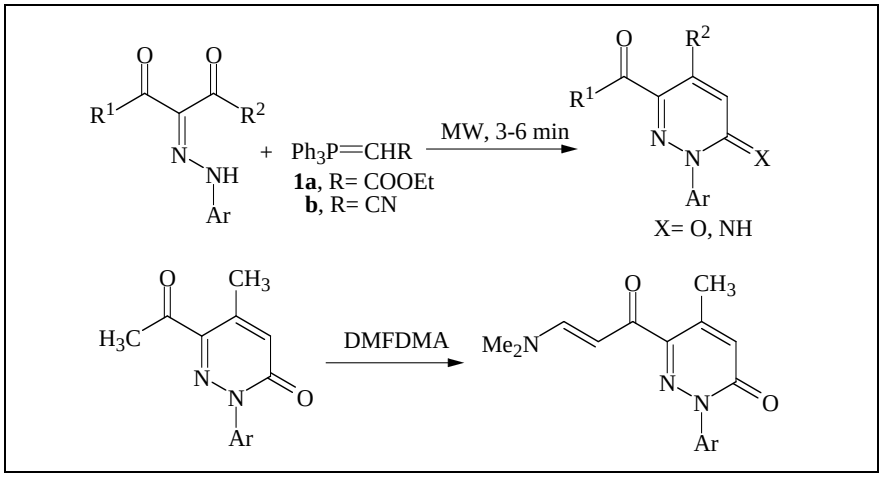
Microwaves in Organic Synthesis: Facile Synthesis of Biologically Active Pyridazinone and Iminopyridazine Derivatives.

Nadia Ragab Mohamed,[*a] Manal Mohamed Talaat El-Saidi,[a] Yasser Mahmoud Ali,[a] Mohamed Hilmy Elnagdi.[b]

a: Department of Photochemistry, National Research Centre, Dokki, Giza, Egypt.
b: Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt.
Corresponding author: E-mail: nadia_ragab_m@hotmail.com
Received November 27, 2006



Condensation of Wittig reagents **1a,b** with arylhydrazones **2a,b** by conventional and by microwave heating techniques furnished the corresponding pyridazines **3a-e**. The arylhydrazones **7a,b** were allowed to react with **1a,b** under the same conditions to produce the pyridazinones **10a,b** and iminopyridazines **11a,b** respectively. On the other hand, the arylhydrazones **12a-c** reacted with **1a** to afford the pyridazinones **13a-c**. Treatment of **3b** with dimethylformamide dimethyl acetal (DMFDMA) produced the adduct **15**. The utility of microwave heating technique led to the reduction of the reaction times to few minutes and to the improvement of the yields of the products. The *in vitro* biological activity of some newly prepared compounds against four types of fungi was studied.

J. Heterocyclic Chem., **44**, 1333 (2007).

INTRODUCTION

The biological activities of poly-functionally substituted azines and condensed azines have recently stimulated considerable interest in the chemistry of these compounds [1-3]. The pharmaceutical uses of azines are shown by the large number of publications filed in this area, for example condensed azines act as anti-bacterials [4], and antihypertensive agents [5]. Recent studies in this field have also revealed their activities as antiplatelet agents [6], and inhibitors for platelet aggregation [7].

Since the first report by Gedye *et al.* [8] on the utility of microwaves as energy source in organic synthesis, the adoption of this technique as an environmentally friendly synthetic approach has been of considerable interest [9-11].

Two environmentally friendly simple methods that either do not utilize organic solvents or utilize a small quantity of high boiling solvents have been adopted [9].

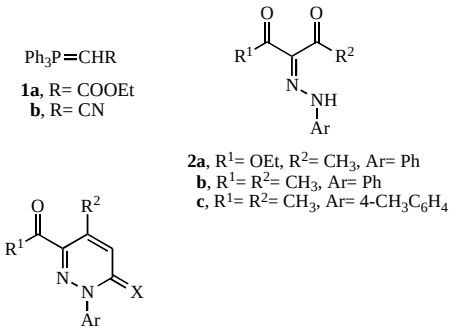
RESULTS AND DISCUSSION

We reported earlier on the synthesis of polyfunctional bioactive azines using microwave heating as an efficient heating method [12,13]. In conjunction to this previous interest in developing polyfunctionally substituted hetero-aromatics utilizing readily obtainable building blocks, we report here on the utility of arylhydrazones as precursors to substituted pyridazines (Scheme I).

The condensation of Wittig reagent **1a** with arylhydrazones **2a,b** in refluxing toluene has been shown earlier by us to produce pyridazinone **3a,b** [14]. Likewise reacting **2c** with **1a** afforded a product that could be formulated as either **3c** or isomeric **6**. Structure **6** was ruled out based on ^{1}H-NMR that revealed the presence of two methyl groups at δ= 2.41 and 2.54 ppm respectively. Similarly the reaction of **1b** with **2b,c** afforded **3d,e** while **3e** was converted into **3c** on reflux in AcOH-HCl (Scheme II).

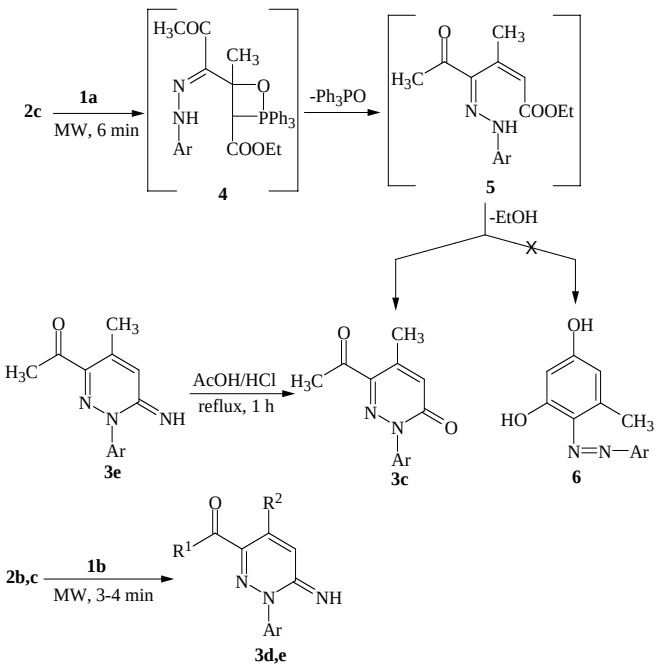
Furthermore, we have investigated the previously reported reactions by microwave heating technique. Reactions of **2a-c** with **1a,b** could be carried out in

Scheme I



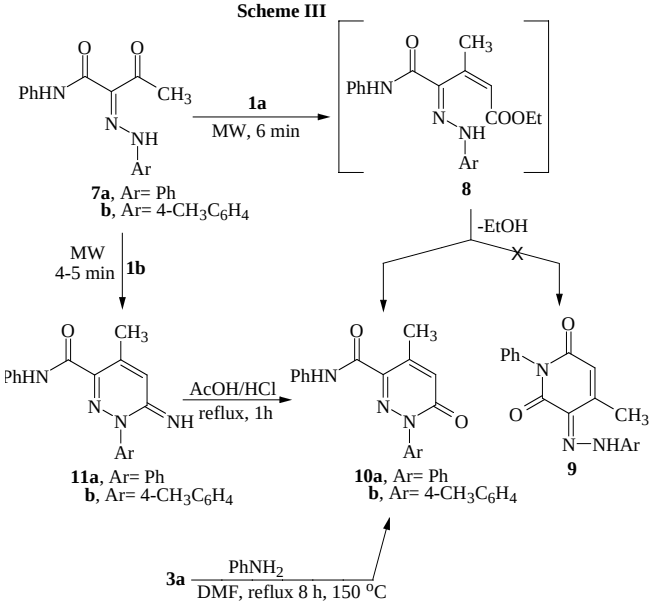
microwave oven using a small amount of dimethylformamide adopting MORE (Microwave-induced Organic Reactions Enahancement) technology invented by Bose [15,16]. The reactions discussed above were completed within 3-6 min. The yields were also improved (*cf.* Table 1).

Scheme II



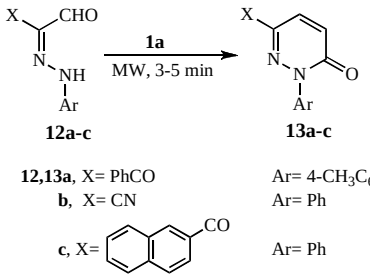
The arylhydrazones **7a,b**, which were prepared according to the classical method [17,18], were allowed to react with **1a** under reflux and by microwave heating. The products may be formulated as pyridine **9** or pyridazinone **10**. The pyridazinone structure **10** was established for the reaction product based on the identity of the product obtained from reaction of **3a** prepared earlier [14] with aniline in DMF under reflux at 150 °C. Similarly reacting **7a,b** with **1b** under the same conditions, afforded **11a,b** in good yields. The latter was converted to **10a,b** on reflux in AcOH-HCl (Scheme III).

Scheme III



The reactivity of the arylhydrazones **12a-c** [19] with **1a** was also investigated. Refluxing **1a** with **12a-c** in toluene for 8 hours afforded the pyridazinones **13a-c**. In contrast, the same reaction was completed within a range of 3-5 minutes using microwave heating technique. Trials to condense **12a-c** with **1b** failed under a variety of conditions (Scheme IV).

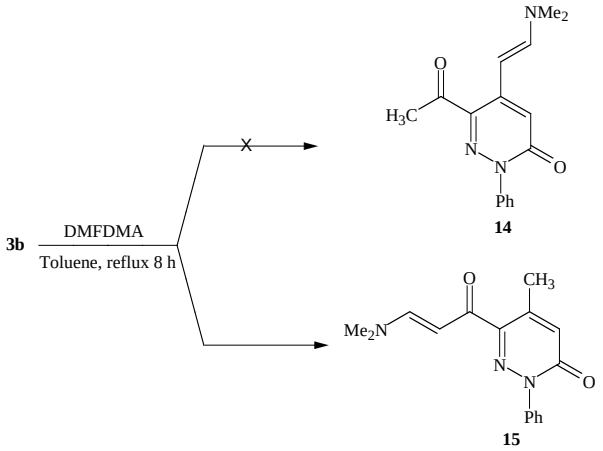
Scheme IV



The reactivity of methyl functions in **3b** and **10a** toward dimethyformamide dimethyl acetal (DMFDMA) was also investigated. Although methyl group in 3,5-difunctionally substituted pyridazinone has been reported to react readily with DMFDMA [20], the methyl group in **10a** failed to condense with DMFDMA under variety of conditions. Treatment of **3b** with DMFDMA in toluene afforded a condensation product that may be formulated as **14** or isomeric **15**. Structure **14** was excluded because all spectroscopic data were in accordance with structure **15**.

Furthermore, structure **15** seemed more likely as the methyl group in **10a** has failed to condense with DMFDMA. (Scheme V).

Scheme V



The mass spectrum of **15** revealed a base peak at m/z= 98 characteristic to the fragment $[Me_2N\text{-}CH{=}CHCO]^+$. The IR spectrum showed two bands at ν= 1647, 1681 cm^{-1} for the carbonyl group and the pyridazine carbonyl group respectively. In addition, the ^{1}H-NMR spectrum revealed two doublet signals at δ= 5.71 ppm, (J= 12 Hz) and 7.42 ppm, (J= 12 Hz) for the two olefinic protons of compound **15**. If the produced product was **14**, the chemical shifts for the two olefinic protons in this case expected to appear at δ= 5.25, 6.05 ppm [21].

The comparison between the conventional and microwave heating techniques in terms of the reaction times and the yields of the produced products is summarized in Table 1.

Table 1

Comparison between the conventional and microwave heating techniques.

Compound	Conventional heating		Microwave heating	
	Reaction time (hours)	Yield %	Reaction time (minutes)	Yield %
3a[14]	10	82	5	89
3b[14]	10	80	6	90
3c	10	70	6	87
3d	10	60	4	85
3e	10	73	3	87
10a	30	65	6	85
10b	30	70	6	87
11a	30	60	4	80
11b	30	65	5	82
13a	8	60	5	80
13b	8	65	6	85
13c	8	62	4	87

Bioactivity. The *in vitro* antifungal activity of some newly prepared compounds **3b**,**c**, **10a**,**b**, **11a**,**b** and **15** against four types of fungi was investigated. The seven tested compounds were capable of inhibiting the growth of *Candida Albicans* and *Saccharomyces Cerviseae*. They were inactive towards *Asperiglus Flavus* and *Aspragillus Niger*. The examined compounds **3b,c**, **10b**, **11b**, **15** exhibited significant antifungal activity, while the compounds **10a**, **11a** showed moderate activity.

Conclusion. Microwave heating is considered to be a green method for the synthesis of bioactive pyridazines *via* the utility of simply prepared arylhydrazones and Wittig reagents. The newly prepared pyridazinones and iminopyridazines have shown antifungal activity. In this technique: 1) A small amount of solvent like dimethylformamide was used (MORE technology). 2) The reaction times of were reduced to a few minutes. 3) The yields of the products were improved.

EXPERIMENTAL

All melting points were determined on gallenkamp electrothermal melting point and were uncorrected. The IR spectra were expressed in cm^{-1} and recorded in KBr pellets on a FT IR-8201 PC spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian Gemini NMR spectrometer, 300 MHz spectrometer in $CDCl_3$ as solvent and using tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) were expressed in ppm. Mass spectra were performed on MS-50 Kratos (A.E.I) spectrometer. Elemental analyses were performed with all final compounds on Elmentro, Vario EL. Microbiological analyses were carried out by the Micro-analytical Centre Cairo University, Egypt. Microwave experiments were conducted in a domestic microwave oven SHARP model 340D, 1000 W at medium power. The reactions were monitored by thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F254 (Merck).

General procedure for the Reaction of Wittig reagents 1a,b with 2a-c, 7a,b and 12a-c.

Method A: Conventional heating. A mixture of arylhydrazone **2a-c** or **7a,b** and or **12a-c** (0.01 mol) and the ylides **1a,b** (0.01 mol) in 30 ml toluene was heated under reflux with stirring until the starting materials could no longer be detected by TLC. The solvent was evaporated under reduced pressure and the residue was treated with petroleum ether 60-80 °C. The solid product was collected by filtration and either crystallized from benzene or purified with column chromatography. Triphenylphoshine oxide (TPPO) was separated from the reaction medium as white crystals mp 157 °C (by mixed mp) [22].

Method B: Using microwave heating technique. A mixture of arylhydrazones **2a-c** or **7a,b** and or **12a-c** (0.01 mol) and the ylides **1a,b** (0.01 mol) in 2 ml DMF were placed in domestic microwave oven and irradiated for 3-6 min. The reaction mixture was left to cool at room temperature. The resulting products were triturated with petroleum ether 60-80 °C. The formed precipitates were collected by filtration and crystallized from benzene.

Ethyl 4-methyl-6-oxo-1-phenyl-1,6-dihydro-pyridazin-3-carboxylate, 3a. Conventional heating afforded yield 2.11 g (82%) after 10 h (Lit.[14]); microwave heating afforded 2.29 g (89%) after 5 min; mp 103 °C; yellow crystals; ms: (m/z) 258

(M^+, 32%); Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C 65.11%, H 5.46%, N 10.85%. Found: C 64.89%, H 5.32%, N 10.78%.

6-Acetyl-5-methyl-2-phenylpyridazin-3(*2H*)-one, 3b. Conventional heating afforded yield 1.82 g (80%) after 10 h (Lit.[14]); microwave heating afforded 2.05 g (90%) after 6 min; mp 132 °C; yellow crystals; ms: (m/z)= 228 (M^+, 47%); Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C 68.41%, H 5.30%, N 12.27%. Found: C 68.38%, H 5.21%, N 12.20%.

6-Acetyl-5-methyl-2-(4-methylphenyl)pyridazin-3-(*2H*)-one, 3c. Conventional heating afforded yield 1.60 g (70%) after 10 h; microwave heating afforded 2.10 g (87%) after 6 min; mp 140 °C; yellow crystals; ir (KBr): ν 2923 (CH_3), 1689 (CO), 1624 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 1.65 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 6.81 (s, 1H, H-5 pyridazine), 7.41-7.66 (m, 4H, aromatic protons); ms: (m/z) 242 (M^+, 33%); Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C 69.41%, H 5.82%, N 11.56%. Found: C 69.38%, H 5.74%, N 11.45%.

1-(6-Imino-4-methyl-1-phenyl-1,6-dihydropyridazin-3-yl)-ethanone, 3d. Conventional heating afforded yield 1.36 g (60%) after 10 h; microwave heating afforded 1.93 g (85%) after 4 min; mp 126 °C; yellow crystals; ir (KBr): ν 3436 (NH), 2927 (CH_3), 1693 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 2.50 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.30 (s, 1H, H-5, pyridazine), 7.34-7.67 (m, 5H, aromatic protons), 14.75 (s, 1H, NH); ms: (m/z) 227 (M^+, 29%); Anal. Calcd. for $C_{13}H_{13}N_3O$: 68.71%, H 5.77%, N 18.49%. Found: C 68.62%, H 5.63%, N 18.35%.

1-(6-Imino-4-methyl-1-(4-methylphenyl)-1,6-dihydropyridazin-3-yl)-ethanone, 3e. Conventional heating afforded yield 1.76 g (73%) after 10 h; microwave heating afforded 2.10 g (87%) after 3 min; mp 128 °C; yellow crystals; ir (KBr): ν 3421 (NH), 2993 (CH_3), 1678 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 1.58 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 6.29 (s, 1H, H-5 pyridazine), 7.42-7.68 (m, 4H, aromatic protons), 14.38 (s, 1H, NH); ms: (m/z) 241 (M^+, 42%); Anal. Calcd. for $C_{14}H_{15}N_3O$: C 69.69%, H 6.27%, N 17.41%. Found: C 69.64%, H 6.19%, N 17.37%.

4-Methyl-6-oxo-*N*,1-diphenyl-1,6-dihydropyridazine-3-carboxamide, 10a. Conventional heating afforded yield 1.98 g (65%) after 30 h; microwave heating afforded 2.59 g (85%) after 6 min; the product was isolated by silica gel (60 mesh) column chromatograohy using eluent (ethyl acetate: petroleum ether 40-60 °C, 3:7); mp 212 °C; yellow crystals; ir (KBr): ν 3407 (NH), 2922 (CH_3), 1677 (CO), 1629 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 2.40 (s, 3H, CH_3), 6.31 (s, 1H, H-5 pyridazine), 7.21-7.36 (m, 5H, aromatic protons), 7.39-7.57 (m, 5H, aromatic protons), 14.40 (s, 1H, NH); ms: (m/z) 305 (M^+, 95%); Anal Calcd for $C_{18}H_{15}N_3O_2$: C 70.81%, H 4.95%, N 13.76%. Found: C 70.78%, H 4.87%, N 13.60%.

4-Methyl-1-(4-methylphenyl)-6-oxo-*N*-phenyl-1,6-dihydropyridazine-3-carboxamide, 10b. Conventional heating afforded yield 2.23 g (70%) after 30 h; microwave heating afforded 2.77 g (87%) after 6 min; the product was isolated by silica gel (60 mesh) column chromatograohy using eluent (ethyl acetate: petroleum ether 40-60 °C, 3:7); mp 216 °C; yellow crystals; ir (KBr): ν 3422 (NH), 2925 (CH_3), 1668 (CO), 1629 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 1.58 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.27 (s, 1H, H-5 pyridazine), 7.22-7.25 (m, 5H, aromatic protons), 7.26-7.53 (m, 4H, aromatic protons), 14.41 (s, 1H, NH); ms: (m/z) 319 (M^+, 100%); Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C 71.46%, H 5.37%, N 13.16%. Found: C 71.34%, H 5.23%, N 13.12%.

6-Imino-4-methyl-*N*,1-diphenyl-1,6-dihydropyridazine-3-carboxamide, 11a. Conventional heating afforded yield 1.82 g (60%) after 30 h; microwave heating afforded 2.43 g (80%) after 4 min; the product were isolated by silica gel (60 mesh) column chromatography using eluent (ethyl acetate: petroleum ether 40-60 °C, 2:8); mp 222 °C; yellow crystals; ir (KBr): ν 3421 (NH), 2923 (CH_3), 1678 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 2.41 (s, 3H, CH_3), 6.31 (s, 1H, CH), 7.22-7.42 (m, 5H, aromatic protons), 7.49-7.58 (m, 5H, aromatic protons), 13.16 (s, 1H, NH), 14.40 (s, 1H, NH); ms: (m/z) 304 (M^+, 25%); Anal. Calcd. for $C_{18}H_{16}N_4O$: C 71.04%, H 5.30%, N 18.41%. Found: C 70.93%, H 5.22%, N 18.35%.

6-Imino-4-methyl-1-(4-methylphenyl)-*N*-phenyl-1,6-dihydropyridazine-3-carboxamide, 11b. Conventional heating afforded yield 2.06 g (65%) after 30 h; microwave heating afforded 2.60 g (82%) after 5 min; the product was isolated by silica gel (60 mesh) column chromatograohy using eluent (ethyl acetate: petroleum ether 40-60 °C, 2:8); mp 228 °C; yellow crystals; ir (KBr): ν 3445 (NH), 2918 (CH_3), 1682 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 1.61 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 6.26 (s, 1H, H-5 pyridazine), 7.22-7.25 (m, 5H, aromatic protons), 7.26-7.53 (m, 4H, aromatic protons), 13.18 (s, 1H, NH), 14.40 (s, 1H, NH); ms: (m/z) 318 (M^+, 100%); Anal. Calcd. for $C_{19}H_{18}N_4O$: C 71.68%, H 5.70%, N 18.60%. Found: C 71.52%, H 5.64%, N 18.51%.

Conversion of 3e, 11a,b to 3c, 10a,b respectively. A solution of **3e or 11a,b** (0.01 mol) in 10 ml AcOH containing 2 ml of concentrated hydrochloric acid was heated under reflux for 1 h. After cooling the reaction mixture was poured on ice/water mixture. The solid product formed was collected by filtration and crystallized from benzene. A comparison with authentic samples **3c** and **10a,b** was carried out.

Reaction of 3a with aniline. A mixture of **3a** (0.01 mol, 2.58 g) and aniline (0.01 mol, 0.93 g) in 10 ml DMF was heated for 8 h at 150 °C. The reaction mixture was poured onto ice/water mixture. The formed product was collected by filtration then crystallized from ethanol. The product was confirmed by comparison with an authentic sample **10a** (mp 212 °C).

2-(4-Methylphenyl)-6-(phenylcarbonyl)-pyridazin-3(*2H*)-one, 13a. Conventional heating afforded yield 1.74 g (60%) after 8 h; microwave heating afforded 2.32 g (80%) after 5 min; mp 132 °C; yellow crystals; ir (KBr): ν 1681 (CO), 1647 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 2.38 (s, 3H, CH_3), 7.13 (d, 1H, H-5 pyridazine, J= 6 Hz), 7.27 (d, 1H, H-4 pyridazine, J= 6 Hz), 7.44-7.48 (m, 5H, aromatic protons), 7.50 (d, 2H, aromatic protons, J= 9 Hz), 8.06 (d, 2H, aromatic protons, J= 9 Hz); ms: (m/z) 290 (M^+, 76%); Anal Cacld. for $C_{18}H_{14}N_2O_2$: C 74.74%, H 4.86%, N 9.65%. Found: C 74.69%, H 4.77%, N 9.59%.

6-Oxo-1-phenyl-1,6-dihydropyridazine-3-carbonitrile, 13b. Conventional heating afforded yield 1.16 g (65%) after 8 h; microwave heating afforded 1.52 g (85%) after 6 min; mp 125 °C; red crystals; ir (KBr): ν 2241 (CN), 1689 (CO) cm^{-1}; ^1H nmr (CD_3Cl): δ= 7.12 (d, 1H, H-5 pyridazine, J= 6 Hz), 7.43 (d, 1H, H-4 pyridazine, J= 6 Hz), 7.44-7.64 (m, 5H, aromatic protons); ms: (m/z) 197 (M^+, 31%); Anal. Cacld. for $C_{11}H_7N_3O$: C 67.0%, H 3.58%, N 21.31%. Found: C 66.98%, H 3.53%, N 21.24%.

6-(2-Naphthalen-2ylcarbonyl)-2-phenylpyridazin-3(*2H*)-one, 13c. Conventional heating afforded yield 2.02 g (62%) after 8 h; microwave heating afforded 2.83 g (87%) after 4 min; mp 122 °C; yellow crystals; ir (KBr): ν 1678 (CO), 1627 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ (ppm)= 7.13 (d, 1H, H-5 pyridazine, J= 6 Hz), 7.29 (d, 1H, H-4 pyridazine, J= 6 Hz), 7.47-7.67 (m, 5H, aromatic protons), 7.69-7.94 (m, 6H, naphthyl proton), 8.74 (s, 1H, naphthyl proton); ms: (m/z) 326 (M^+, 22%); Anal. Calcd. for

$C_{21}H_{14}N_2O_2$: C 77.29%, H 4.32%, N 8.58%. Found: C 77.19%, H 4.23%, N 8.55%.

Reaction of 3b with dimethylformamide dimethyl acetal (DMFDMA). A mixture of **3b** (0.01 mol, 2.28 g) with dimethylformamide dimethyl acetal (DMFDMA) (0.01 mol, 1.19 g) in 30 ml toluene was heated under reflux for 8 h. The solvent was evaporated under reduced pressure and the residue was treated with n-hexane. The solid product was collected by filtration and crystallized from ethanol.

6-[3-(Dimethylamino)prop-2-enoyl]-5-methyl-2-phenylpyridazin-3(*2H*)-one, 15. Yield 2.49 g (88 %); mp 142 °C; yellow crystals; ir (KBr): ν 2920 (CH_3), 1681 (CO), 1647 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ= 2.48 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 5.71 (d, 1H, CH olefinic, J= 12 Hz), 6.85 (s, 1H, H-5 pyridazine), 7.42 (d, 1H, CH olefenic, J= 12 Hz), 7.44-7.67 (m, 5H, aromatic protons); ms: (m/z) 283 (M^+, 42%); Anal Cacld for $C_{16}H_{17}N_3O_2$: C 67.83%, H 6.05%, N 14.83%. Found: C 67.76%, H 5.97%, N 14.83%.

Bioassay. A filter paper sterilized disc saturated with measured quantity of the sample is placed on plate containing fungal medium (Dox's medium), which has been heavily seeded with spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism [23,24].

Acknowledgment. The authors would like to express their great thanks for Prof. Dr. Ebtisam A. Hafez for her interest and help.

REFERENCES AND NOTES

[1] Sabat, M.; VanRens, J. C.; Brugel, T. A.; Maier, J. *Bioorganic Med. Chem. Lett.* **2006**, *16*, 4257.

[2] Pieretti, S.; Dominici, L.; Di Giannuario, A. *Life Sciences*, **2006**, *79*, 791.

[3] Elnagdi, M. H.; Abdel Aal, F. A.; Hafez, E. A.; Yassin, Y. M. *Z. Naturforsch B*, **1989**, *44*, 683.

[4] a) Heinisch, H.; Frank, H. "Progress in Medicinal Chemistry". Ellis, G. P., West G. G., Eds.; Elsevier: Amsterdam, (1990). b) Domagala, J. M.; Peterson, P. *J. Heterocycl. Chem.* **1989**, *26*, 1147.

[5] Demirayak, S.; Karaburun, A. C.; Beis, R. *Eur. J. Med. Chem.* **2004**, *39*, 1089.

[6] Crespo, A.; Meyers, C.; Coelho, A.; Yáñez, M.; Fraiz, N.; Sotelo, E.; Maes, B. U. W.; Laguna, R.; Cano, E.; Lemière, G. L. F.; Raviña, E. Bioorganic Med. Chem. Lett. **2006**, 16, 1080.

[7] Sotelo, E.; Fraiz, N.;Yáñez, M.; Terrades, V.; Laguna, R.; Cano, E.; Raviña, E. Bioorganic Med. Chem. **2002**, 10, 2873.

[8] Gedye, R.; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Roussell, J. Tetrahedron Lett. **1986**, 27, 279.

[9] Matlack, A. S. in "Introduction to Green Chemistry", Marcel Dekker Inc., New York Bassel, (2001).

[10] Clark, J. H.; Macquarrie, D. J. in "Handbook of Green Chemistry and Technology", Blackwell Science Ltd., Paris, (2002).

[11] Lange, F.; De La Hoz. A.; Diaz-Ortiz. A.; Diez-Barra, E. Contmp. Org. Synth. **1997**, 373.

[12] Al-Shiekh, M. A.; Salah El-Din, A. M.; Hafez, E. A.; Elnagdi, M. H. J. Chem. Research (S), **2004**, 174.

[13] Al-Zaydi, K. M.; Borik, R. M.; Elnagdi, M. H. Molecules, **2003**, 8, 910.

[14] Nada, A. A.; Erian, A. W.; Mohamed, N. R.; Mahran, A. M. J. Chem. Research (S), **1997**, 236.

[15] Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S..; Bari, S. S.; Newaz, S. N.; Banki, B. K.; Chaudhary, A. G.; Barakat, K. J. Org. Chem. **1991**, 56, 6968.

[16] Bose, A. K.; Banki, B. K.; Manhas, M. S. Chemtec, **1997**, 27, 18.

[17] Elnagdi, M. H.; Erian, A. W.; Sadek, K. U.; Selim, M. A. J. Chem. Research (S), **1990**, 148.

[18] Ibrahim, N. S.; Abdel-Gilil, E. M.; Abdel-Motalb, R, M.; Elnagdi, M. H. *Bull. Chem. Soc. Jpn.* **1987**, 60, 4488.

[19] Behbehani, H.; Abdel Khalik, M. M.; Elnagdi, M. H. *Org. Prep. Proced. Int.* **1999,** 31, 551.

[20] Al-Saleh, B., Hilmy, N. M.; El-Apasery, M. A.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2006**, 43, 1575.

[21] Pretsch, E.; Simon, W.; Seibl, J.; Clerc, T. "Tables of Spectral Data for Determination of Organic Compounds". Springer-Verlag, Berlin, 2nd Edition. 1989, pp. 215.

[22] Michaelis, A.; Gleichman, L. *Chem. Ber.* **1882**, 15, 801.

[23] Grayer, R. J.; Harbone, J. B. *Phytochemistry*, **1994**, 37, 19.

[24] Muanza, D. N.; Kim, B. W.; Euler, K. L.; Williams, L. *Internat. J. Pharmacog.* **1994**, 32, 337.