: C, 66.20; H, 6.03; N, 14.90; S, 8.80; HRMS calcd. for $C_{20}H_{20}N_4OS$ 364.46; found 364.13.

4-(2-Methoxybenzyl)-6-methyl-2-(piperidin-1-ylmethyl)pyridazine-3(2H)-thiones **10a**

To a suspension of **3a,b** (0.01 mol) in ethanol and mixture of formaldehyde (30 ml, 0.015 mol), piperidine (0.01 mol) was added dropwise. The reaction mixture was heated under reflux for 3 h and then cooled, and the solvent evaporated. The solid product was collected by filtration and recrystallized from ethanol for **10a** to give 2.42 g, 70% yield, mp 162–164°C; IR (KBr pellet): 1625 (s) for (C=N), 1267–1275 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.90–7.13 (m, 4H, Ar-H), 6.78 (s, 1H, 5-H), 4.98 (d, 1H, J = 15.2 Hz, N–C<u>H</u>2), 4.24 (s, 2H, $-C\underline{H}_2$), 3.87 (s, 3H, $-OCH_3$), 3.77 (d, 1H, J = 15.2 Hz, N–C$\underline{H}_2$), 3.15–3.47 (m, 6H, pip), 2.68 (s, 3H, 6-CH_3), 1.42–1.47 (m, 4H, pip-) ppm; Anal. calcd. for $C_{19}H_{25}N_3OS$ (343.49); C: 66.43; H: 7.33; N: 12.23; S: 9.33; found; C, 63.30; H,

5.10; N, 16.02; S, 8.40; HRMS calcd. for $C_{19}H_{25}N_3OS$ 343.48; found 343.17.

4-(1-Naphtylmethyl)-6-methyl-2-(piperidin-1-ylmethyl)pyridazine-3(2H)-thiones **10b**

Following the procedure of **10a** the solid product was collected by filtration and recrystallized from benzene to give 2.55 g, 70% yield, mp 196–198°C; IR (KBr pellet): 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.66–8.65 (m, 7H, Ar-H), 6.77 (s, 1H, 5-H), 5.29 (d, 1H, J = 15.2 Hz, N—C$\underline{H}_2$), 4.26 (s, 2H, —C$\underline{H}_2$), 3.77 (d, 1H, J = 15.2 Hz, N—C$\underline{H}_2$), 3.17–3.48 (m, 6H, pip), 2.68 (s, 3H, 6-CH_3), 1.45–1.48 (m, 4H, pip-) ppm; Anal. calcd. for $C_{22}H_{25}N_3S$ (363.52); C: 72.68; H: 6.93; N: 11.55; S: 8.81; found; C, 72.40; H, 6.60; N, 11.20; S, 8.70; HRMS calcd. for $C_{22}H_{25}N_3S$ 363.52; found 363.17.

N^1-[(1E)-Phenylmethylene]-N^2-[(3E)-4-(2-methoxybenzyl)-6-arylpyridazin-3(2H)-ylidene]hydrazones **11d–f**

General Procedure G. To a solution of **8d–f** (0.01 mol) in 50 ml ethanol, benzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and then cooled. The solid product was collected by filtration and recrystallized from benzene to give the title compound.

N^1-[(1E)-Phenylmethylene]-N^2-[(3E)-4-(2-methoxybenzyl)-6-phenylpyridazin-3(2H)-ylidene]hydrazone **11d**. Colourless crystals 1.6 g, 40% yield, mp 188–189°C; IR (KBr pellet): 3100–3150 (br) for (NH), 1630 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.78 (s, 1H, NH), 8.27 (s, 1H, —N=C$\underline{H}$), 7.15–8.12 (m, 14H, Ar-H), 6.74 (s, 1H, 5-H), 4.22 (s, 2H, —C$\underline{H}_2$), 3.88 (s, 3H, —OCH_3) ppm; Anal. calcd. for $C_{25}H_{22}N_4O$ (394.47); C: 76.1202; H: 5.62125; N: 14.2027; found; C, 76.65; H, 5.40; N, 13.82; HRMS calcd. for $C_{25}H_{22}N_4O$ 394.47; found 394.17.

N^1-[(3E)-4-(2-Methoxybenzyl)-6-(4-methylphenyl)-pyridazin-3(2H)-ylidene]-N^2-[(1E)-phenylmethylene]-hydrazones **11e**. Colourless crystals 2.05 g, 50% yield, mp 202–203°C; IR (KBr pellet): 3100–3150 (br) for (NH), 1634 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.80 (s, 1H, NH), 8.25 (s, 1H, —N=C$\underline{H}$), 7.26–8.19 (m, 9H, Ar-H), 7.82 (d, 2H, J = 8.6 Hz, $C_6\underline{H}_4CH_3$), 7.32 (d, 2H, J = 8.6 Hz, $C_6\underline{H}_4CH_3$), 6.73 (s, 1H, 5-H), 4.26 (s, 2H, —C$\underline{H}_2$), 3.88 (s, 3H, —OCH_3), 2.43 (s, 3H, —CH_3) ppm; Anal. calcd. for $C_{26}H_{24}N_4O$ (408.50); C: 76.44; H: 5.92; N: 13.71; found: C, 76.37; H, 6.05; N, 13.50; HRMS calcd. for $C_{25}H_{24}N_4O$ 408.50; found 408.19.

N^2-[(3E)-6-(4-Chlorophenyl)-4-(2-methoxybenzyl)-pyridazin-3(2H)-ylidene]-N^1-[(1E)-phenylmethylene]-hydrazones **11f**. Colourless crystals 2.15 g, 60% yield, mp 219–220°C; IR (KBr pellet): 3100–3250 (br) for (NH), 1635 (s) for (C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 8.80 (s, 1H, NH), 8.25 (s, 1H, —N=C$\underline{H}$), 7.26–8.19 (m, 9H, Ar-H), 7.93 (d, 2H, J = 8.6 Hz, $C_6\underline{H}_4Cl$), 7.41 (d, 2H, J = 8.6 Hz, $C_6\underline{H}_4Cl$), 6.73 (s, 1H, 5-H), 4.26 (s, 2H, —C$\underline{H}_2$), 3.88 (s, 3H, —OCH_3) ppm; Anal. calcd. for $C_{26}H_{24}ClN_4O$ (428.92); C: 70.00; H: 4.93; N: 13.06; Cl: 8.26; found; C, 70.46; H, 5.06; N, 12.53; Cl, 8.60; HRMS calcd. for $C_{25}H_{21}N_4OCl$ 428.92; found 428.14.

N-[4-(2-Methoxybenzyl)-6-(4-methylphenyl)-pyridazin-3-yl]-N′-[(1E)-phenylmethylene]-thiourea **12e**

To a solution of *N*[4-(2-methoxybenzyl)-6-(4-methylphenyl)pyridazin-3-yl]thiourea **9e** (0.01 mol) in (50 ml) ethanol, benzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h and then cooled to precipitate the products. By following the general procedure (G), the solid product was collected by filtration and recrystallized from benzene to afford **12e**. (2.75 g, in 75% yield), mp 123–125°C; IR (KBr pellet): 1630 (s) for (C=N), 1267–1274 (v) for (C=S) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26–8.16 (m, 8H, Ar-H), 6.76 (s, 1H, 5-H), 4.22 (s, 2H, —C$\underline{H}_2$), 3.88 (s, 3H, —OCH_3), 3.32 (s, 3H, —N—C$\underline{H}_3$), 2.63 (s, 3H, CH_3) ppm; Anal. calcd. for $C_{27}H_{24}N_4OS$ (452.57); C: 71.65; H: 5.34; N: 12.37; S: 7.08; found: C, 71.59; H, 5.80; N, 12.18; S, 6.27; HRMS calcd. for $C_{19}H_{20}N_4O$ 452.57; found 452.16.

REFERENCES

[1] Tisler, M.; Stanovnik, B. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W. (Eds.); Pergamon Press: Oxford, 1984; Vol. 3, pp. 1–56.
[2] Kleemann, A.; Engel, J. Pharmazeutische Wirkstoffe, Synthesen, Patente, 2nd ed.; Anwendungen, Thieme Verlag: Stuttgart, 1982.
[3] (a) Dhal, P. N.; Achary, T. E.; Nayak, A. Indian J Chem 1975, 1–8; (b) Smith, R. J Indian Chem Soc 1975, 52, 734–735.
[4] Mallick, S. K.; Martin, A. R.; Lingard, R. G. J Med Chem 1971, 14, 528–532.
[5] Coates, W. J. In Pyridazines and Their Benzo Derivatives, Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. (Eds.); R. C. Storr, Ed, Pergamon: Oxford, 1996; Vol. 6, pp. 1–91.
[6] Nannini, G.; Biasoli, G.; Perrone, E.; Forgione, A.; Buttinoni, A.; Ferrari, M. Eur J Med Chem Chim Ther 1979, 14, 53.
[7] Curran, M. V. J Med Chem 1974, 17, 273.

[8] Mohareb, R. M.; Manhi, F. M. Heteroat Chem 2000, 11, 403.
[9] Mohareb, R. M.; El-Omran, F. A.; Jonathan Z. Ho. Heteroat Chem 2001, 12, 168–174.
[10] Kandile, N. G.; El-Sawi, E. A.; Selim, V. R.; Ismail, M. F. Acta Chem Hung 1988, 125, 631.
[11] Hamad, A.-S. S.; Hashem, A. I. Molecules 2000, 5, 895–907.
[12] Liu, Z.; Yang, G.; Qin, X. J Chem Technol Biotechnol 2001, 76, 1154–1158.
[13] (a) Goldoni, F.; Antolini, L.; Pourtois, G.; Schenning, A. P. H. J. Jaussen, R. A. J.; Lazzaroui, R.; Bredas, J.-L.; Mejer, E. W. Eur J Inorg Chem 2001, 821–828; (b) Raslan, M. A.; Sayed, S. M.; Khalil, M. A.; Farag, A. M. Heteroat Chem 2000, 11, 94–100.
[14] Ragnarsson, U. Chem Soc Rev 2001, 30, 205–213.
[15] (a) Hydrazine and its Derivatives in Kirk-Othmer Ecyclopedia of Chemical Technology; Wiley, New York, 4th edn., 1995, Vol.13. 2 L. A. Carpino, J. Am. Chem. Soc., 1957, 79, 98–100; (b) Encyclopedia of reagents for organic synthesis, ed. L. A. Paquette, Wiley, Chichester, 1995.
[16] Huddleston, P. R.; Coutts, I. G. C. In Comprehensive Organic Functional Group Transformations, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; (Eds.); Pergamon/Elsevier: Oxford, 1995; Vol. 2, pp. 371–383.
[17] Hassaneen, H. M.; Atta, S. M. S.; Fawzy, N. M.; Hegazi, A. G.; Abdalla, F. A.; Abd El Rahman, A. H. Arch Pharm Pharm Med Chem 2002, 6, 251–261.