Synthesis of Some Pyrazole-3-Carboxylic Acid-Hydrazide and Pyrazolopyridazine Compounds

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Furan-2,3-diones **1a-c** react with various hydrazines **2a-c** under different conditions to yield the pyrazole-3-carboxylic acid-hydrazide **3a-d**. Cyclocondensation reactions of **1a** or **7** with phenylhydrazine lead to derivatives of pyrazolo[3,4-*d*]pyridazinones **6** and **8**, respectively. The structures of all products were confirmed by elemental analysis, IR, ^{1}H- and ^{13}C-NMR spectroscopic measurements.

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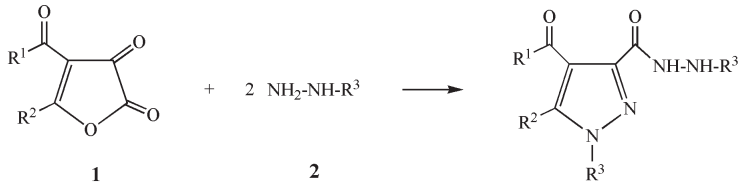
Introduction.

Pyrazole nucleus and its chemistry [1] has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives appearing as anti-microbial [2], anti-viral [3], anti-tumor [4], anti-inflammatory [5], anti-histaminic [6], pesticidal [7], anti-fungal [8], against rheumatoid arthritis [9], anti-convulsant [10], anti-depressant [11], anti-pyretic [12] and commercially important dyestuffs [13] agents. Recently, reactions of cyclic oxalyl compounds have been reported to give substituted heterocyclic compounds [14]. The reactions of 4-benzoyl-5-phenylfuran-2,3-dione with several semicarbazones, ureas and their thio-anologues and oximes have been reported in different solvents and at various temperatures [15]. The general reactivity of 4-benzoyl-5-phenylfuran-2,3-dione and the mechanism of the reactions with NH-nucleophiles have recently been reviewed with semi-empirical (AM1 and PM3) calculations [16]. The reactions are generally initiated by nucleophilic attack of the nitrogen atom of semicarbazone, urea and hydrazines, on the furan ring [17,18]**.** The reaction of furan-2,3-dione **1a**, obtained easily from dibenzoylmethane and oxalyl dichloride [14a], with various phenyl hydrazones and phenylhydrazine leads to pyrazole carboxylic acids and pyridazinones [19].

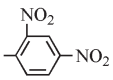
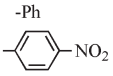
In the present study, we carried out the reaction of the furans-2,3-diones **1a,c** with hydrazine derivatives **2a-c** yielding pyrazole-3-carboxylic acid-hydrazide derivatives **3a-d**, (Scheme 1). The structures of synthesized compounds were assigned on the basis of analytical results as well as spectroscopic data. Product **3a** was obtained in 45% yield by treating **1a** with 2,4-dinitrophenylhydrazine **2a** and refluxing the mixture in toluene for 6 hours. The moderate yield of the reaction can be explained by the chemical behavior of furandiones **1a-c** towards H-active nucleophiles. In compounds **1a-c** carbon atoms C-2, C-3

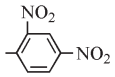
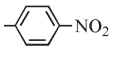
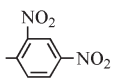
Scheme 1



1 **2** **3**

1	R^1	R^2
a	*p*-$CH_3OC_6H_4$-	*p*-$CH_3OC_6H_4$-
b	EtO-	Ph-
c	Ph-	Ph-

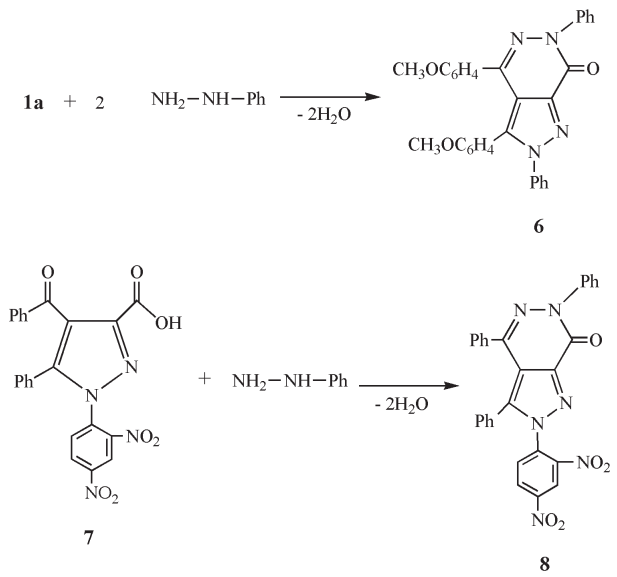
2	R^3
a	
b	-Ph
c	

3	R^1	R^2	R^3
a	*p*-$CH_3OC_6H_4$-	*p*-$CH_3OC_6H_4$-	
b	EtO-	Ph-	-Ph
c	Ph-	Ph-	
d	Ph-	Ph-	

and C-5 represent electrophilic sites of different reactivity and could be used for the construction reaction with nucleophiles [16a,17,20]. It should start with a nucleophilic attack of the nitrogen atoms lone pair electrons of **2a-c** to the antibonding (π*) orbital at the C5 position of the furandione ring similar to a Michael-type addition. Simultaneous attack of H-active nucleophiles to both C-2 and C-3 positions of the furan ring could convert furandiones **1a-c** into starting materials; these materials are dibenzoylmethane and oxalic acid derivatives [15a]. The by-products formed this way are removed when the raw product is treated with diethyl ether. In the ir spectra of compound **3a**, the –NH absorption bands were found to be at about 3450-3300 cm^{-1}, and the C=O absorption was at 1700 cm^{-1}. The ^{1}H-nmr signals were found to be at 11.68 (b, 2H, -NH); 8.23-6.74 (m, 14, ArH), 3.87 and 3.63 ppm (q, 6H, $2CH_3O$). The ^{13}C-nmr signals were observed at δ 191.68 (t, PhCO), 173.67 (s, C=O), 148.90 (s, C3), 57.30 and 57.00 ppm (q, $2CH_3O$). Finally, the elemental analysis data along with spectroscopic data (see Experimental) confirm the structure of **3a**.

In a similar way, the reaction of the 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid chloride **4** [19b] with 2,4-dinitrophenylhydrazine **2a** leads to form 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid 2,4-dinitrophenyl-hydrazide **5**, (Scheme-2).

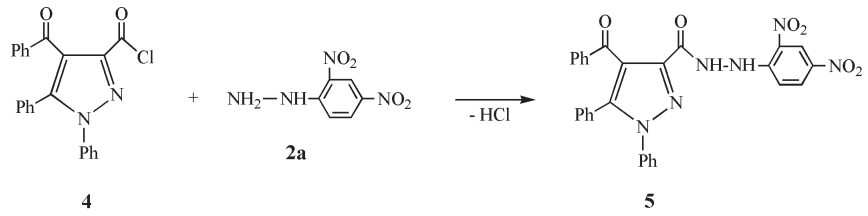
Scheme 3



EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected.

Scheme 2



Reaction of suitable vicinal dicarbonyl pyrazole derivatives with hydrazines in general are a convenient method to build the pyrazolo[3,4-*d*]pyridazine systems [17,19b,21]. Similiarly, the reaction of 4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-furan-2,3-dione **1a** and 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **7** [18] with phenylhydrazine **2b** leads to the formation of 2,6-diphenyl-3,4-di-(4-methoxyphenyl)–2.6-dihydropyrazolo[3,4-*d*]pyridazin-7-one **6** and 2-(2,4-dinitrophenyl)-3,4,6-triphenyl-2,6-dihydropyrazolo[3.4-*d*]-pyridazin-7-one **8** in approximately 40-60 % yields, (Scheme-3). In the ir spectra of compound **6**, the C=O absorption band was observed at 1690 cm^{-1}. The ^{1}H-nmr signals were observed at δ 7.78-6.56 (m, 18H, ArH) and 3.75 and 3.73 ppm (q, 6H, $2CH_3O$) and the ^{13}C-nmr signals at δ 162.18 (s, C=O); 149.52 (s, C-7a), 145.36 (s, C4), 142.03 (s, C3), 57.29 and 56.75 ppm (q, $2CH_3O$).

Microanalyses were performed on a Carlo Erba elemental analyser, Model 1108; the results agree favorably with the calculated values. The IR spectra were recorded on a Shimadzu Model 435 V-04 spectrometer, using potassium bromide discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Gemini-Varian 200 instrument. The chemical shifts are reported in ppm from tetramethylsilane and are given in δ (ppm).

4-(4-Methoxybenzoyl)-5-(4-metoxyphenyl)-1-(2,4-dinitrophenyl)-1*H*-pyrazole-3-carboxylic acid-2,4-dinitro phenylhydrazide (3a).

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)furan-2,3-dione **1a** (0.2 g, 0.59 mmol) and 2,4-dinitrophenylhydrazine **2a** (0.234 g, 1.18 mmol) were refluxed in benzene for 4.5 hours. The solvent was evaporated and the remaining oily residue was treated with ether to give the crude product which was recrystallized from acetic acid and allowed to dry on P_2O_5; 45% yield (0.19 g); m.p. 229 °C; ir ; 3450-3300 (broad, N-H), 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 11.68 (b, 2H, -NH), 8.23-6.74 (m, 14H, ArH), 3.87 and 3.63 (q, 6H, $2CH_3O$); ^{13}C-nmr ($CDCl_3$): δ 191.68 (t,

PhCO), 173.67 (s, C=O), 148.90 (s, C-3), 57.30 and 57.00 (q, $2CH_3O$).

Anal. Calcd. for $C_{31}H_{22}N_8O_{12}$: C, 53.29; H, 3.15; N, 16.05. Found; C, 53.36; H, 3.07; N, 16.10.

4-(Ethoxycarbonyl)-1,5-diphenyl-1*H*-pyrazole-3-carboxylic Acid Phenylhydrazide (**3b**).

Ethyl-4,5-dioxo-2-phenyl-4,5-dihydrofuran-3-carboxylate **1b** (0.5 g, 2.03 mmol) and phenyl hydrazine **2b** (0.44 g, 0.4 ml, 4.07 mmol) were refluxed in benzene for 1 hour or stirred in benzene at room temperature for 24 hours. The solvent was evaporated and the remaining oily residue was treated with *n*-hexane and ether and stirred for 24 hours to give the colorless product which was recrystallized from *n*-butyl alcohol and allowed to dry on P_2O_5; 67% yield (0.54 g); m.p. 204 °C; ir; 3450-3300 (b, N-H), 1680 (amide C=O), 1661 (ester C=O), 1620-1480 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 10.62 and 10.60 (2H, -NH); 8.02-6.57 (m, 14H, ArH); 4.26 (O-CH_2), 1.20 (CH_3); ^{13}C-nmr ($CDCl_3$): δ 163.61 (N-C=O); 161.30 (O-C=O); 150.21 (s, C-5); 143.20 (C-3).

Anal. Calcd. for $C_{23}H_{18}N_4O_3$: C, 69.29; H, 4.75; N, 14.10. Found; C, 69.19; H, 4.96; N, 13.97.

4-Benzoyl-5-phenyl-1-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylic Acid- 4-Nitrophenylhydrazide (**3c**).

4-Benzoyl-5-phenylfuran-2,3-dione **1c** (0.5 g, 1.798 mmol) was heated in toluene and allowed to cool to room temperature at which time 4-nitrophenyl hydrazine **2c** (0.55 g, 3.59 mmol) was added and the mixture was stirred at room temperature for 2 days. The solvent was evaporated and the remaining oily residue was treated with diethyl ether. The yellow precipitate was collected by filtration and washed in a mixture of petroleum ether and cyclohexane and allowed to dry on P_2O_5; 45% yield (0.35 g); m.p. 197 °C; ir; 3450-3250 (b, N-H), 1720 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 11.05 and 10.80 (2H, –NH); 8.51-6.49 (m, 13H, Ar-H); ^{13}C-nmr ($CDCl_3$): δ 193.16 (t, PhCO), 166.74 (s, C-7),151.16 (s, C-5), 150.90 (s, C-3); 140.33-112.22 (m, Aromatic C).

Anal. Calcd. for $C_{25}H_{15}N_3O_5$: C, 63.50; H, 3.65; N, 15.33. Found; C, 63.65; H, 3.83; N, 15.01.

4-Benzoyl-5-phenyl-1-[2,4-dinitrophenyl]-1*H*-pyrazole-3-carboxylic Acid 2,4-Dinitro phenylhydrazide (**3d**).

4-Benzoyl-5-phenylfuran-2,3-dione **1c** (0.5 g, 1.798 mmol) and 2,4-dinitrophenylhydrazine **2a** (0.712 g, 3.60 mmol) were refluxed in toluene for 6 hours. The solvent was evaporated and the remaining oily residue was treated with diethyl ether. The yellow crude by-product that did not dissolved in diethyl ether was removed by filtration. The precipitate was collected by filtration and washed in hot ethyl alcohol and recrystallized from acetic acid and allowed to dry on P_2O_5; 45% yield (0.52 g); m.p. 158-159 °C; ir: 3500-3150 (b, N-H), 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 9.40 and 9.28 (2H, –NH), 7.32-6.97 (m, 16H, ArH); ^{13}C-nmr ($CDCl_3$): δ 196.54 (t, PhCO), 159.84 (s, C-7), 157.29 (s, C-5), 149.97-116.00 (m, Aromatic C).

Anal. Calcd. for $C_{29}H_{18}N_8O_{10}$: C, 54.55; H, 2.82; N, 17.55. Found; C, 54.27; H, 2.99; N, 17.56.

4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic Acid 2,4-Dinitrophenylhydrazide (**5**).

4-Benzoyl-1,5-diphenyl-1*H*-3-pyrazole carboxylic acid chloride **4** (0.5 g, 1.29 mmol) and 2,4-dinitrophenylhydrazine **2a** (0.256 g, 1.29 mmol) were refluxed in xylene for 10 hours. The solvent was evaporated and the remaining oily residue was treated with diethyl ether to give an orange crude product which was recrystallized from ethyl alcohol and allowed to dry on P_2O_5; 30% yield (0.21 g); m.p. 167 °C; ir: 3500-3150 (b, N-H), 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 9.45 and 9.19 (2H, -NH), 7.32-6.97 (m, 18H, ArH); ^{13}C-nmr ($CDCl_3$): δ 193.44 (t, PhCO), 162.09 (s, C-7), 150.63 (s, C-5), 149.97-116.00 (m, Aromatic C).

Anal. Calcd. for $C_{29}H_{20}N_6O_6$: C, 63.50; H, 3.65; N, 15.33. Found; C, 63.63; H, 3.82; N, 15.06.

2,6-Diphenyl-3,4-di-(4-methoxyphenyl)–2.6-dihydropyrazolo[3,4-*d*]pyridazin-7-one (**6**).

4-(4-Methoxybenzoyl)-5-(4-methoxyphenyl)furan-2,3-dione **1a** (0.3 g, 0.89 mmol) and phenylhydrazine **2b** (0.192 g, 0.174 ml, 1.78 mmol) were refluxed in benzene for 5 hours. The solvent was evaporated and the remaining oily residue was treated with diethyl ether to give a crude product that was recrystallized from methanol and allowed to dry on P_2O_5. Compound **6** was obtained in 40% yield (0.176 g); m.p. 234 °C; ir: 1690 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 7.78-6.56 (m, 18H, ArH), 3.75-3.73 (q, 6H, $2CH_3O$); ^{13}C-nmr ($CDCl_3$): δ 162.18 (s, C=O), 149.52 (s, C-7a), 145.36 (s, C-4), 142.03 (s, C-3), 129.04 (s, C-3a), 57.29 and 56.75 (q, $2CH_3O$).

Anal. Calcd. for $C_{31}H_{24}N_4O_3$: C, 74.40; H, 4.80; N, 11.20. Found; C, 74.15; H, 4.85; N, 11.23.

2-(2,4-Dinitrophenyl)-3,4,6-triphenyl-2,6-dihydropyrazolo-[3,4-*d*]pyridazin-7-one (**8**).

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-3-pyrazole carboxylic acid **7** (0.5 g, 1.09 mmol) and phenylhydrazine **2b** (0.12 g, 0.11 ml, 1.11 mmol) were refluxed in xylene for 9 hours. The solvent was evaporated and the remaining oily residue was treated with diethyl ether to give a yellow crude product which was recrystallized from *n*-butyl alcohol and allowed to dry on P_2O_5, resulting in 60% yield (0.35 g); m.p. 279 °C; ir: 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$): δ 8.77-6.97 (m, 18H, ArH); ^{13}C-nmr ($CDCl_3$): δ 159.84 (s, C=O); 149.25 (s, C-7a), 145.48 (s, C-4), 142.88 (C-NO_2), 141.59 (s, C-3), 136.36 (N-Ph), 119.50 (s, C-3a).

Anal. Calcd. for $C_{29}H_{18}N_6O_5$: C, 65.66; H, 3.42; N, 15.84. Found; C, 65.88; H, 3.52; N, 15.89.

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REFERENCES AND NOTES

[1a] A. N. Kost and I. I. Grandberg, *Adv. Heterocyclic Chem.*, **6**, 347 (1966); [b] M. P. Sammes and A. R. Katritzky, *Adv. Heterocyclic Chem.*, **34**, 1, 38 (1983); [c] J. Elguero, in Comprehensive Heterocyclic Chem., Vol **4**, A. R. Katritzky and C. W. Rees, Eds, Pergamon Press, Oxford, 1984, Chapter 4,4; [d] R. S. Theobald, in: S. Coffey and M. F. Ansell (Eds.), Rodd's Chemistry of Carbon Compounds, 2nd Edn., Vol **IV**c, Elsevier Science Publishers, Amsterdam, p 1 (1986); [e] M. H. Elnagdi, G. E. H. Elgemeie, F. A. E. Abd-Elaal, *Heterocycles*, **23**, 3121 (1985); [f] S. T. Mullins, in: S. Coffey and M. F. Ansell, (Eds.), Rodd's Chemistry of Carbon Compounds, Suppl. of Vol **IV**c/d , Elsevier Science Publishers, Amsterdam, p 1 (1994).

[2a] A. M. Farghaly, N. S. Habib, M. A. Khalil and O. A. El-Sayed, *Alexandria J. Pharm. Sci.*, **3**, 90 (1989); [b] R. N. Mahajan, F. H. Havaldar and P. S. Fernandes, *J. Indian Chem. Soc.*, **68**, 245 (1991).

[3a] P. G. Baraldi, S. Manfredini, R. Romagnoli, L. Stevanato, A. N. Zaid and R. Manservigi, *Nucleosides and Nucleotides*, **17**, 2165 (1998); [b] S. L. Janus, A. Z. Magdif, B. P. Erik and N. Claus, *Monatsh. Chem.*, **130**, 1167 (1999).

[4a] S. Suzuki and A. Inoue, Jpn. Kokai Tokyo Koho JP 02 172 988 [90172988]; *Chem. Abstr.*, **113**, 218276t (1990); [b] G. J. Hatheway, C. Hansch, K. H. Kim. S. R. Milstein, C. L. Schimidt, R. N. Smith and F. R. Quin, *J. Med. Chem.*, **21**, 563 (1978); [c] H. Katayama and T. Oshiyama, *Can. J. Chem.*, **75**, 913 (1997).

[5a] R. Von Riedel, *Arezneim Forsch/Drug Res.*,**31**, 65 (1981); [b] E. Badawey and I. M. El-Ashmawey, *Eur. J. Med. Chem.*, **33**, 349 (1998); [c] O. Bruno, A. Ranise, F. Bondavalli, P. Schenone and M. D'amico, *Farmaco*, **47**, 1235 (1992).

[6] P. D. Mishra, S. Wahidullah and S. Y. Kamat, *Indian J. Chem. Soc. Sec. B*, **37**, 199 (1998).

[7a] W. T. Thomson, Agricultural Chemicals-Book II Herbicides, 13th. Ed., Thomson Publications, California-USA, 1997, pp 268-269-278; [b] M. Londershausen, *Pestic. Sci.*, **48**, 269 (1996).

[8a] V. V. Badiger and S. C. Bennur, *Indian J. Heterocyclic, Chem.*, **6**, 63 (1996); [b] H. S. Chen and Z. M. Li, *Chem. J. Chinese Univ.*, **19**, 572 (1998).

[9] M. Kurowaski, A. Dunky and M. Geddawi, *Eur. J. Clin. Pharmacol.*, **307**, 31 (1987).

[10] F. Lepage, B. Hublot, Eur. Pat. Appl. EP.459, 887; *Chem. Abstr.*, **116**, 128917 (1992).

[11] D. M. Bailey, P. E. Hansen, A. G. Hlavac, E. R. Baizman, J. Pearl, A. F. Defelice and M. E. Feigenson, *J. Med. Chem.*, **28**, 256 (1985).

[12] R. H. Wiley, P. Wiley, Pyrazolones, Pyrazolidones and Derivatives, John Wiley and Sons, New York, 1964, pp.102.

[13a] G. A. Hanson, *Bull. Soc. Chim. Belg.*, **67**, 707 (1958); [b] O. Neunhoeffer, G. Alsdorf and H. Ulrich. *Chem. Ber.*, **92**, 252 (1959); [c] E. E. Baroni and K. A. Kovyrzina, *Zh. Obshch. Khim.*, **31**, 1641, (1961).

[14a] E. Ziegler, M. Eder, C. Belegratis and E. Prewedourakis, *Monatsh. Chem.*, **98**, 2249 (1967); [b] G. Kollenz, C. O. Kappe and H. A. El Nabey, *Heterocycles*, **32**, 669 (1991); [c] R. W. Saalfrank, T. Lutz, B. Hörner, J. Gündel, K. Peters and H. G. von Schnering, *Chem. Ber.*, **124**, 2289 (1991); [d] E. Sarıpınar, Y. Güzel, Z. Önal, İ. Ö. İlhan and Y. Akçamur, *J. Chem., Soc., Pak.*, **22**, 308 (2000).

[15a] G. Kollenz, E. Ziegler, W. Ott and H. Igel, Z. *Naturforsch*, **31B**, 1511 (1976); [b] W. Ott, E. Ziegler and G. Kollenz, *Synthesis*, **7**, 477 (1976); [c] Y. Akçamur, B. Altural, E. Sarıpınar, G. Kollenz, C. O. Kappe, E. M. Peters and H. G. von Schnering, *J. Heterocyclic Chem.*, **25**, 1419 (1988); [d] B. Altural, Y. Akçamur, E. Sarıpınar, İ. Yıldırım and G. Kollenz, *Monatsh. Chem.* **120**, 1015 (1989); [e] Y. Akçamur and G. Kollenz, *Oppi Briefs*, **19**, 52 (1987); *Chem. Abstr.*, **107**, 7020t (1987).

[16a] İ. Yıldırım, E. Sarıpınar, Y. Güzel, Ş. Patat and Y. Akçamur, *J. Mol. Struct., (Theochem)*, **334**, 165 (1995); [b] E. Sarıpınar, İ. Yıldırım, Y. Güzel and Y. Akçamur, *Monatsh. Chem.*, **127**, 505 (1996); [c] İ. Yıldırım, M. Tezcan, Y. Güzel, E. Sarıpınar and Y. Akçamur, *Tr. J. Chem.*, **20**, 27 (1996).

[17] A. Şener, R. Kasımoğulları, M. K. Şener, İ. Bıldırıcı and Y. Akçamur, *J. Heterocyclic Chem*., **39**, 869 (2002).

[18] İ. Ö. İlhan, Y. Akçamur, E. Sarıpınar and E. Aslan, *Asian J. Chem*., **15**, 1373 (2003).

[19a] Y. Akçamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E. M. Peters, H. G. von Schnering, *Monatsh Chem.*, **117**, 231 (1986); [b] Y. Akçamur, A. Şener, A. M. İpekoğlu and G. Kollenz, *J. Heterocyclic Chem.*, **34**, 221 (1997).

[20] C. O. Kappe, E. Terpetschnig, G. Penn, G. Kollenz, K. Peters, E. M. Peters and H. G. Von Schnering, *Liebigs Ann.*, 537 (1995).

[21a] J. P. Marguet, J. D. Bourzat, J. Andre-Louisfert and E. Bisaghi, *Tetrahedron*, 29, 435 (1953); [b] A. S. Shawali, *J. Heterocyclic Chem*., **14**, 375 (1977).