Reactions of Cyclic Oxalyl Compounds, Synthesis of Functionalized Hydrazono-2H-imidazol-4,5(1H, 3H)dione: Experimental Data and AM1 Calculations

EMIN SARIPINAR*, YUNUS AKÇAMUR and GERT KOLLENZ†
Department of Chemistry, Faculty of Arts and Sciences, Erciyes University
38039 Kayseri, Turkey
E-mail: emin@erciyes.edu.tr

The reaction of the 4-benzoyl-5-phenylfuran-2,3-dione (**1**) with guanylhydrazones, (**2a–d**) gives hydrazono-2H-imidazol-4.5-(1H,3H)-dione derivatives (**4a–d**) (yield *ca.* 30–40%). The structure of these compounds were determined by spectroscopic methods. Quantum chemical calculations were carried out for **2a–d** and **4a–d** by AM1 method.

Key Words: Furan-2,3-dione, Guanylhydrazones, Imidazol, Semiempirical calculations.

INTRODUCTION

The 4-arylcarbonyl-5-aryl-2,3-dioxo-2,3-dihydrofuranes were obtained starting from 1,3-dicarbonyl compounds with oxalyl halides[1]. Recently, the reactions of cyclic oxalyl compounds have been reported to give substituted heterocyclic compounds[2]. The reactions of substituted 2,3-furandiones with various dienophiles and nucleophiles[2] in different solvents and at various temperatures have also been studied. Concerning the attempts to gain some insight into the chemical behaviour of five-membered heterocyclic furan-2,3-diones against NH-nucleophiles, a convenient preparation of functionalized ^{1}H-pyrimidine from 4-benzoyl-5-phenyl furan-2,3-dione (**1**) and several semicarbazones, ureas and their thio analogues has recently been reported by us[3]. Also conformational analysis and quantum chemical calculations were carried out by means of MMP_2, CNDO. MNDO and AM1 approximation methods for the series of compounds being functionalized ^{1}H-pyrimidines[4].

RESULTS AND DISCUSSION

We have now extended our investigations to the reactions of **1** with various guanylhydrazones (**2a–d**). It was thought that the reactions of 4-benzoyl-5-phenyl furan-2,3-dione (**1**) with guanylhydrazones should give 1H-pyrimidine-2-imines (**3**). similar to those reactions of thio- and semicarbazones with 4-benzoyl-5-phe-

†Institute of Organic Chemistry, Isotope Department, University of Graz, A-8010 Graz, Austria

nyl furan-2,3-dione[3]. Unfortunately it was not possible for us to synthesize 1H-pyrimidine-2-imines (**3**). Instead of these, the reaction yielded about 30–50% imidazole derivatives (**4a–d**). It is briefly outlined in **Scheme-1**. It was previously suggested that the amine group of *o*-phenylene diamine reacts with the oxalyl group of 4-benzoyl-5-phenyl furan-2,3-dione[2f]. The semicarbazones and oxalyl chloride cyclize to give the corresponding imidazoltriones[5]. Many imidazol compounds are also reported to show a broad spectrum of biological activities. Some of these compounds have been known to exhibit cardiotonic, antisecretory and antiulcer activity, bactericide, fungicide, antiviral and herbicide properties[6].

Treatment of carbonyl compounds with aminoguanidinehydrochloride led to the formation of guanylhydrazone hydrochlorides, which were transformed into the corresponding free bases by treatment with aqueous NaOH[7]. Protomeric tautomerism is of much interest in experimental as well as theoretical chemistry, since it is an important reaction in biological processes. Guanylhydrazones of type **2** can exist in two tautomeric forms[8] (**2A** and **2B**, Fig. 1). They may undergo

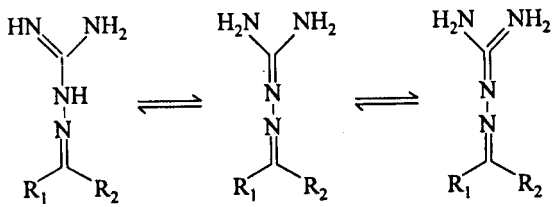


Fig. 1.

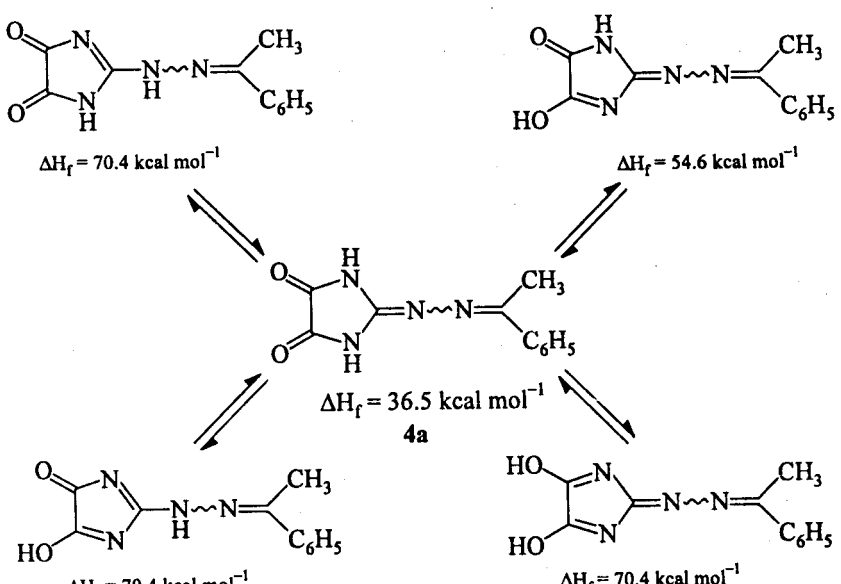


Fig. 2

proton shifts (tautomerism) rapidly and easily, and the chemical reactivity of the two isomers may be quite different. The AM1 calculations were carried out with the help of MOPAC7 program package[9]. According to data, we obtained by semi-empirical calculation methods (AM1), between **2A** and **2B** tautomers (for **2a)** the structure of amino form **2B** was found to be more stable than that of **2A**. It was calculated that the formation energies of **2A** and **2B** are 83.38 and 74.13 kcal mol^{-1}, respectively (The difference is about 8.130 kcal mol^{-1}.) The compound **2B** can also exist in two different configurations, as **(E)-2B** or **(Z)-2A** isomers, at the C=N double bond[8]. Our calculations have revealed that the energy difference between **(E)-2B** and **(Z)-2B** isomers is 0.1 kcal mol^{-1}. Torsion angle of C_1—C_2—N_3—N_4 at **(E)-2B** and **(Z)-2A** isomers is calculated to be −175.9 and 2.5 degree, respectively (Fig. 3).

In continuation of our interest in the chemical versatility of **1**, we determined that it represents easily accessible building blocks for the synthesis of heterocyclic systems. In compound **1**, the carbon atoms C_2 (0.2378 e^-), C_3 (0.2730 e^-) and C_5 (0.2271 e^-) represent electrophilic sites of different reactivity and could be used

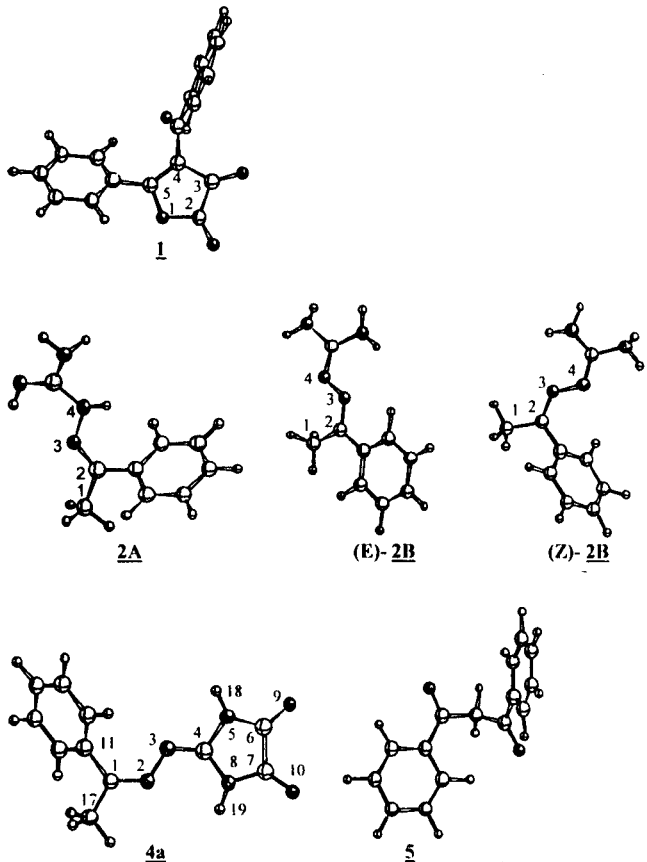
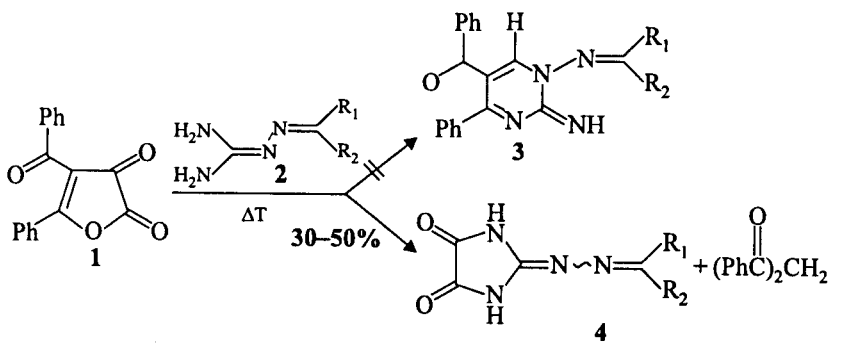


Fig. 3. Atom-numbering scheme and structures of **1, 2A, (E)-2B, (Z)-2B, 4a** and **5.**

for the construction of new heterocyclic systems upon reaction with ambidentate nucleophiles. In this work, we would like to present our findings during the course of synthesizing the imidazoles, as well as further investigations of their electronic structures. It was observed that guanylhydrazones (for **2a** $\Delta H_f = 74.13$ kcal mol^{-1}) reacted with the oxalyl group of **1**, which was obtained from the reaction of dibenzoylmethane **5** ($\Delta H_f = -19.90$ kcal mol^{-1}) with oxalyl chloride[1a] and imidazoles **4a–d** derivatives and dibenzoylmethane were formed (**Scheme-1**). The structures of **4a–d** are confirmed by elemental analysis, IR, ^1H nmr and ^{13}C nmr spectroscopic data. In the IR spectrum of **4a**, the absorption bands at 1760 and 1690 cm^{-1} are assigned to the carbonyl (C=O) and imine groups (C_2=N), respectively. In the ^{13}C-nmr spectrum, the signal due to C=O and C_2=N —N= appeared at 164 (s) and 160 (s) ppm, respectively.



2, 4	R_1	R_2
a	CH_3	C_6H_5
b	H	C_6H_5
c	H	$C_6H_4(CH_3)$-*p*
d	H	$C_6H_4(OCH_3)$-*p*

Scheme-1

Amongst the synthesized compounds, the possible tautomer structure of **4a** was examined and the formation energy values for the imidazole systems are presented in Fig. 2. It was found that the keto form is more stable than the other structures given in Fig. 2. It is clear that the semi-empirical calculations are in agreement with the spectroscopic measurements. The problem of elucidating relationships between structure and biological activity of chemical compounds (in terms of their electronic features) seems to be most important for both theoretical researches and applications. In this paper, the results of quantum chemical investigations are discussed and used to obtain data sets and needed for activity prediction Such data sets have been applied successfully to drug design before[9]. The results of the calculation (heat of formation energy, ΔH_f, kcal mol^{-1}, dipole moment, μ, debye, HOMO and LUMO orbital enegies, eV for **4a–d**) are given in Table-1. The greatest negative charge (Table-2) is concentrated on

TABLE-1
CALCULATED HEAT OF FORMATION (ΔH_f, kcal mol^{-1}), DIPOLE MOMENTS, (μ, DEBYE), SELECTED STRUCTURAL DATA FOR **4a–d**

Bonds	4a	4b	4c	4d	Bond angles	4a	4b	4c	4d
C_1—N_2	1.3097	1.2990	1.2986	1.2990	C_1—N_2—N_3	120.5	122.8	122.7	122.9
N_3—N_2	1.3384	1.3366	1.3373	1.3364	N_2—N_3—C_4	118.5	118.6	118.3	118.2
C_4—N_3	1.3255	1.3280	1.3280	1.3272	N_3—C_4—N_8	130.9	130.8	130.8	130.7
N_5—C_6	1.4026	1.4034	1.4034	1.3997	C_4—N_5—C_6	110.4	110.7	110.7	110.7
N_5—H_{18}	0.9889	0.9888	0.9886	0.9891	C_6—C_7—O_{10}	127.7	127.7	128.3	128.3
C_6—O_9	1.2271	1.2268	1.2269	1.2276	C_4—N_5—H_{18}	123.0	123.1	123.1	123.2
C_6—C_7	1.5511	1.5509	1.5506	1.5510	N_2—C_1—C_{11}	127.5	134.6	135.1	134.5
C_7—O_{10}	1.2275	1.2272	1.2273	1.2267	$H(C)_{17}$—C_1—N_2	118.7	111.3	111.1	111.3
N_8—H_{19}	0.9889	0.9892	0.9890	0.9887	H_{18}—N_8—C_4	123.2	123.2	123.1	123.0
N_8—C_4	1.4339	1.4330	1.4326	1.4323	**Torsion angles**				
C_1—$C_{17}(H_{17})$	1.5013	1.1157	1.1166	1.1153	C_4—N_3—N_2—C_1	–165.7	–177.8	–177.8	–178.4
C_1—C_{11}	1.4779	1.4616	1.4603	1.4593	N_5—C_4—N_3—N_2	–177.7	–179.9	–180.0	–179.8
ΔH_f (kcal/mol)	36.5000	41.2000	33.5000	2.9000	N_8—C_4—N_3—N_2	3.3	0.1	0.1	0.1
HOMO eV	–9.2360	–9.1881	–8.9951	–8.8816	C_6—N_5—C_4—N_3	–178.9	–179.1	–179.6	–179.3
LUMO eV	–0.9830	–1.1452	–1.1192	–0.3603	O_9—C_6—N_5—C_4	179.5	179.8	179.7	179.6
DM (debye)	4.8100	4.5800	4.9400	5.8500	C_7—C_6—N_5—C_4	–0.6	–0.1	–0.4	–0.6
					O_{10}—C_7—C_6—N_5	–179.3	–179.6	–179.5	–179.5

TABLE-2
EFFECTIVE ATOMIC CHARGES (Qi) CALCULATED (ELECTRON CHARGE UNIT)

Atoms	4a	4b	4c	4d
C_1	0.0487	0.0025	0.0043	0.0107
N_2	–0.1509	–0.1550	–0.1561	–0.1618
N_3	–0.1960	–0.2093	–0.2084	–0.2074
C_4	0.2429	0.2510	0.2491	0.2483
N_5	–0.3454	–0.3470	–0.3470	–0.3476
C_6	0.2944	0.2940	0.2942	0.2948
C_7	0.2939	0.2944	0.2941	0.2939
N_8	–0.3654	–0.3622	–0.3619	–0.3618
O_9	–0.2491	–0.2464	–0.2471	–0.2471
O_{10}	–0.2513	–0.2486	–0.2494	–0.2505
$H(C)_{17}$	–0.1824	0.1487	0.1474	0.1469
C_{11}	–0.1344	–0.0959	–0.1019	–0.1330
C_{12}	–0.1969	–0.1046	–0.1002	–0.2146
C_{14}	–0.1356	–0.1394	–0.1413	–0.1723
C_{15}	–0.1180	–0.1085	–0.0461	0.1017

N_5, N_8, O_9 and O_{10}. C_4, C_6 and C_7 bear positive charges. It is also seen that a small positive charge is on C_1. This is due to the ability of phenyl ring of stronger polarization of the nearby atoms and bonds. The analysis of the electron density distributions on bonds is given in Table-3 in the form of the Wiberg's indices

TABLE-3
CALCULATED WIBERG'S INDICES (W_{ij})

Bond	4a	4b	4c	4d
C_1—N_2	1.8006	1.8111	1.8109	1.8060
N_3—N_2	1.0643	1.0631	1.0620	1.0623
C_4—N_3	1.6678	1.6562	1.6582	1.6599
N_5—C_4	1.0314	1.0226	0.9952	0.9966
C_6—N_5	1.0233	1.0314	1.0326	1.0339
C_7—C_6	0.8131	0.8130	0.8132	0.8131
N_8—C_7	1.0326	1.0314	1.0195	1.0200
N_8—C_4	0.9926	0.9973	1.0223	1.0214
O_9—C_6	1.8592	1.8625	1.8560	1.8547
O_{10}—C_7	1.8544	1.8571	1.8619	1.8621
$H(C_{17})$—C_1	0.9767	0.9252	0.9253	0.9256
N_{18}—N_5	0.8663	0.8656	0.8658	0.8656
H_{19}—N_8	0.8663	0.8656	0.8670	0.8670
C_{11}—C_1	0.9671	1.0050	1.0058	1.0101

(W_{ij}). Index W_{ij} may be considered as quantum-chemical analogue of the bond (i–j) multiplicity and characterizes the strength of the bond. The structures of the HOMOs and LUMOs are given in Table-4. The LCAO coefficient analysis has shown that the nature of these MOs is determined by the $2p_z$-orbitals of the atoms belonging to the imidazol ring and C_1—N_2—N_3—C_4 atoms (Table-4). As a rule, the orbitals of negatively charged atoms form HOMO and the orbitals of positively charged atoms form LUMO. Therefore a molecule will demonstrate donor (acceptor) features when participating in the reaction by the HOMO (the LUMO).

TABLE-4
MAIN ORBITAL COMPONENTS AND HOMO-LUMO ENERGIES OF COMPOUNDS **4a–d**

4a $E_{HOMO} = -9.24$ eV

$\Psi_{HOMO} = 0.36p_zC_1 + 0.34p_zN_2 - 0.43p_zN_3 - 0.28p_zC_4 + 0.25p_zN_5 + 0.25p_zN_8 - 0.19p_zC_{11}$

$E_{LUMO} = -0.98$ eV

$\Psi_{LUMO} = 0.35p_zC_1 - 0.20p_zN_2 - 0.29p_zN_3 + 0.42p_zC_4 - 0.37p_zC_6 - 0.37p_zC_7 + 0.31p_zO_9 + 0.31p_zO_{10}$

4b $E_{HOMO} = -9.18$ eV

$\Psi_{HOMO} = -0.33p_zC_1 - 0.36p_zN_2 - 0.40p_zN_3 + 0.28p_zC_4 - 0.23p_zN_5 - 0.23p_zN_8 + 0.35p_zC_{11}$

$E_{LUMO} = -1.15$ eV

$\Psi_{LUMO} = -0.36p_zC_1 + 0.24p_zN_2 + 0.27p_zN_3 - 0.44p_zC_4 + 0.35p_zC_6 + 0.34p_zC_7 - 0.29p_zO_9 - 0.29p_zO_{10}$

4c $E_{HOMO} = -9.00$ eV

$\Psi_{HOMO} = -0.30p_zC_1 + 0.35p_zN_2 - 0.36p_zN_3 - 0.26p_zC_4 - 0.21p_zN_5 + 0.21p_zN_8 - 0.37p_zC_{11}$

$E_{LUMO} = -1.19$ eV

$\Psi_{LUMO} = 0.36p_zC_1 - 0.23p_zN_2 - 0.27p_zN_3 + 0.44p_zC_4 - 0.35p_zC_6 - 0.34p_zC_7 + 0.30p_zO_9 + 0.29p_zO_{10}$

4d $E_{HOMO} = -8.88$ eV

$\Psi_{HOMO} = -0.25p_zC_1 - 0.31p_zN_2 + 0.34p_zN_3 + 0.24p_zC_4 - 0.18p_zN_5 - 0.18p_zN_8 + 0.41p_zC_{11}$

$E_{LUMO} = -1.10$ eV

$\Psi_{LUMO} = -0.36p_zC_1 + 0.23p_zN_2 + 0.28p_zN_3 - 0.44p_zC_4 + 0.34p_zC_6 + 0.35p_zC_7 - 0.29p_zO_9 - 0.30p_zO_{10}$

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined by use of Büchi melting point apparatus and not corrected. Microanalyses were performed on a Carlo Erba elemental analyser Model 1108. The IR spectra were obtained as potassium bromide pellet using a Shimadzu Model 435 V-04 spectrometer. The ^1H and ^{13}C-nmr spectra were recorded on a Varian X 4200 Gemini spectrophotometer using tetramethysilane as an internal standard. All experiments were followed by

TLC using DC Alufolion kieselgel 60 GF 254 Merck and with a Model Camag TLC lamp (254/366 nm).

Synthesis of 2H-imidazol-4,5(1H,3H)dione (4): General Procedures

Method A. An equimolar mixture of **1** and the corresponding guanylhydrazones **2** was heated to 115–120°C for 15 min without any solvent. After cooling to room temperature the residue was treated with dry ether and so formed crude product crystallized from a suitable solvent (ethanol and acetic acid).

Method B. The equimolar mixture of the reactants (1 + 2) was refluxed in boiling toluene for 3–4 h. After evaporation the oily residue was worked up as described in Method A.

2-(1-Phenylethyliden)-hydrazono-2H-imidazol-4,5(1H,3H)dione (4a)

1.0 g **1** and 0.56 g **2a** (molar ratio 1/1) were refluxed in boiling toluene for 3 h and after the cooling procedure, the precipitate was collected yielding 0.34 g (40%) of **4a**, m.p. 243°C (from dry acetic acid and ethanol); IR (KBr, cm^{-1}): 3100 ν(NH), 1785 ν(CO). ^1H nmr (DMSO-d_6); δ = 11.64 (broad, NH), 7.10–7.90 (m, 5H, aromatic), 8.30 (s, —N=C—H), 2.39 (3H, CH_3); ^{13}C nmr (DMSO): δ 164.00 (s, C=O), 160.50 (s, N—C=N), 150.01 (s, Ar—C=N), 132.00–128.35 (aromatic C), 15.30 (q, CH_3) ppm. Anal., Cal. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34; found: C, 57.59; H, 4.44: N, 24.42.

2-(1-Phenylmethyliden)-hydrazone-2H-imidazol-4,5(1H,3H)dione (4b)

1.12 g **1** and 0.64 g **2b** (molar ratio 1/1) were refluxed in boiling toluene for 4 h. After cooling the precipitate was collected yielding 0.44 g (50%) of **4b**, m.p. 280°C (from dry acetic acid and ethanol); IR (KBr, cm^{-1}): 3410 ν(NH), 1785 ν(CO). ^1H nmr (DMSO-d_6): 11.99 (broad, NH), δ = 7.10–7.90 (m, 5H, aromatic), 8.30 (s, —N=C—H), ppm; Anal., Cal. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92; found: C, 55.48; H, 3.81; N, 25.78.

2-(4-Methylphenylmethyliden)-hydrazone-2H-imidazol-4,5 (1H,3H)dione (4c)

3.16 g **1** and 2.0 g **2c** (molar ratio 1/1) were refluxed in boiling toluene for 3 h. After cooling the precipitate was collected yielding 1.06 g (40%) of **5c**, m.p. 290°C (from dry acetic acid and ethanol); IR (KBr, cm^{-1}): 3400 ν(NH), 1780 ν(C=O). Anal. Cal. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34; found: C, 57.32; H, 4.37; N, 24.34.

2-(4-Methoxyphenylmethyliden)-hydrazone-2H-imidazol-4,5(1H,3H)dione (4d)

2.78 g **1** and 1.92 g **2d** (molar ratio 1/1) were refluxed in boiling toluene for 3 h. After cooling the precipitate was collected yielding 0.68 g (28%) of **4d**, m.p. 288°C (from dry acetic acid and ethanol); IR (KBr, cm^{-1}): 3400 ν(NH), 1780 ν(C=O). Anal., Cal. for $C_{11}H_{10}N_4O_3$: C, 53.65; H, 4.09; N, 22.76; found: C, 53.69; H, 4.08; N, 22.75.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to Dr. Ş. Patat and Arş. Gör. D. Ünal. This work was financially supported by Research Center of Erciyes University.

REFERENCES

1. (a) E. Ziegler, M. Eder, C. Belegratis and E. Prewedourakis, *Monatsh. Chem.*, **98**, 2249 (1967); (b) E. Ziegler, G. Kollenz and H. Igel, *Monatsh. Chem.*, **102**, 1769 (1971); (c) G. Kollenz, C.O. Kappe and H.A. E-Nabe, *Heterocycles*, **32**, 669 (1991); (d) R.W. Saalfrank, T. Lutz, B. Hörner, J. Gündel, K. Peters and H.G. von Schnering, *Chem. Ber.*, **124**, 2289 (1991).
2. (a) G. Kollenz, G. Penn, G. Dolenz, Y. Akçamur, K. Peters, E.M. Peters and H.G. von Schnering, *Chem. Ber.*, **117**, 1299 (1984); (b) G. Kollenz G. Penn, W. Ott, K. Peters, E.M. Peters and H.G. von Schnering, *Heterocyclic*, **26**, 625 (1987); (c) G. Kollenz, H. Sterk and G. Hutter, *J. Org. Chem.*, **56**, 235 (1991); (d) E. Terpetschnig, G. Penn, G. Kollenz, K. Peters, E.M. Peters and H.G. von Schnering, *Tetrahedron*, **47**, 3045 (1991); (e) G. Kollenz, E. Ziegler, W. Ott and H. Igel, Z. *Naturforsch*, **31b**, 1511 (1976); (f) W. Ott, E. Ziegler and G. Kollenz, *Synthesis*, **7**, 477 (1976); (g) Y. Akçamur, A. Sener A.M. Ipekoğlu and G. Kollenz, *J. Heterocyclic Chem.*, **34**, 221 (1997).
3. (a) Y. Akçamur, B. Altural, E. Saripinar, G. Kollenz, C.O. Kappe, E.M. Peters and H.G. von Schnering, *J. Heterocyclic Chem.*, **25**, 1419 (1988); (b) B. Altural, Y. Akçamur, E. Saripinar, I. Yildirim and G. Kollenz, *Monatsh. Chem.*, **120**, 1015 (1989).
4. (a) İ. Yildirim, E. Saripinar, Y. Güzel, Ş. Patat and Y. Akçamur, *J. Mol. Struct.*, **334**, 165 (1995); (b) E. Saripinar, İ. Yildirim, Y. Güzel and Y. Akçamur, *Monatsh. Chem.*, **127**, 505 (1996); (c) İ. Yildiri, M. Tezcan, Y. Güzel, E. Saripinar and Y. Akçamur, *Tr. J. Chem.*, **20**, 27 (1996).
5. B. Altural, Y. Akçamur and G. Kollenz, *Organic Preparations and Procedures Int.*, **23**, 147 (1991).
6. (a) C.A. Higley, R.G. Wilde, T.P. Maduskuie, A.L. Johnson, P. Pennev, J.T. Billheimer, C.S. Robinson, P.J. Gillies and R.R. Wexler, *J. Med. Chem.*, **37**, 3511 (1994); (b) D.P. Matthews, J.R. McCarthy, J.P. Whitten, P.R. Kastner, C.L. Barney, F.N. Marshall, M.A. Ertel, T. Burkhard, P.J. Shea and T. Kariya, *J. Med. Chem.*; B.J. Burke and A.J. Hopfinger, *J. Med. Chem.*, **33**, 274 (1990).
7. J. Thiele, *Liebigs Ann. Chem.*, **1**, 270 (1892).
8. G. Zoltan, W. Holzer and K. Mereiter, *Monatsh. Chem.*, **130**, 899 (1999).
9. J.J.P. Stewart, MOPAC, Version 7.00, QCPE Program No. 455.
10. (a) E. Saripinar, Y. Güzel, Ş. Patat, I. Yildirim, Y. Akçamur and A. Dimoglo *Arzneim-Forsch/Drug Res.*, **46**, 824 (1996); (b) Y. Güzel, E. Saripinar and I. Yildirim, *Theo. Chem.*, **418**, 83 (1997); (c) I.B. Bersuker and A. Dimoglo, Reviews in Computational Chemistry-II, VCH Publlisher, Ch. 10, pp. 423–460 (1991).

(*Received*: 14 April 2004; *Accepted:* 25 August 2004) AJC-3543