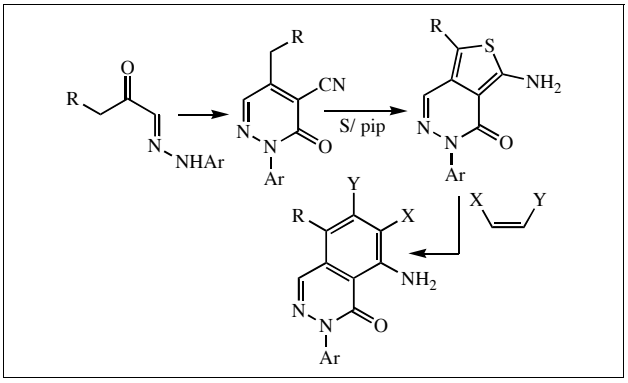
Microwaves in Organic Synthesis: Synthesis of Pyridazinones, Phthalazinones and Pyridopyridazinones from 2-Oxo-Arylhydrazones Under Microwave Irradiation.

Balkis AL-Saleh[a*], Noha M. Hilmy[b], Morsy Ahmed EL-Apasery[a] and Mohamed H. Elnagdi[b].

[a]Chemistry Department; Faculty of Science; University of Kuwait; P.O. Box 5969; Safat; 13060-Kuwait.
[b]Department of Chemistry; Faculty of Science; Cairo University, Giza; A. R. Egypt
E-mail: shelmy@access.com.eg

Received February 21, 2006



The phenylhydrazones **1a-d** condensed with ethyl cyanoacetate to yield pyridazinones **2a-d** that reacted with sulphur in presence of piperidine to yield the aminothienopyridazineones **3a,b** that reacted with electron poor olefins and acetylenes to yield phthalazines **10-12**. The condensed aminothiophenes **3a,b** reacted with dimethylformamide dimethylacetal to yield amidines **13a,b**. Compounds **2a,b** condensed with dimethylformamide dimethylacetal to yield the *trans* enamines **16a,b** that cyclized readily into the pyridopyridazinones **17a,b** on treatment with ammonium acetate in presence of acetic acid. Compounds **2a-d** reacted also with benzylidenemalononitrile to yield the phthalazinones **21a-d**. The reactions were conducted both by microwave heating and conventional heating. Better yields in much shorter reaction times were achieved by microwave heating.

J. Heterocyclic Chem., **43**, 1575 (2006).

In conjunction to previous recent interest in adopting microwaves as energy source for synthesis of polyfunctional heteroaromatics [1-5], we report here efficient synthesis of title compounds utilizing **1a-d** as starting materials and microwaves as energy source. The title compounds are biologically interesting molecules and their chemistry and pharmacology is receiving considerable recent interest [6-8]. Moreover utilizing microwaves as environmentally eco-friendly energy sources is being also now explored [9-12].

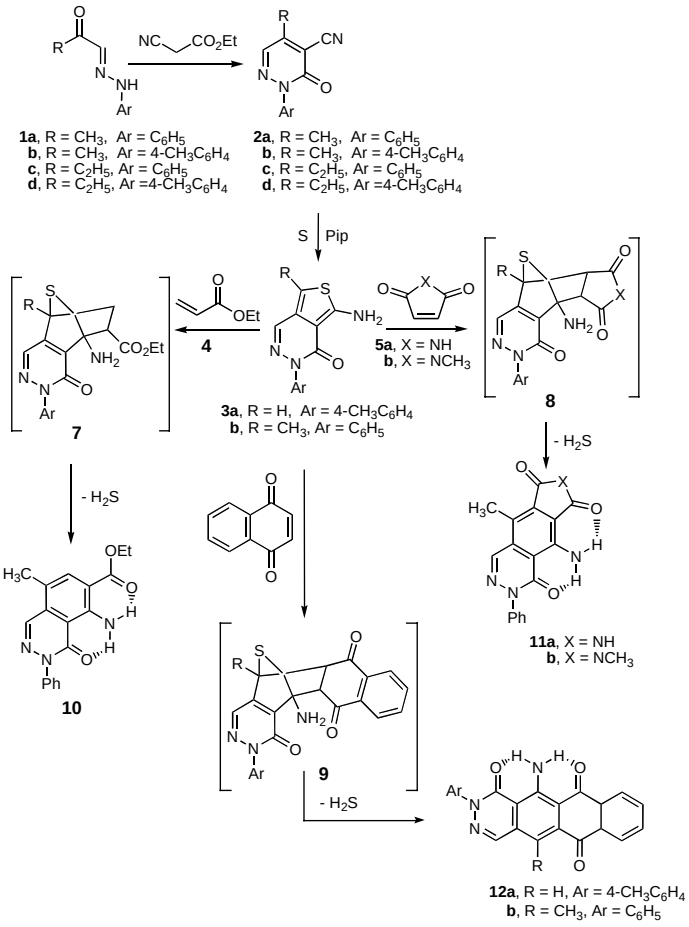
The starting **1a-d** condensed with ethyl cyanoacetate on heating in focused microwave at 170 ºC for 4 minutes in presence of ammonium acetate to yield pyridazinones **2a-d** in 52 to 62% yields. The same compounds could also be obtained on heating **1a-d** with ethyl cyanoacetate in acetic acid and in presence of ammonium acetate for ten hours, in 50 to 55% yields.

The pyridazinones **2a-d** readily reacted with sulphur in presence of piperidine on heating in a focused microwave oven for 5 minutes in dioxane as reaction medium to yield aminothienopyridazines **3a,b** in 74 and 76% yields. Again thienopyridazines **3a,b** were obtained in 69 and 72% yields on refluxing **3a,b** with sulphur in DMF solution in presence of piperidine for 4 hours. The synthesis of **2** and **3** is an extension to our previously well-established synthesis 3-carboxylic ester derivatives of **2** and **3** [13-15].

Compound **3b** reacted readily with ethyl acrylate **4**, maleimide **5a** and *N*-methylmaleimide **5b** in a mixture of acetic acid and dioxane in focused microwave at 210 ºC for 15 minutes and compounds **3a,b** reacted with naphthoquinone **6** in ethanol at 100 ºC for 15 minutes in focused microwave to yield products of addition and hydrogen sulphide elimination. These products were also obtained on refluxing **3a,b** with **4-6** in the same solvents for 8 hours.

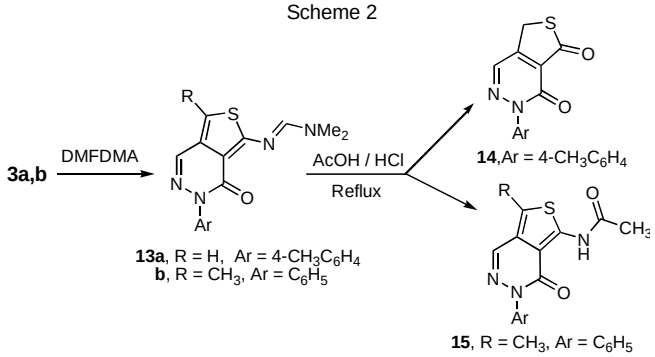
The condensation products of **3** with **4-6** were assumed to be formed *via* intermediary of 4+2 cycloadducts **7-9** which readily loses hydrogen sulphide to yield products **10-12** respectively. In no case C-1 alkylation products of thiepines similar to those claimed earlier to be formed on reacting thienocoumarin with dimethyl acetylene-dicarboxylate and ethyl propiolate were formed [16-20] (Scheme 1).

Scheme 1



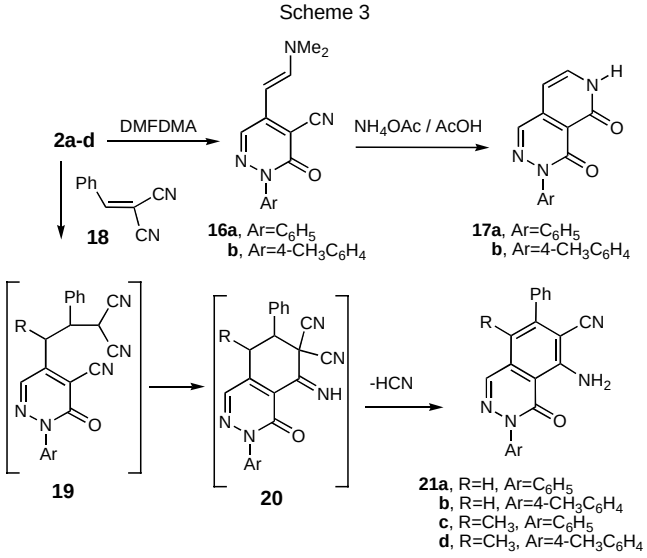
Reaction of compounds **3a,b** with dimethylformamide dimethylacetal (DMFDMA) in focused microwave at 200 ºC for 15 minutes in the presence of a few drops of dimethylformamide afforded condensation products **13a,b**; no trace of C-1 alkylation products were observed. Compounds **3a** upon reflux in AcOH/c.HC1 mixture (3:1 by volume), afforded derivative **14** whose structure based on the ^{1}H NMR and ^{13}C NMR spectra, that reveal the presence of methylene proton at δ_H = *ca* 4.41 and δ_C = *ca* 32.7 ppm respectively, while compound **3b** when treated with the same reagent and under the same reaction condition, formed compound **15** (Scheme 2).

Scheme 2



Compounds **2a,b** reacted with dimethylfrormamide dimethylacetal on heating in focused microwave oven at 180 ºC for 5 minutes or on reflux in DMF for 6 hours. The condensation products were assigned the *trans* structure **16a,b** based on the ^{1}H NMR which showed olefinic doublets at ~ δ_H 5.1 and 8.3 (J = 12.8 Hz). Cis-olefinic protons should show lower J values (8-10 Hz). Compounds **16a,b** were readily converted into the pyrido[3,4-*d*]pyridazine-4,5-diones **17a,b** on treatment with ammonium acetate and acetic acid in focused microwave oven at 150 ºC for 5 minutes or on reflux in the same mixture for 3 hours. Compounds **2a-d** reacted with benzylidenemalononitrile **18** in pyridine in focused microwave oven at 175 ºC for 5 minutes to yield **21a-d** or on reflux in pyridine for 5 hours. This is a further extension to our established phthalazine synthesis [21,22], which is believed to proceed *via* intermediary of **19** and **20** (Scheme 3).

Scheme 3



In conclusion microwaves heating is an efficient method for obtaining polyfunctionally substituted title compounds in equal or much higher yields than those obtained by conventional heating in much shorter time.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DPX 400, 400MHz super-conducting NMR spectrometer in deuteriochloroform or dimethylsulfoxide-d_6 as solvent and TMS as internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on a VG Autospec-Q (high resolution, high performance, tri-sector GC/MS/MS).

Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. Focused microwave experiments were conducted in a CEM Explorer microwave. Compounds **1a** was prepared following published procedure [23].

General Procedure for the Preparation of Compounds **1a-d**.

The mixture of (3.5 g) of potassium hydroxide in (100 ml) of water, (6.5 g) of ethyl acetoacetate was allowed to stir at room temperature for 24 hours. The solution of potassium acetate was cooled to 0 ºC and (4.5 ml) of concentrated hydrochloric acid in (15 ml) of ice-water was added slowly with stirring, then gradually treated under stirring with a solution of aryldiazonium chloride (prepared from the corresponding aromatic amine (0.01 mol) and the appropriate quantities of both hydrochloric acid and sodium nitrite. The mixture is made basic by addition of (8.2 g) of sodium acetate dissolved in (30 ml) of water. The solid product, so formed, was collected by filtration and crystallized from toluene.

1-(Phenyl-hydrazono)-propan-2-one (**1a**).

Compound **1a** was obtained as yellowish green crystals (1.44 g, 89%), mp. 152 ºC (Lit.,150 ºC), ir (KBr) ν_{max} = 3249 (NH), 1649 (CO) cm^{-1}; ms: m/z = 162 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.31 (s, 3H, CH_3), 6.93 (t, 1H, *J* = 7.4 Hz, phenyl-H), 7.17 (t, 2H, *J* = 7.7 Hz, phenyl-H), 7.24 (s,1H, imine-H), 7.29 (d, 2H, *J* = 8 Hz, phenyl-H), 11.33 (s, 1H, NH, D_2O exchangeable).

Anal. Calcd. For $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27. Found C, 66.63; H, 6.07; N, 17.27.

1-(*p*-Tolyl-hydrazono)-propan-2-one (**1b**).

Compound **1b** was obtained as light green crystals (1.06 g, 60%), mp. 128-130 ºC, ir (KBr) ν_{max} = 3246 (NH), 1652 (CO) cm^{-1}; ms: m/z = 176 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.24 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 7.07 (d, 2H, *J* = 8.6 Hz, p-tolyl-H), 7.11 (d, 2H, *J* = 8.6 Hz, p-tolyl-H), 7.21 (s, 1H, imine-H), 11.25 (s, 1H, NH, D_2O exchangeable), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 197.0 (CO), 141.9, 135.0, 131.5, 130.8, 114.4, 25.1 (CH_3), 21.3 (CH_3).

Anal. Calcd. For $C_{10}H_{12}N_2O$ (176.22): C, 68.16; H, 6.86; N, 15.90. Found C, 68.26; H, 6.81; N, 15.91.

1-(Phenyl-hydrazono)-butan-2-one (**1c**).

Compound **1c** was obtained as red crystals (1.08 g, 61%), mp. 150-152 ºC, ir (KBr) ν_{max} = 3251 (NH), 1656 (CO) cm^{-1}; ms: m/z = 176 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 1.01 (s, 3H, *J* = 7.6 Hz, CH_3), 2.77 (q, 2H, *J* = 7.2 Hz, CH_2), 6.92 (t, 1H, *J* = 7.4 Hz, phenyl-H), 7.17 (t, 2H, *J* = 7.7 Hz, phenyl-H), 7.24 (s,1H, imine-H), 7.29 (d, 2H, *J* = 8 Hz, phenyl-H), 11.27 (s, 1H, NH, D_2O exchangeable), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 200.2 (CO), 144.3, 134.9, 130.4, 122.5, 114.4, 30.1 (CH_2), 9.5 (CH_3).

Anal. Calcd. For $C_{10}H_{12}N_2O$ (176.22): C, 68.16; H, 6.86; N, 15.90. Found C, 68.50; H, 6.89; N, 15.92.

1-(*p*-Tolyl-hydrazono)-butan-2-one (**1d**).

Compound **1d** was obtained as wine red crystals (1.26 g, 66%), mp. 134-136 ºC, ir (KBr) ν_{max} = 3236 (NH), 1651 (CO) cm^{-1}; ms: m/z = 190 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 1.01 (t, 3H, *J* = 7.4 Hz, CH_3), 2.24 (s, 3H, CH_3), 2.75 (q, 2H, *J* = 7.4 Hz, CH_2), 7.05 (d, 2H, *J* = 8.4 Hz, p-tolyl-H), 7.10 (d, 2H, *J* = 8.4 Hz, p-tolyl-H), 7.21 (s, 1H, imine-H), 11.21 (s, 1H, NH, D_2O exchangeable), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 200.0 (CO), 142.0, 134.3, 131.4, 130.4, 114.4, 30.0 (CH_2), 21.3 (CH_3), 9.5 (CH_3).

Anal. Calcd. For $C_{11}H_{14}N_2O$ (190.24): C, 69.45; H, 7.42; N, 14.73. Found C, 69.56; H, 7.34; N, 14.73.

General Procedure for the Preparation of Compounds **2a-d**.

A mixture of **1a-d** (0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol), ammonium acetate (2 g) and acetic acid (0.6 mol) was irradiated in focused microwave at 150 Watt, 170 ºC for 4 minutes, then left to cool and triturated with ethanol. The solid product, so formed, was collected by filtration and crystallized from toluene.

5-Methyl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**2a**).

Compound **2a** was obtained as gray crystals (1.21 g, 57%), mp. 158.160 ºC, ir (KBr) ν_{max} = 2233 (CN), 1659 (CO) cm^{-1}; ms: m/z = 211 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.60 (s, 3H, CH_3), 7.53-7.55 (m, 5H, phenyl-H), 8.24 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 157.0 (CO), 152.6, 141.5, 139.9, 129.8, 129.7, 126.8, 114.4, 114.0, 19.1 (CH_3).

Anal. Calcd. For $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found C, 68.37; H, 4.38; N, 19.42.

5-Methyl-3-oxo-2-p-tolyl-2,3-dihydropyridazine-4-carbonitrile (**2b**).

Compound **2b** was obtained as gray crystals (1.18 g, 52%), mp. 209 ºC, ir (KBr) ν_{max} = 2229 (CN), 1658 (CO) cm^{-1}; ms: m/z = 225 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.37 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.31 (d, 2H, *J* = 8.3 Hz, p-tolyl-H), 7.41 (d, 2H, *J* = 8.3 Hz, p-tolyl-H), 8.22 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 157.0 (CO), 152.4, 139.7, 139.3, 139.1, 130.2, 126.3, 114.5, 113.9, 21.7 (CH_3), 19.0 (CH_3).

Anal. Calcd. For $C_{13}H_{11}N_3O$ (225.25): C, 69.32; H, 4.92; N, 18.66. Found C, 69.18; H, 4.90; N, 18.34.

5-Ethyl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**2c**).

Compound **2c** was obtained as light green crystals (1.26 g, 56%), mp. 100 ºC, ir (KBr) ν_{max} = 2234 (CN), 1657 (CO) cm^{-1}; ms: m/z = 225 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 1.26 (t, 3H, *J* = 7.6 Hz, CH_3), 2.74 (q, 2H, *J* = 7.6 Hz, CH_2), 7.47-7.57 (m, 5H, phenyl-H), 8.32 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 157.2 (CO), 157.0, 141.6, 138.9, 129.8, 129.7, 126.6, 114.2, 113.2, 26.4 (CH_2), 13.8 (CH_3).

Anal. Calcd. For $C_{13}H_{11}N_3O$ (225.25): C, 69.32; H, 4.92; N, 18.66. Found C, 69.56; H, 5.05; N, 18.77.

5-Ethyl-3-oxo-2-*p*-tolyl-2,3-dihydropyridazine-4-carbonitrile (**2d**).

Compound **2d** was obtained as light green crystals (1.49 g, 62%), mp. 91 ºC, ir (KBr) ν_{max} = 2231 (CN), 1659 (CO) cm^{-1}; ms: m/z = 239 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 1.26 (t, 3H, *J* = 7.6 Hz, CH_3), 2.37 (s, 3H, CH_3), 2.73 (q, 2H, *J* = 7.6 Hz, CH_2), 7.31 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 7.42 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 8.30 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 157.2 (CO), 156.8, 139.3, 139.2, 138.8, 130.2, 126.3, 114.2, 113.1, 26.3 (CH_2), 21.7 (CH_3), 13.7 (CH_3).

Anal. Calcd. For $C_{14}H_{13}N_3O$ (239.27): C, 70.28; H, 5.48; N, 17.56. Found C, 70.21; H, 5.52; N, 17.51.

General Procedure for the Preparation of Compounds **3a**,**b**.

To a suspension of compounds **2a** or **2c** (0.01 mol) in dioxane (2 ml), elemental sulphur (0.32 g, 0.01 mol) and few

drops of piperidine were added. The reaction mixture was irradiated in focused microwave at 150 Watt, 200 ºC for 5 minutes and then poured onto water. The solid product, so formed, was collected by filtration and crystallized from ethanol.

7-Amino-2-*p*-tolyl-2*H*-thieno[3,4-*d*]pyridazin-1-one (**3a**).

Compound **3a** was obtained as green crystals (1.91 g, 74%), mp. 135 ºC, ir (KBr) ν_{max} = 3410 and 3299 (NH_2), 1648 (CO) cm^{-1}; ms: m/z = 257 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.33 (s, 3H, CH_3), 6.76 (s, 1H, H-5), 7.21 (d, 2H, *J* = 7.7 Hz, p-tolyl-H), 7.36 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.48 (s, 2H, NH_2, D_2O exchangeable). 7.93 (s, 1H, pyridazine-H), ^{13}C nmr (deuteriochloroform): δ = 168.1 (CO), 164.2, 144.5, 141.7, 135.5, 134.9, 134.4, 131.0, 109.8, 107.8, 26.4 (CH_3).

Anal. Calcd. For $C_{13}H_{11}N_3OS$ (257.31): C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found C, 60.79; H, 4.30; N, 16.30; S, 11.87.

7-Amino-5-methyl-2-phenyl-2*H*-thieno[3,4-*d*]pyridazin-1-one (**3b**).

Compound **3b** was obtained as brown crystals (1.96 g, 76%), mp. 209 ºC, ir (KBr) ν_{max} = 3422 and 3285 (NH_2), 1627 (CO) cm^{-1}; ms: m/z = 257 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.44 (s, 3H, CH_3), 7.27 (t, 1H, *J* = 7.6 Hz, phenyl-H), 7.33 (s, 2H, NH_2, D_2O exchangeable). 7.40 (t, 2H, *J* = 8.3 Hz, phenyl-H), 7.48 (d, 2H, *J* = 8.6 Hz, phenyl-H), 8.01 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 160.8 (CO), 159.4, 142.3, 135.4, 129.8, 128.9, 127.3, 126.6, 116.7, 104.2, 12.4 (CH_3).

Anal. Calcd. For $C_{13}H_{11}N_3OS$ (257.31): C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found C, 60.73; H, 4.34; N, 16.33; S, 12.57.

General Procedure for the Preparation of Compounds **10** and **11a,b**.

A mixture each of maleimide, *N*-methylmaleimide and ethyl acrylate (0.01 mol) and **3b** (2.57 g, 0.01 mol) in a mixture of acetic acid (2 ml) and dioxane (2 ml) was irradiated in focused microwave at 250 Watt, 210 ºC for 15 minutes. The reaction mixture was evaporated then washed with ethanol. The solid products, so formed, were collected by filtration and crystallized from dioxane.

Ethyl 5-Amino-8-methyl-4-oxo-3-phenyl-3,4-dihydrophthalazine-6-carboxylate (**10**).

Compound **10** was obtained as wine red crystals (2.23 g, 69%), mp. 185 ºC, ir (KBr) ν_{max} = 3419 and 3288 (NH_2), 1687, 1638 (CO) cm^{-1}; ms: m/z = 323 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 1.32 (t, 3H, *J* = 7.0 Hz, CH_3), 2.57 (s, 3H, CH_3), 4.27 (q, 2H, *J* = 7.0 Hz, CH_2), 7.41-7.57 (m, 5H, phenyl-H), 8.01 (s, 1H, H-7), 8.14 (br s, 1H, NH, D_2O exchangeable), 8.46 (s, 1H, pyridazine-H), 9.17 (br s, 1H, NH, D_2O exchangeable). ^{13}C nmr (dimethylsulfoxide-d_6): δ = 167.5, 161.7 (CO), 152.1, 142.5, 138.4, 137.3, 133.7, 129.8, 128.8, 127.3, 119.1, 113.0, 110.3, 67.3 (CH_2), 18.0 (CH_3), 15.1 (CH_3).

Anal. Calcd. For $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found C, 66.48; H, 5.29; N, 13.01.

9-Amino-5-methyl-2-phenyl-2*H*-pyrrolo[3,4-*g*]phthalazine-1,6,8-trione (**11a**).

Compound **11a** was obtained as yellow crystals (2.02 g, 63%), mp. > 300 ºC, ir (KBr) ν_{max} = 3426 and 3289 (NH_2), 3180 (NH), 1751, 1708, 1651 (CO) cm^{-1}; ms: m/z = 320 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.72 (s, 3H, CH_3), 7.11 (br s, 1H, NH, D_2O exchangeable). 7.43 (t, 1H, *J* = 7.0 Hz, phenyl-H), 7.51 (t, 2H, *J* = 7.4 Hz, phenyl-H), 7.58 (d, 2H, *J* = 7.8 Hz, phenyl-H), 8.56 (br s, 1H, NH, D_2O exchangeable). 8.67 (s, 1H, pyridazine-H), 11.38 (br s, 1H, NH, D_2O exchangeable). ^{13}C nmr (dimethylsulfoxide-d_6): δ = 170.8, 170.0, 161.3 (CO), 146.6, 142.1, 137.3, 136.3, 134.6, 129.7, 129.1, 127.1, 120.6, 117.1, 111.3, 12.1 (CH_3).

Anal. Calcd. For $C_{17}H_{12}N_4O_3$ (320.30): C, 63.75; H, 3.78; N, 17.49. Found C, 63.77; H, 3.92; N, 17.69.

9-Amino-5,7-dimethyl-2-phenyl-2*H*-pyrrolo[3,4-*g*]phthalazine-1,6,8-trione (**11b**).

Compound **11b** was obtained as yellow crystals (1.98 g, 59%), mp. 273 ºC, ir (KBr) ν_{max} = 3444 and 3307 (NH_2), 1747, 1696, 1650 (CO) cm^{-1}; ms: m/z = 334 (M^+); ^1H nmr (deuteriochloroform): δ = 2.82 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 6.99 (br s, 1H, NH, D_2O exchangeable). 7.44 (t, 1H, *J* = 7.0 Hz, phenyl-H), 7.52 (t, 2H, *J* = 7.4 Hz, phenyl-H), 7.61 (d, 2H, *J* = 8.0 Hz, phenyl-H), 8.48 (s, 1H, pyridazine-H), 8.77 (br s, 1H, NH, D_2O exchangeable). ^{13}C nmr (deuteriochloroform): δ = 169.6, 169.0, 161.5 (CO), 146.9, 141.5, 136.3, 136.1, 133.7, 129.5, 129.0, 126.3, 120.8, 117.6, 110.5, 24.3 (CH_3), 12.2 (CH_3).

Anal. Calcd. For $C_{18}H_{14}N_4O_3$ (334.33): C, 64.66; H, 4.22; N, 16.76. Found C, 64.23; H, 4.33; N, 16.77.

Reaction of Compounds **3a,b** with 1,4-Naphthoquinone.

A mixture of each of **3a,b** (10 mmol) with 1,4-naphthoquinone (1.58 g, 0.01 mol) in ethanol (4 ml) was irradiated in focused microwave at 125 Watt, 100 ºC for 15 minutes. The solvent was removed and the residue cooled to deposit a solid, which was crystallized from dimethylformamide.

12-Amino-2-*p*-tolyl-2*H*-2,3-diazanaphthacene-1,6,11-trione (**12a**).

Compound **12a** was obtained as red crystals (2.13 g, 82%), mp. 264 ºC, ir (KBr) ν_{max} = 3349 and 3235 (NH_2), 1658 (br) (CO), 1573 (CO) cm^{-1}; ms: m/z = 381 (M^+); ^1H nmr (deuteriochloroform): δ = 2.45 (s, 3H, CH_3), 7.34 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.49 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 7.73-7.81 (m, 2H, arom-H), 7.84 (t, 1H, *J* = 7.4 Hz, arom-H), 8.28(s, 1H, pyridazine-H), 8.30 (d, 1H, *J* = 7.6 Hz, arom-H), 8.38 (d, 1H, *J* = 7.6 Hz, arom-H), 9.98 (br s, 1H, NH, D_2O exchangeable), 10.21 (br s, 1H, NH, D_2O exchangeable). ^{13}C nmr (dimethylsulfoxide-d_6): δ = 184.6, 183.3, 161.5 (CO), 154.9, 139.4, 139.1, 139.0, 138.8, 137.0, 135.8, 135.4, 135.2, 134.0, 133.1, 130.1, 127.7, 127.6, 126.1, 116.6, 111.5, 21.8 (CH_3).

Anal. Calcd. For $C_{23}H_{15}N_3O_3$ (381.38): C, 72.43; H, 3.96; N, 11.02. Found C, 71.97; H, 4.07; N, 11.27.

12-Amino-5-methyl-2-phenyl-2*H*-2,3-diazanaphthacene-1,6,11-trione (**12b**).

Compound **12b** was obtained as wine red crystals (3.24 g, 85%), mp. > 300 ºC, ir (KBr) ν_{max} = 3351 and 3240 (NH_2), 1650 (br) (CO), 1593 (CO) cm^{-1}; ms: m/z = 381 (M^+); ^1H nmr (deuteriochloroform): δ = 2.66 (s, 3H, CH_3), 7.45 (t, 1H, *J* = 7.2 Hz, arom-H), 7.54 (t, 2H, *J* = 7.6 Hz, arom-H), 7.63 (d, 2H, *J* = 7.9 Hz, arom-H), 7.74 –7.82 (m,2H, arom-H), 8.17 (d, 1H, *J* = 7.4 Hz, arom-H), 8.27 (d, 1H, *J* = 7.4 Hz, arom-H), 8.64 (s,1H, pyridazine-H), 10.10 (s, 1H, NH, D_2O exchangeable), 10.42 (s, 1H, NH, D_2O exchangeable).

Anal. Calcd. For $C_{23}H_{15}N_3O_3$ (381.38): C, 72.43; H, 3.96; N, 11.02. Found C, 72.15; H, 4.08; N, 11.31

General Procedure for the Preparation of Compounds **13a**,**b**.

A solution of each of **3a**,**b** (10 mmol) and DMFDMA (1.19 g, 10 mmol) in the presence of a few drops of dimethylformamide was irradiated in focused microwave at 250 Watt, 200 ºC for 15 minutes. The solid products obtained were crystallized from ethanol.

N,*N*-Dimethyl-*N*'-(4-oxo-3-*p*-tolyl-3,4-dihydrothieno[3,4-*d*]pyridazin-5-yl) formamidine (**13a**).

Compound **13a** was obtained as brown crystals (2.00 g, 64%), mp. 198-200 ºC, ir (KBr) ν_{max} = 1648 (CO) cm^{-1}; ms: m/z = 312 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.30 (s, 3H, CH_3), 2.98 (s, 3H, N-CH_3), 3.06 (s, 3H, N-CH_3), 7.12 (s,1H, thiophene-H), 7.22 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 7.32(d, 2H, *J* = 8.2 Hz, p-tolyl-H), 7.39 (s,1H, amidine-H), 8.06 (s,1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 167.4 (CO), 158.4, 157.6, 140.5, 136.9, 136.2, 132.6, 130.3, 127.2, 126.5, 112.1, 35.1 (N-CH_3), 21.6 (CH_3).

Anal. Calcd. For $C_{16}H_{16}N_4OS$ (312.39): C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found C, 61.47; H, 5.16; N, 17.69; S, 10.01.

N,*N*-Dimethyl-*N*'-(7-methyl-4-oxo-3-phenyl-3,4-dihydrothieno-[3,4-*d*]pyridazin-5-yl) formamidine (**13b**).

Compound **13b** was obtained as light green crystals (2.23 g, 71%), mp. 165 ºC, ir (KBr) ν_{max} = 1655 (CO) cm^{-1}; ms: m/z = 312 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.57 (s, 3H, CH_3), 2.96 (s, 3H, N-CH_3), 3.04 (s, 3H, N-CH_3), 7.29-7.47 (m, 5H, phenyl-H), 7.99 (s,1H, amidine-H), 8.15 (s,1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 164.0 (CO), 158.1, 157.6, 143.0, 134.9, 129.7, 128.9, 127.5, 127.0, 125.6, 112.4, 35.1 (N-CH_3), 13.0 (CH_3).

Anal. Calcd. For $C_{16}H_{16}N_4OS$ (312.39): C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found C, 61.51; H, 5.25; N, 17.82; S, 10.08.

General Procedure for the Preparation of Compounds **14** and **15**.

A solution of each of **13a**,**b** (0.01 mol) in acetic acid / hydrochloric acid (4 ml, 3:1 by volume) was refluxed for 3 hrs, and then allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from ethanol.

2-*p*-Tolyl-2*H*,5*H*-thieno[3,4-*d*]pyridazine-1,7-dione (**14**).

Compound **13a** was obtained as green crystals (1.60 g, 62%), mp. 196 ºC, ir (KBr) ν_{max} = 1794 and 1692 (CO) cm^{-1}; ms: m/z = 258 (M^+); ^1H nmr (deuteriochloroform): δ = 2.32 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 7.28 (d, 2H, *J* = 7.6 Hz, p-tolyl-H), 7.47 (d, 2H, *J* = 7.6 Hz, p-tolyl-H), 8.15 (s, 1H, pyridazine-H), ^{13}C nmr (deuteriochloroform): δ = 192.2, 155.7 (CO), 139.5, 138.6, 134.6, 131.5, 130.0, 126.1, 125.6, 32.7 (CH_2), 21.8 (CH_3).

Anal. Calcd. For $C_{13}H_{10}N_2O_2S$ (258.30): C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found C, 60.37; H, 4.08; N, 11.52; S, 12.38.

N-(7-Methyl-4-oxo-3-phenyl-3,4-dihydrothieno[3,4-*d*]pyridazin-5-yl)acetamide (**15**).

Compound **13b** was obtained as light green crystals (2.10 g, 70%), mp. 235 ºC, ir (KBr) ν_{max} = 3306 (NH), 1684 and 1637 (CO) cm^{-1}; ms: m/z = 299 (M^+); ^1H nmr (deuteriochloroform): δ = 2.29 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 7.28-7.59 (m, 5H, phenyl-H), 8.07 (s,1H, pyridazine-H), 10.97 (s, 1H, NH, D_2O exchangeable). ^{13}C nmr (deuteriochloroform): δ = 167.6, 159.7 (CO), 142.9, 141.2, 134.7, 129.4, 128.2, 127.8, 126.4, 124.9, 112.1, 23.7 (CH_3), 12.4 (CH_3)

Anal. Calcd. For $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found C, 60.19; H, 4.44; N, 14.18; S, 10.77.

General Procedure for the Preparation of Compounds **16a**,**b**.

A solution of each of **2a**,**b** (10 mmol) and DMFDMA (1.19 g, 10 mmol) was irradiated in a focused microwave at 150 Watt, 180 ºC for 5 minutes. The solid product obtained was crystallized from dioxane.

5-(2-Dimethylamino-vinyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**16a**).

Compound **16a** was obtained as yellowish green crystals (1.92 g, 72%), mp. 225 ºC, ir (KBr) ν_{max} = 2203 (CN), 1616 (CO) cm^{-1}; ms: m/z = 266 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.99 (s, 3H, N-CH_3), 3.24 (s, 3H, N-CH_3), 5.17 (d, 1H, *J* = 12.8 Hz, vinylic-H), 7.36-7.52 (m, 5H, phenyl-H), 8.32 (d, 1H, *J* = 12.8 Hz, vinylic-H), 8.43 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 158.4 (CO), 154.1, 148.8, 142.0, 134.4, 129.5, 128.5, 126.5, 117.2, 92.0, 90.3, 46.1 (N-CH_3), 37.8 (N-CH_3).

Anal. Calcd. For $C_{15}H_{14}N_4O$ (266.30): C, 67.69; H, 5.30; N, 21.04. Found C, 67.58; H, 5.41; N, 20.96.

5-(2-Dimethylamino-vinyl)-3-oxo-2-p-tolyl-2,3-dihydropyridazine-4-carbonitrile (**16b**).

Compound **16b** was obtained as green crystals (2.10 g, 75%), mp. 210 ºC, ir (KBr) ν_{max} = 2209 (CN), 1630 (CO) cm^{-1}; ms: m/z = 280 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.34 (s, 3H, CH_3), 2.97 (s, 3H, N-CH_3), 3.22 (s, 3H, N-CH_3), 5.15 (d, 1H, *J* = 12.8 Hz, vinylic-H), 7.24 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 7.37 (d, 2H, *J* = 8.2 Hz, p-tolyl-H), 8.18 (d, 1H, *J* = 12.8 Hz, vinylic-H), 8.39 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 158.4 (CO), 154.0, 148.7, 139.6, 137.9, 134.2, 129.9, 126.1, 117.2, 92.1, 90.2, 46.1 (N-CH_3), 37.9 (N-CH_3), 21.6 (CH_3).

Anal. Calcd. For $C_{16}H_{16}N_4O$ (280.32): C, 68.55; H, 5.75; N, 19.99. Found C, 68.52; H, 5.87; N, 19.96.

General Procedure for the Preparation of Compounds **17a**,**b**.

A solution of each of **16a,b** (0.01 mol), acetic acid (2 ml) and ammonium acetate (1 g) was irradiated in focused microwave at 150 Watt, 150 ºC for 5 minutes, then allowed to cool to room temperature. The solid product so formed was collected by filtration and crystallized from acetic acid.

3-Phenyl-3*H*,6*H*-pyrido[3,4-*d*]pyridazine-4,5-dione (**17a**).

Compound **17a** was obtained as light green crystals (1.87 g, 89%), mp. 298 ºC, ir (KBr) ν_{max} = 3300 (NH), 1691 (CO) cm^{-1}; ms: m/z = 239 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 6.49 (d, 1H, *J* = 6.4 Hz H-8), 7.39-7.52 (m, 5H, phenyl-H), 7.80 (d, 1H, *J* = 6.4 Hz H-7), 8.28 (s, 1H, pyridazine-H), 12.10 (s, 1H, NH, D_2O exchangeable). ^{13}C nmr (dimethylsulfoxide-d_6): δ = 159.7, 157.2 (CO), 154.7, 142.8, 142.3, 139.0, 137.1, 129.6, 127.2, 107.7, 101.7.

Anal. Calcd. For $C_{13}H_9N_3O_2$ (239.23): C, 65.27; H, 3.79; N, 17.56. Found C, 65.09; H, 3.98; N, 17.64.

3-*p*-Tolyl-3*H*,6*H*-pyrido[3,4-*d*]pyridazine-4,5-dione (**17b**).

Compound **17b** was obtained as light green crystals (1.62 g, 64%), mp. 295 ºC, ir (KBr) ν_{max} = 3290 (NH), 1689 (CO) cm^{-1}; ms: m/z = 253 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.36 (s, 3H, CH_3), 6.48 (d, 1H, *J* = 6.4 Hz H-8), 7.27 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.29 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.79 (d, 1H, *J* = 6.4 Hz H-7), 8.25 (s, 1H, pyridazine-H), 12.00 (s, 1H, NH, D_2O exchangeable). ^{13}C nmr (dimethylsulfoxide-d_6): δ = 159.7, 157.2 (CO), 154.8, 142.7, 140.0, 138.2, 136.9, 130.0, 126.8, 107.7, 101.7, 21.7 (CH_3).

Anal. Calcd. For $C_{14}H_{11}N_3O_2$ (253.26): C, 66.40; H, 4.38; N, 16.59. Found C, 66.30; H, 4.45; N, 16.60.

General Procedure for the Preparation of Compounds **21a-d**.

A solution of each of **2a-d** (10 mmol) in pyridine (3 ml) was treated with benzylidenemalononitrile (1.54 g, 0.01 mol). The reaction mixture was irradiated in a focused microwave at 150 Watt, 175 ºC for 5 minutes, then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from dioxane

5-Amino-4-oxo-3,7-diphenyl-3,4-dihydrophthalazine-6-carbonitrile (**21a**).

Compound **21a** was obtained as gray crystals (2.21 g, 65%), mp. 259-261 ºC, ir (KBr) ν_{max} = 3455 and 3301 (NH_2), 2208 (CN), 1658 (CO) cm^{-1}; ms: m/z = 338 (M^+); ^1H nmr (deuteriochloroform): δ = 6.92 (s, 1H, H-8), 7.28 (br s, 2H, NH_2, D_2O exchangeable), 7.43-7.47 (m, 1H, arom-H), 7.53-7.57 (m, 5H, arom-H), 7.61-7.64 (m, 4H, arom-H), 8.17 (s, 1H, pyridazine-H), ^{13}C nmr (deuteriochloroform): δ = 161.0 (CO), 154.2, 151.5, 141.6, 139.2, 138.1, 134.2, 130.2, 129.6, 129.3, 129.0, 128.9, 126.4, 117.0, 113.8, 110.8, 96.4.

Anal. Calcd. For $C_{21}H_{14}N_4O$ (338.36): C, 74.54; H, 4.17; N, 16.56. Found C, 74.66; H, 4.17; N, 16.59.

5-Amino-4-oxo-7-phenyl-3-*p*-tolyl-3,4-dihydrophthalazine-6-carbonitrile (**21b**).

Compound **21b** was obtained as light green crystals (2.36 g, 67%), mp. 283 ºC, ir (KBr) ν_{max} = 3454 and 3302 (NH_2), 2207 (CN), 1656 (CO) cm^{-1}; ms: m/z = 352 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.38 (s, 3H, CH_3), 7.11 (s, 1H, H-8), 7.31 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.44 (d, 2H, *J* = 8.0 Hz, p-tolyl-H), 7.56-7.64 (m, 7H, arom-H and NH_2), 8.43 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 161.0 (CO), 154.6, 151.2, 139.8, 138.6, 138.4, 134.8, 130.4, 130.2, 130.1, 129.8, 129.5, 127.0, 126.3, 117.5, 114.2, 110.7, 21.7 (CH_3).

Anal. Calcd. For $C_{22}H_{16}N_4O$ (352.39): C, 74.98; H, 4.58; N, 15.90. Found C, 74.54; H, 4.72; N, 16.22.

5Amino-8-methyl-4-oxo-3,7-diphenyl-3,4-dihydrophthalazine-6-carbonitrile (**21c**).

Compound **21c** was obtained as brown crystals (2.15 g, 61%), mp. 260 ºC, ir (KBr) ν_{max} = 3464 and 3322 (NH_2), 2208 (CN), 1647 (CO) cm^{-1}; ms: m/z = 352 (M^+); ^1H nmr (deuteriochloroform): δ = 2.26 (s, 3H, CH_3), 7.28 (br s, 2H, NH_2, D_2O exchangeable), 7.30-7.33 (m, 2H, arom-H), 7.45-7.64 (m, 8H, arom-H), 8.43 (s, 1H, pyridazine-H), ^{13}C nmr (deuteriochloroform): δ = 161.1 (CO), 151.6, 151.0, 141.7, 138.1, 136.8, 132.9, 130.7, 129.9, 129.7, 129.2, 128.9, 126.0, 119.4, 118.8, 112.0, 98.8, 15.4 (CH_3).

Anal. Calcd. For $C_{22}H_{16}N_4O$ (352.39): C, 74.98; H, 4.58; N, 15.90. Found C, 75.36; H, 4.62; N, 15.92.

5-Amino-8-methyl-4-oxo-7-phenyl-3-*p*-tolyl-3,4-dihydrophthalazine-6-carbonitrile (**21d**).

Compound **21d** was obtained as yellowish green crystals (2.50 g, 68%), mp. 238 ºC, ir (KBr) ν_{max} = 3454 and 3310 (NH_2), 2207 (CN), 1651 (CO) cm^{-1}; ms: m/z = 366 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ = 2.15 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.28 (br s, 2H, NH_2, D_2O exchangeable), 7.32-7.35 (m, 4H, arom-H), 7.42-7.47 (m, 2H, arom-H), 7.50-7.58 (m, 3H, arom-H), 8.59 (s, 1H, pyridazine-H), ^{13}C nmr (dimethylsulfoxide-d_6): δ = 161.0 (CO), 152.1, 151.0, 139.8, 138.8, 138.4, 137.5, 133.2, 130.2, 130.1, 129.6, 126.9, 126.3, 119.3, 117.2, 111.8, 97.8, 21.7 (CH_3), 15.6 (CH_3).

Anal. Calcd. For $C_{23}H_{18}N_4O$ (366.42): C, 75.39; H, 4.95; N, 15.29. Found C, 74.88; H, 5.09; N, 15.40.

Acknowledgement.

The authors are grateful to University of Kuwait, Research Administration for financial support through project SC 02/02. Analytical facilities provided by SAF are greatly appreciated.

REFERENCES AND NOTES

[1] M. A. Al-Shiekh, A. M. S. El-Din, E. A. Hafez and M. H. Elnagdi, *J. Chem. Res.,* 174 (2004).

[2] M. A. Al-Shiekh, A. M. S. El-Din, E. A. Hafez and M. H. Elnagdi, *J. Heterocyclic Chem.,* **41**, 647 (2004).

[3] B. Al-Saleh, H. Bahbehani, M. A. El-Apasery and M. H. Elnagdi, *J. Chem. Res.,* 575 (2004).

[4] B. Al-Saleh, M. A. El-Apasery and M. H. Elnagdi, *J. Chem. Res.,* 578 (2004)..

[5] K. M. Al-Zaydi, R. M. Borik and M. H. Elnagdi, *Molecules,* **8**, 910 (2003).

[6] A. Bhandari, B. Li, M. A. Gallop, *J. Synthetic Organic Chemistry,* **11**, 1951 (1999).

[7] G. P. Miller, E. T. Kool, *J.Organic Chemistry,* **69**, 2404 (2004).

[8] P. Grosche, A. Höltzel, T. B. Walk and A. Trautwein, *J. Synthetic Organic Chemistry,* **11**, 1971 (1999).

[9] J. Clark, P. Macquarriee, "Hand Book of Green Chemistry & Technology", Blackwell Science, page 402 (2002).

[10] K. Tanaka," Solvent- Free Organic Synthesis", WILEY-VCH GmbH & Co. KGaA, (2003).

[11] V. Santagada, E. Perissuti and G. Galiendo, *Current Medicinal Chemistry,* **9**,1251 (2002).

[12] P. Lidström, J. Tierney, B. Wathey and J. Westman. *Tetradedron*, **51**, 9225 (2001).

[13] M. H. Elnagdi, N. S. Ibraheim, F. M. Abdelrazek and A. W. Erian, *Liebigs Ann. Chem.,* 909 (1988).

[14] M. H. Elnagdi, N. S. Ibraheim, Sadek and M. H. Mohamed, *Liebigs Ann. Chem.,* 1009 (1988).

[15] H. Al-Awadi, F. Al-Omran, M. H. Elnagdi, L. Infantes, C. Foces-Foces, N. Iagerovic, J. Elguero, *Tetrahedron,* **51**, 12745 (1995).

[16] F. Al-Omran, M. M. Abdelkhalik, H. Al-Awadi and M. H. Elnagdi, *Tetrahedron*, **52**, 11915 (1996).

[17] A. Al-Etaibi, N. Al-Awadi, F. Al-Omran, M. M. Abdelkhalik and M. H. Elnagdi, *J. Chem. Res. (S)*, 4 *Ibid. (M).* 151 (1999).

[18] M. M. Abdelkhalik, A. M. Negm, A. I. Elkhouly and M. H. Elnagdi, *Heteroatom Chemistry,* **15**, 502 (2004).

[19] E. Nyiondi-Bonguen, E. Sopbue Fondjo, T. Fomum and D. Döpp, *J. Chem. Soc. Perkin Trans. 1,* 2191 (1994).

[20] F. Al-Omran, N. Al-Awadi, A. Elassar, A. El-Khair, *J. Chem. Res. (S)*, 20 *Ibid. (M).* 237 (2000).

[21] M. H. Elnagdi, F. M. Abdelrazek, H. S. Ibrahim and A. W. Evian, *Tetrahedron,* **45**, 3597 (1989).

[22] M. H. Elnagdi, A. M. Negm and K. U. Sadek, *Synlett.,* 27 (1994).

[23] N. Rabjohn, "Organic Synthesis, Collective Volume 4", John Wiley & Sons, Inc., page 633 (1963).