

SYNTHESIS AND THEORETICAL CALCULATIONS OF THE 1*H*-PYRAZOLE-3-CARBOXAMIDE AND -3-CARBOXYLATE DERIVATIVES

Ismail Yıldırım¹ and Fatma Kandemirli^{2*}

¹Department of Chemistry, Erciyes University, TR -38039, Kayseri, Turkey

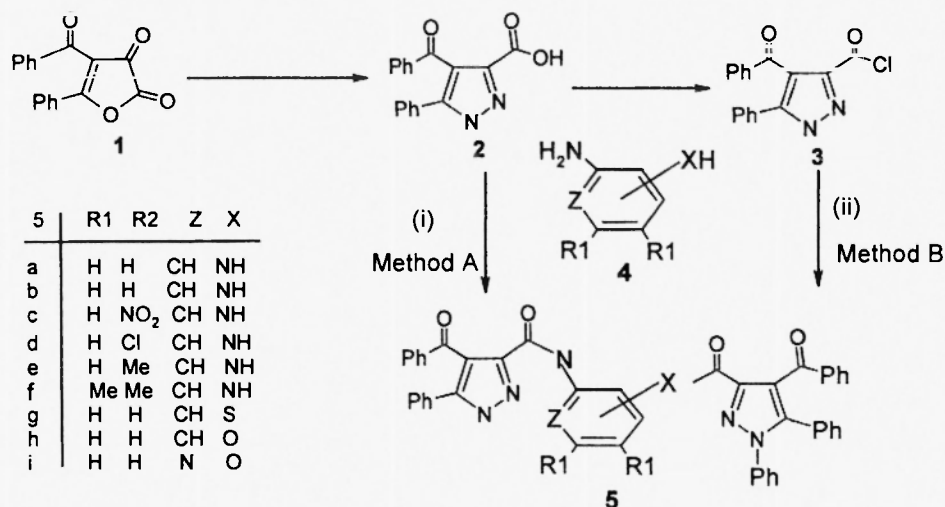
^{2*}Department of Chemistry, Kocaeli University, TR -41300, Izmit, Turkey

Abstract: The 1*H*-pyrazole-3-carboxylic acid **2** is obtained easily from the furan-2,3-dione **1** and phenylhydrazine and converted via reactions to its acid chloride **3** which reacts with various binucleophiles diamine derivatives **4a-i** and gives the corresponding 1*H*-pyrazole-3-carboxamides and -3-carboxylates **5a-i** in good yields (50-90 %). The structures of all new synthesized compounds were determined with the ¹³C NMR, ¹H NMR, IR, MS spectroscopic data and elemental analyses. Most of them were compared with their previously obtained analogues. The electronic structures of the reactants, their transition states, intermediate states and final products of the reactions were investigated on the base of the AM1 method.

Introduction

The chemistry of furan-2,3-diones which belong to an important group of oxygen-containing heterocyclic starting materials has been widely explored in general during the last few decades [1-4]. The cyclocondensation reactions of 1,3-dicarbonyl compounds with oxalyl chloride represent a convenient synthesis of furan-2,3-dione systems [5,6]. In particular, derivatives of such vicinal-dione compounds have been found to serve as versatile synthons in (a) thermolysis reactions [7-12] (b) cycloaddition reactions [13-19] and (c) reactions with nucleophiles [20-22]. A convenient method for the synthesis, the mechanism of reactions and semiempirical (AM1) calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) with several semicarbazones, ureas, thioureas and oximes have been reported recently [23-28]. The reaction of the furan-2,3-dione **1** with various phenyl-hydrazones and phenylhydrazine leads to pyrazole-carboxylic acid **2** and pyridazinones [29-31].

Pyrazole derivatives are well-known nitrogen-containing heterocyclic compounds, and various procedures have been developed for their syntheses [32-35]. The chemistry of pyrazole derivatives continues to attract interest due to a wide spectrum of their potential biological and pharmacological activities such as anti-microbial, anti-viral, anti-tumor, anti-fungal, pesticidal, anti-convulsant, anti-depressant ones [36-43]. For these reasons, in this study we attempted both to prove reproducibility of the reaction of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **2** with various binucleophiles **4** and to extend our investigations related to the preparation of new heterocycles possessing one or two pyrazole rings in their structure. In this paper we report the synthesis and characterization of the 1*H*-pyrazole-3-carboxamides and -3-carboxylates **5a-i** obtained from the reaction of the pyrazole-3-carboxylic acid **2** or the pyrazole-3-carboxylic acid chloride **3** with the corresponding diamine or aminophenol derivatives **4a-i** such as substituted 1,2-phenylenediamines and 2-aminophenols or 2-aminothiophenols reagents (Scheme-1). The reaction pathways leading to the compounds **5** are discussed, too. To probe the electron structure of reagents, products, and transition and intermediate states as well, quantum-chemical calculations were carried out.



Scheme-1

To clear up the mechanism of the reactions of 1*H*-pyrazole-3-carboxylic acid **2** with diamine derivatives **4a-j**, we carried out quantum-chemical calculations related to the main steps of the reaction. These calculations were done by means of semi-empirical method AM1 with full geometry optimization for reactants, intermediates and products. Calculation of vibration frequencies was performed for transition molecules, and negative imaginary frequencies were found for transitional states. This means that the structure is a true transition state; thus, we can determine if the structure connects the correct reactants and products, by examining its imaginary frequency being the result of an intrinsic reaction coordinate (IRC) calculation. AM1 calculations were carried out by means of the GAUSSIAN 98W program package (Version 6.0 Rev B.04) [44].

Results and Discussion

The compounds of substituted furan-2,3-dione **1** and 1*H*-pyrazole-3-carboxylic acid **2**, as well as 1*H*-pyrazole-3-carboxylic acid chloride **3**, which are used as important initial materials in the synthesis of the target heterocycles, were prepared using the literature procedures [1-3, 29, 30], as shown in Scheme-1. The reaction of two-fold molar excess of the compounds **2** or **3** with some diamines or aminophenols **4** led to the formation of the corresponding dicarboxamide or amide-ester derivatives **5** in good yields (65-90 %), without opening the pyrazole ring. All the reactions were performed in boiling benzene, toluene or xylene under reflux for 4-14 hours, by the usual chemical methods (for details see the Experimental). Addition of binucleophiles to the acid **2** or acid chloride **3** usually starts with nucleophilic attack at the acid or acid chloride moieties in compounds **2** or **3**. Therefore, from the sequential attacks of the diamine or aminophenol at the acid chloride moieties of two respective molecules of **3**, followed by elimination of hydrogen chloride (or by elimination of water, in the case of compound **2**), new products **5a-i** arise. The structures of the compounds **5** were confirmed by IR and NMR spectroscopic techniques, besides the elemental analysis. These results are in full agreement with those obtained for substituted 1*H*-pyrazole-3-carboxamides and -3-carboxylates [29-31]. In the first experiment, product **5a** was obtained in 85 % yield by treating **3** with 1,2-phenylenediamine (**4a**) and

refluxing in boiling benzene for 12 hours. The formation of **5a** was affirmed by the results of both analytical and spectroscopic measurements (by the presence of four carbonyl characteristic absorption bands FT-IR: 1702, 1686, 1670, 1659 cm^{-1}). The broad absorption bands of NH groups were at 3376 and 3235 cm^{-1} [29-31,44], and skeleton bands related to benzene or pyrazole rings with NH bending vibrations were observed at 1600, 1590, 1546, 1520, 1500, 1489, 1460 cm^{-1} (C=C, C=N). Important structural information about **5a** can be obtained from its ^{13}C NMR spectrum. The ^{13}C NMR peaks were found to be at 193.60 (t, $J = 4.3$ Hz, PhCO), 161.34 (s, HNCO), 147.10 (s, C_3 , C_3), 145.80 (t, $J = 4.6$ Hz, C_5 , C_5), 141.01, 140.16 (N-Ph), 134.99, 132.12, 131.83, 131.50, 131.23, 131.04, 130.53, 130.26, 128.09, 127.28 (C-Ph) and 124.53 ppm (s, C_4 , C_4). Final confirmation of structure **5a** was derived from its ^1H NMR spectrum: $\delta = 9.43$ ppm (s, broad, NH) and 7.90-7.13 ppm are a set of signals for aromatic protons [45]. Structural data for these compounds **5** are depicted in Table-1.

Conformational and electron characteristics of reagents and intermediate product that have been calculated with AM1 method are given in Table-2. Reaction mechanism of 1H-pyrazole-3-carboxylic acid **2a** with amine group of o-phenylenediamine **4a** and formation of intermediate product **5a(I)** are given in Figure-1. Reaction mechanism of intermediate product **5a(I)** with 1H-pyrazole-3-carboxylic acid **2a** and the structure of the obtained **5a** product are given in Figure 2. Bond distances and Mulliken atomic charges are given in Table-3.

Table-1 : Spectroscopic data of 1H-pyrazole-3-carboxamides and -3-carboxylates **5a-i**

Compd.	IR (KBr): δ (cm^{-1})	^1H NMR(CDCl_3): δ (ppm)	^{13}C NMR (CDCl_3): δ (ppm)
5a	3376, 3235 (b, NH), 1702, 1686, 1670, 1659 (s, CO)	9.43 (s, 2H, NH), 7.90-7.13 (m, 34H, Ar-H)	193.60 (t, $J=4.3$ Hz, PhCO), 161.34 (s, CON), 147.10 (s, C-3, C-3'), 145.80 (t, $J=4.6$ Hz, C_5 , C_5), 141.01-127.28 (C-Ph), 124.53 (s, C_4 , C_4)
5b	3425, 3233 (b, NH), 1684, 1652, 1640 (s, CO), 1598, 1512, 1480 (C=C, C=N, arom. rings, NH bend)	(d_6 -DMSO): 10.46 (s, 2H, NH), 7.82-7.18 (m, 34H, Ar-H)	(d_6 -DMSO): 192.48 (t, $J=4.2$ Hz, PhCO), 160.85 (s, CON), 147.52 (s, C_3 , C_3), 145.15 (t, $J=4.7$ Hz, C_5 , C_5), 140.32, 139.41 (N-Ph), 136.03-127.86 (C-Ph), 123.39, 122.25 (s, C_4 , C_4)
5c	3380, 3274 (b, NH), 1699, 1679, 1661 (s, CO), 1596, 1579, 1527, 1461 (C=C, C=N), 1500, 1326 (asym. and sym. N=O)	9.88 (s, 1H, NH), 9.54 (s, 1H, NH), 8.42-7.17 (m, 33H, Ar-H)	193.53 (t, $J=4.4$ Hz, PhCO), 161.89, 161.24 (s, CON), 146.62 (s, C-NO ₂), 146.37, 146.32 (s, C_3 , C_3), 146.24, 146.14 (t, C_5 , C_5), 140.79, 139.87, 139.41 (N-Ph), 135.25-124.50 (C-Ph), 123.84, 123.42 (s, C_4 , C_4)
5d	3378, 3326 (b, NH), 1691, 1678, 1667 (s, CO), 1617, 1595, 1581, 1530, 1454 (C=C, C=N, arom. rings, NH bend)	9.47 (s, 1H, NH), 9.38 (s, 1H, NH), 7.87-7.09 (m, 33H, Ar-H)	193.79, 193.74 (PhCO), 161.43, 161.27 (s, CON), 146.73, 146.65 (s, C_3 , C_3), 145.89 (t, $J=4.9$ Hz, C_5 , C_5), 140.83, 139.90 (N-Ph), 135.26-126.71 (C-Ph), 124.44, 124.38 (s, C_4 , C_4)
5e	3390, 3260 (b, NH), 1700, 1685, 1667, 1655, (s, CO), 1590, 1578, 1510, 1460 (C=C, C=N, arom. rings, NH bend)	9.40 (s, 1H, NH), 9.30 (s, 1H, NH), 7.88-6.92 (m, 33H, Ar-H), 2.26 (s, 3H, CH ₃)	193.62 (t, $J=4.3$ Hz, PhCO), 161.37, 161.23 (s, CON), 147.17 (s, C_3 , C_3), 145.77, 145.71 (t, C_5 , C_5), 141.01, 140.16 (N-Ph), 138.27-128.73 (C-Ph), 127.28, 124.51 (s, C_4 , C_4), 22.90 (s, CH ₃)
5f	3368, 3331 (b, NH), 1700, 1680, 1667, 1657, (s, CO), 1596, 1582, 1526, 1499, 1461 (C=C, C=N, NH bend)	9.28 (s, 2H, NH), 7.88-7.20 (m, 32H, Ar-H), 2.18 (s, 6H, CH ₃)	193.64 (t, $J=4.3$ Hz, PhCO), 161.23 (s, CON), 147.24 (s, C_3 , C_3), 145.65 (t, $J=4.8$ Hz, C_5 , C_5), 141.04, 140.16 (N-Ph), 136.67-129.59 (C-Ph), 127.98, 127.26, 124.47 (s, C_4 , C_4), 21.23 (s, CH ₃)
5g	3323 (b, NH), 1689, 1668 (s, CO), 1597, 1582, 1531, 1496, 1446 (C=C, C=N, arom. rings)	9.60 (s, 1H, NH), 8.42-7.13 (m, 34H, Ar-H)	193.26 (t, $J=4.4$ Hz, PhCO), 184.22 (s, COS), 160.32 (s, CON), 147.03, 146.16 (C_3 , C_3 , C_5 , C_5 exchangeable) 141.94, 140.00 (N-Ph), 138.82-126.23 (C-Ph), 124.18, 123.85 (s, C_4 , C_4), 116.91, 114.47, 104.84
5h	3425 (b, NH), 1721, 1655 (s, CO), 1596, 1535, 1496, 1474 (C=C, C=N, arom. rings)	9.66 (s, 1H, NH), 8.29-7.10 (m, 34H, Ar-H)	193.82 (Ph-C=O), 163.02 (OCO), 161.20 (CON), 147.15, 146.46 (C_3 , C_3 , C_5 , C_5 exchangeable), 141.68, 140.83 (N-Ph), 138.12-125.28 (C-Ph), 124.26, 123.96 (C_4 , C_4), 114.76, 105.08
5i	3447 (b, NH), 1733, 1663 (s, CO), 1596, 1580, 1548, 1499, 1461 (C=C, C=N, arom. rings)	9.69 (s, 1H, NH), 8.32-7.15 (m, 33H, Ar-H)	193.69 (PhCO), 167.12 (O-C=O), 161.52 (CON), 158.22 (C-2', pyr.), 147.28, 146.52, 145.73 (C_3 , C_3 , C_5 , C_5 exchangeable) 142.04, 141.40 (N-Ph), 138.16-125.25 (C-Ph), 124.92, 124.64 (C_4 , C_4), 114.26, 111.83

Table-2 : Conformational and electron characteristics of reagents and intermediate product.

	Molecular Parameters	2-4(a)	TS1	5a(I)		Molecular Parameters	2-4(a)	TS1	5a(I)
INTERATOMIC DISTANCES (in Å)	N ₁₀ -C ₁₃	1.41	1.43	1.42	CHARGES (in electronic units e)	N ₂	-0.01	-0.05	-0.03
	N ₁₀ -H ₁₁	1.00	1.01	1.00		C ₃	-0.10	-0.10	-0.11
	N ₁₀ -H ₁₂	1.00	1.13	3.1		C ₄	-0.19	-0.19	-0.21
	C ₁₄ -N ₁₅	1.41	1.39	1.39		C ₆	0.45	0.40	0.46
	N ₁₅ -H ₁₈	1.00	1.00	0.99		O ₇	-0.39	-0.55	-0.42
	N ₁₅ -H ₁₇	0.99	0.99	0.99		O ₈	-0.36	-0.48	-0.49
	C ₆ -N ₁₀	4.21	1.55	1.37		H ₉	0.29	0.22	0.25
	C ₆ -O ₇	1.23	1.27	1.25		N ₁₀	ΔE	-0.13	-0.43
	C ₆ -O ₈	1.36	1.55	2.98		H ₁₁	0.25	0.21	0.32
	O ₈ -H ₁₂	0.97	0.96	0.96		H ₁₂	0.23	0.30	0.24
	O ₈ -H ₉	2.73	1.56	0.96		C ₁₃	0.02	-0.12	-0.02
	C ₆ -C ₃	1.46	1.49	1.48		C ₁₄	0.01	0.09	0.09
	C ₃ -C ₄	1.45	1.45	1.44		N ₁₅	-0.44	-0.37	-0.49
	C ₃ -N ₂	1.36	1.36	1.36		H ₁₆	0.24	0.22	0.28
	Frequencies (cm ⁻¹)	-	-1868	-		H ₁₇	0.22	0.18	0.25

Table-3 : Conformational and electron characteristics of reagents and products.

	Molecular Parameters	5a(I)-4a	TS2	5a		Molecular Parameters	5a(I)-4a	TS2	5a
INTERATOMIC DISTANCES (in Å)	C ₁₄ -N ₁₅	1.40	1.42	1.41	CHARGES (in electronic units e)	C ₄	-0.11	-0.12	-0.11
	N ₁₅ -H ₁₆	0.99	1.00	1.00		C ₆	0.46	0.38	0.46
	N ₁₅ -H ₁₇	0.99	1.62	2.98		O ₇	-0.38	-0.35	-0.36
	N ₁₅ -C ₁₈	3.84	1.53	1.38		N ₁₀	-0.46	-0.32	-0.47
	C ₁₈ -O ₁₉	1.23	1.27	1.24		H ₁₁	0.34	0.26	0.34
	C ₁₈ -O ₂₀	1.36	1.60	2.95		C ₁₂	0.01	0.08	0.07
	O ₂₀ -H ₂₁	0.97	0.98	0.96		C ₁₄	0.08	0.01	0.05
	O ₂₀ -H ₁₆	2.43	1.07	0.96		N ₁₅	-0.47	-0.37	-0.44
	C ₁₈ -C ₂₂	1.46	1.49	1.48		H ₁₆	0.26	0.32	0.24
	C ₂₂ -N ₂₃	1.36	1.36	1.36		H ₁₇	0.24	0.20	0.32
	C ₂₂ -C ₂₄	1.44	1.45	1.44		C ₁₈	0.45	0.42	0.46
	C ₁₂ -N ₁₀	1.41	1.41	1.40		O ₁₉	-0.37	-0.52	-0.39
	N ₁₀ -C ₆	1.37	1.38	1.38		O ₂₀	-0.37	-0.28	-0.48
	N ₁₀ -H ₁₁	1.00	1.00	1.00		H ₂₁	0.29	0.26	0.24
	C ₆ -O ₇	1.24	1.25	1.24		C ₂₂	-0.11	-0.11	-0.11
	C ₆ -C ₃	1.48	1.48	1.48		N ₂₃	-0.01	-0.06	-0.03
	Frequencies (cm ⁻¹)					C ₂₄	-0.19	-0.19	-0.20

Reaction mechanism may be divided into two stages. At the first stage C₆ atom of 1*H*-pyrazole-3-carboxylic acid 2a reacts with N₁₀ atom of one of amine groups of o-phenylenediamine 4a, and intermediate product 5a(I) is formed; at the second stage C₁₈ atom of another molecule of 1*H*-pyrazole-3-carboxylic acid reacts with the N₁₅ atom of amine group of the intermediate product 5(I).

As seen from Table 2, the intermediate product 4(I) is the results of the bond C₆-N₁₀ appearance, and transitional state TS1 is being formed under interatomic distances R_{C6-N10} = 1.55 Å, R_{N10-H11} = 1.01 Å, R_{N10-H12} = 1.13 Å, R_{C6-O8} = 1.55 Å, R_{O8-H9} = 1.56 Å. The intermediate product 4(I) is being formed under R_{C6-N10} = 1.37 Å, R_{N10-H11} = 1.00 Å, R_{N10-H12} = 3.10 Å, R_{C6-O8} = 2.98 Å, R_{O8-H9} = 0.96 Å. The negative charge on N₁₀ increases from -0.46 e to -0.43 e. The negative charge on N₁₅ decreases from -0.44 e to -0.49 e.

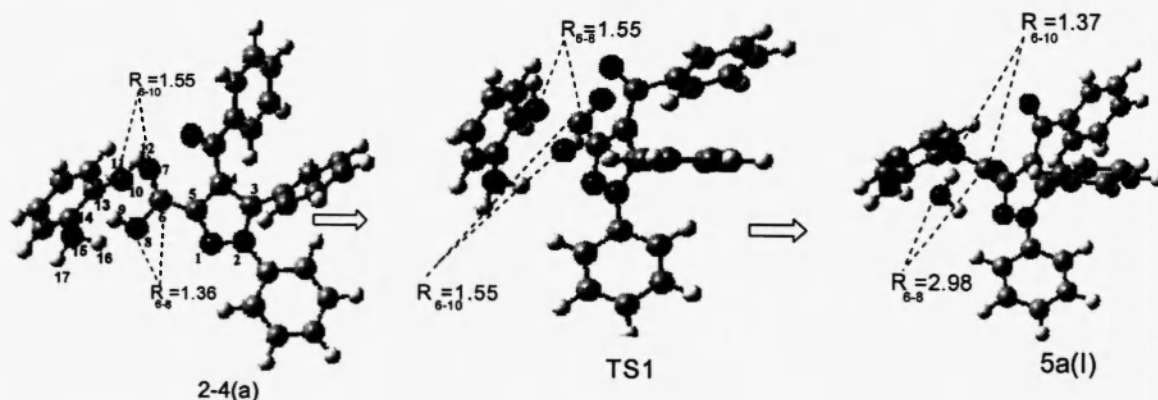


Figure-1 : Pathways of the reaction for the intermediate 5a(l)

At the second stage, product 5a is formed by the $N_{15}-C_1$ bond formation. The transitional state TS2 is being formed, its interatomic distances being $R_{N_{15}-C_{16}} = 1.53$ Å, $R_{N_{15}-H_{16}} = 1.00$ Å, $R_{N_{15}-H_{17}} = 1.62$ Å, $R_{C_{16}-O_{20}} = 1.60$ Å, $R_{O_{8}-H_{21}} = 0.98$ Å, $R_{O_{8}-H_{16}} = 1.07$ Å (see Table 3).

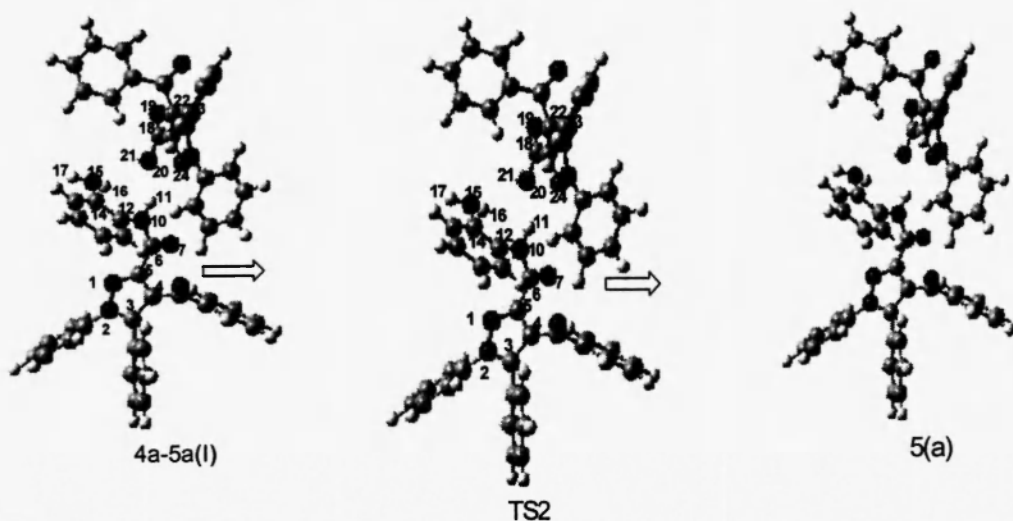


Figure-2 : Pathways of the reaction for product 5a

Transition states, IRC (intrinsic reaction coordinate) and RMS gradient along IRC for 5a, 5b, 5d, 5e products are given respectively in Figure3, in Figure 4, and Figure 5.

All reactions proceed through a strongly asynchronous transition state with the bond C_6-N_{10} formation at the first stage. $R_{C_6-N_{10}}$ bond's lengths for TS1 (b), TS1 (d), and TS1 (e) are 1.53, 1.55, 1.55 Å, respectively. After the C_6-N_{10} bond formation, significant lengthening of bonds $R_{C_6-O_7}$ and $R_{C_6-O_8}$ is observed. As soon as the $R_{C_6-O_7}$ bond equals to 1.22 Å for the reactant, same bond lengths become 1.28, 1.27, and 1.27 Å for TS1 (b), TS1 (d), and TS1 (e), while the C_6-O_8 bond lengths are equal to 1.52, 1.55, 1.56 Å respectively for TS1 (b), TS1 (d), and TS1 (e). For TS1 (d) and TS1 (e) the distance $R_{O_8-H_{11}}$ is equal to 1.13 Å. At the second stage, the $R_{C_{15}-N_{12}}$ bond is formed. For 5b, the $R_{C_{15}-N_{12}}$ bond length in

the transition state is 1.53 Å. After the C15-N12 bond formation, the lengths of the R_{C15-O22} and R_{C15=O16} bonds are equal to 1.26 Å and 1.62 Å, respectively.

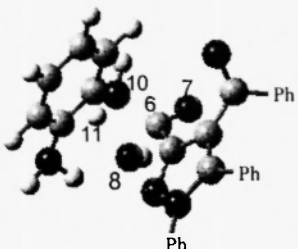
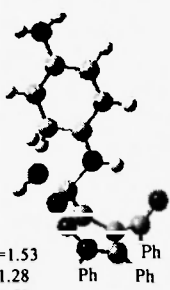
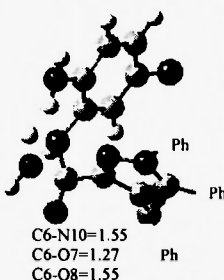
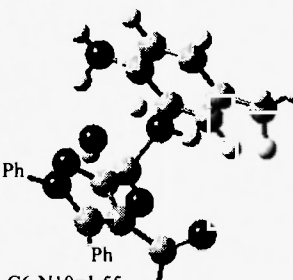
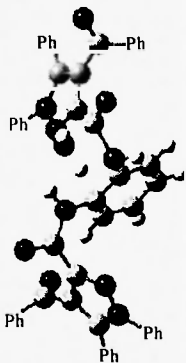
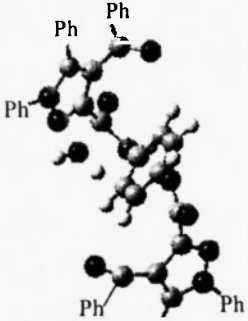
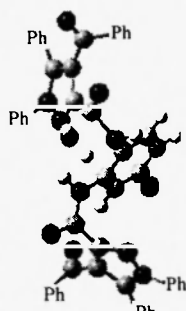
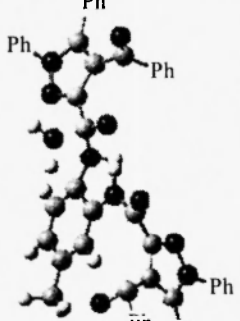
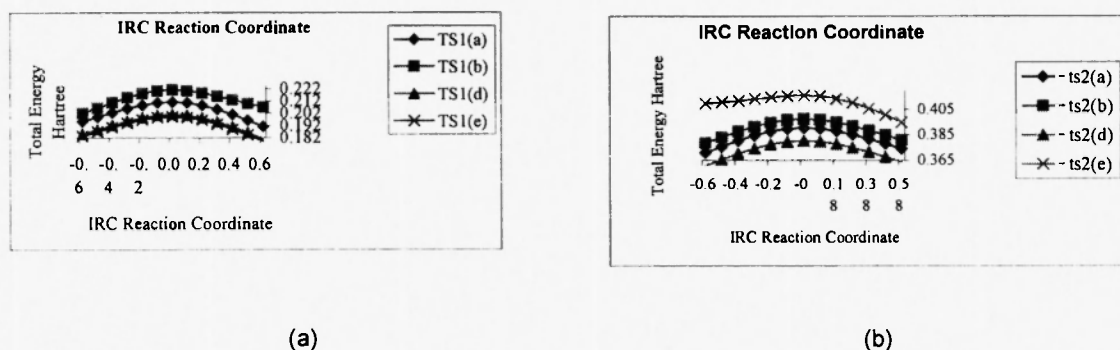
 C6-N10=1.53 C6-O7=1.28 C6-O8=1.52 O8-H11=1.63 N10-H11=2.60	 C6-N10=1.55 C6-O7=1.27 C6-O8=1.55 O8-H11=1.57 N10-H11=1.13	 C6-N10=1.55 C6-O7=1.27 C6-O8=1.56 O8-H11=1.56 N10-H11=1.13	 C6-N10=1.55 C6-O7=1.27 C6-O8=1.56 O8-H11=1.56 N10-H11=1.13
5a(I)	5b(I)	5d(I)	5e(I)
	 C15-N12=1.53 C15-O16=1.26 C15-O22=1.62 O22-H23=1.07 N12-H23=1.60	 C15-N12=1.54 C15-O16=1.27 C15-O22=1.59 O22-H23=1.07 N12-H23=1.62	 C15-N12=1.51 C15-O16=1.29 C15-O22=1.55 O22-H23=1.18 N12-H23=2.12
5a	5b	5d	5e

Figure-3 : Calculated (AM1) transition structures for reaction of 5a, 5b, 5d, 5e

Figure- 3 :

IRC option requests that a reaction path be followed [46, 47]. The geometry is optimized at each point along the reaction path such that the segment of the reaction path between any two adjacent points is described by an arc of a circle, and so that the gradients at the end points of the arc are tangent to the path. The path can be computed in mass-weighted internals, cartesian or internal coordinates. By default, an IRC calculation steps 6 points in mass-weighted internals in the forward direction and 6 points in the reverse direction, in steps of $0.1 \text{ amu}^{1/2} \text{ bohr}$ along the path. In Figure 5a, IRC reaction coordinates of TS1 and TS2 for 5(a), 5(b), 5(d) and 5(e) products are given. In Figure 5b, RMS gradient along IRC of TS1 and TS2 for 5(a), 5(b), 5(d) and 5(e) products are given as well.



Figur-4 : IRC Reaction Coordinates of TS1 and TS2 for 5(a), 5(b), 5(d) and 5(e) products

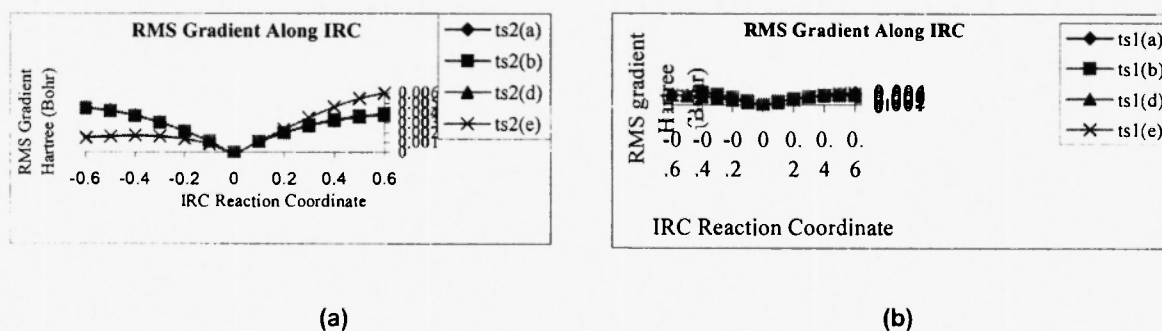


Figure-5. RMS gradient along IRC of TS1 and TS2 for 5(a), 5(b), 5(d) and 5(e) products

Energy characteristic of reactants, intermediates, transition states and product are given in Figure 6. As seen from Figure 6a, electronic energy for initial reagents 2 and 4a, TS1 and intermediate product of 5a(l) are respectively 0.981149 Hartree, 0.1913671 Hartree, and 0.1015897 Hartree. Electronic

energy for intermediate products **5a(l)** TS2, and **5a** are respectively 0.27500536 Hartree, 0.37420906 Hartree, and 0.28234948 Hartree.

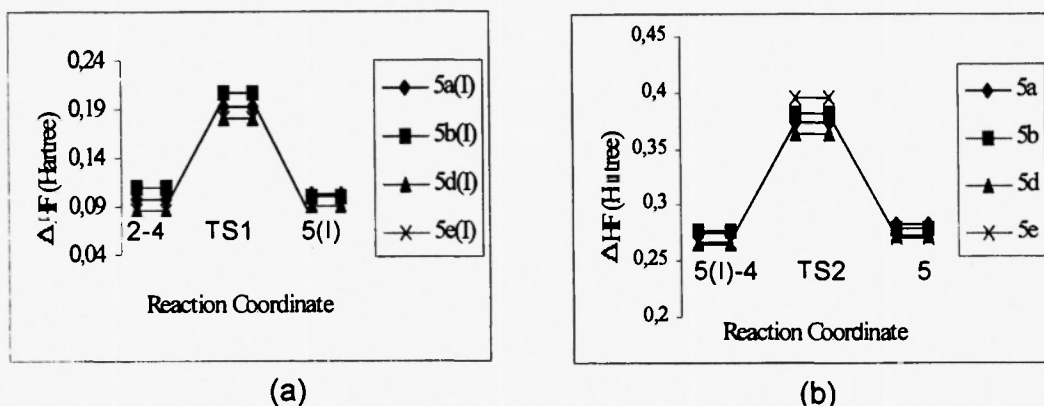


Figure-6 : ΔH for reactants, intermediates, transition states and products

Experimental

Melting points were determined on an Electrothermal 9200 apparatus; they were uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser Model 1108. The IR spectra were recorded on a Jasco FT-IR spectrometer model 460, using potassium bromide pellets. The ^1H and ^{13}C NMR spectra were obtained on Varian Gemini 200 instrument with TMS as internal standard. Mass spectra were measured on a Shimadzu GC/MS-QP 5050A spectrometer, using DI method with EI. After completion of the reactions, solvents were evaporated with rotary evaporator (Buchi RE model 111). All experiments were followed with TLC using DC Alufolien Kieselgel 60 F₂₅₄ Merck and Camag TLC lamp (254/366 nm). Solvents were dried by refluxing with the appropriate drying agent and distilled before use. All other reagents were purchased from Merck, Fluka, Aldrich, Sigma and Acros Chemical Co. and used without further purification.

Synthesis of the 1*H*-Pyrazole-3-carboxamides and -3-carboxylates **5a-j**.

General Procedures.

Method A. From 1*H*-Pyrazole-3-carboxylic Acid (**2**).

Appropriate amounts of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **2** (0.50 g, 1.80 mmoles), and the corresponding diamine or aminophenol derivatives **4** (molar ratio 2:1) were dissolved in benzene or toluene and heated by stirring under reflux together with catalytic amounts of sulfuric acid for 4-24 hours. Then the solution was cooled to 5°C in a refrigerator, and the corresponding reaction products **5** were either precipitated or obtained after evaporation of the solvent and triturating with ether or petroleum ether. After suction filtration, the crude products were re-crystallized from the proper solvent (methanol, ethanol, *n*-butanol or xylene) or washed with DMF or petroleum ether and cyclohexane for several times and dried on P₂O₅.

Method B. From 1*H*-Pyrazole-3-carboxylic Acid Chloride (**3**).

Appropriate amounts of the acid chloride 3 (0.50 g, 1.30 mmoles) and the corresponding diamine or aminophenol derivatives 4 (molar ratio 2:1) were dissolved in benzene or toluene and refluxed together with catalytic amounts of pyridine for 4-16 hours. After cooling, the solution was acidified by adding diluted hydrochloric acid to give crude products 5, and either re-crystallized from the suitable alcohol or washed carefully with DMF for several times and dried on P_2O_5 .

4-Benzoyl-1,5-diphenyl-*N*-(2-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)phenyl)-1*H*-pyrazole-3-carboxamide (5a).

This compound was obtained by the general procedure method B with a reflux time of 12 hours (*o*-phenylenediamine) resulting in a yield of 85 % (0.45 g); m.p. 267-268 °C (1-butanol). Anal. Calcd. for $C_{52}H_{36}N_6O_4$: C, 77.21; H, 4.49; N, 10.39. Found: C, 77.02; H, 4.42; N, 10.17.

4-Benzoyl-1,5-diphenyl-*N*-(4-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)phenyl)-1*H*-pyrazole-3-carboxamide (5b).

This compound was obtained from method B by the general procedure with a reflux time of 8 hours (*p*-phenylenediamine) resulting in a yield of 89 % (0.47 g); m.p. 357-358°C (DMF). Anal. Calcd. for $C_{52}H_{36}N_6O_4$: C, 77.21; H, 4.49; N, 10.39. Found: C, 76.98; H, 4.38; N, 10.32.

4-Benzoyl-1,5-diphenyl-*N*-(2-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)-4-nitrophenyl)-1*H*-pyrazole-3-carboxamide (5c).

This compound was obtained by the method B with a reflux time of 4 hours (4-nitro-1,2-phenylenediamine), and resulted in a yield of 80 % (0.44 g); m.p. 257-258 °C (xylene). Anal. Calcd. for $C_{52}H_{35}N_7O_6$: C, 73.14; H, 4.13; N, 11.48. Found: C, 73.19; H, 4.24; N, 11.27.

4-Benzoyl-1,5-diphenyl-*N*-(2-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)-4-chlorophenyl)-1*H*-pyrazole-3-carboxamide (5d).

This compound was obtained by the method B with a reflux time of 12 hours (4-chloro-1,2-phenylenediamine) resulting in a yield of 80 % (0.43 g); m.p. 240°C (methanol). Anal. Calcd. for $C_{52}H_{35}N_6O_4Cl$: C, 74.06; H, 4.18; N, 9.97. Found: C, 74.19; H, 4.12; N, 9.89.

4-Benzoyl-1,5-diphenyl-*N*-(2-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)-4-methylphenyl)-1*H*-pyrazole-3-carboxamide (5e).

This compound was obtained by the method A with a reflux time of 14 hours (4-methyl-1,2-phenylenediamine) resulting in a yield of 84 % (0.45 g); m.p. 234°C (ethanol). Anal. Calcd. for $C_{53}H_{38}N_6O_4$: C, 77.36; H, 4.65; N, 10.21. Found: C, 77.21; H, 4.72; N, 9.99.

4-Benzoyl-1,5-diphenyl-*N*-(2-(((4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)-4,5-dimethylphenyl)-1*H*-pyrazole-3-carboxamide (5f).

This compound was obtained by the method B with a reflux time of 7 hours (4,5-dimethyl-1,2-phenylenediamine) resulting in a yield of 82 % (0.45 g); m.p. 269-270°C (ethanol). Anal. Calcd. for $C_{54}H_{40}N_6O_4$: C, 77.50; H, 4.82; N, 10.04. Found: C, 77.32; H, 4.79; N, 9.92.

S-(2-(((4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)phenyl)-4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carbothioate (**5g**).

This compound was obtained by the method B with a reflux time of 4-5 hours (2-aminothiophenol) resulting in a yield of 43 % (0.23 g); m.p. 246°C (1-butanol). Anal. Calcd. for C₅₂H₃₅N₅O₄S: C, 75.62; H, 4.27; N, 8.48; S, 3.88. Found: C, 75.75; H, 4.12; N, 8.32; S, 3.90.

2-(((4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)phenyl 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate (**5h**).

This compound was obtained by the method B with a reflux time of 10 hours, and with catalytic amounts of triethylamine (3-amino-4-hydroxybenzenesulphonic acid) resulting in a yield of 65 % (0.34 g); m.p. 260°C (xylene). Anal. Calcd. for C₅₂H₃₅N₅O₅: C, 77.12; H, 4.36; N, 8.65. Found: C, 76.95; H, 4.52; N, 8.78.

2-(((4-Benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)carbonyl)amino)pyridin-3-yl 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylate (**5i**).

This compound was obtained by the method B with a reflux time of 6 hours, and with catalytic amounts of triethylamine (2-amino-3-hydroxy pyridine) resulting in a yield of 80 % (0.42 g); m.p. 272°C (1-butanol). Anal. Calcd. for C₅₁H₃₄N₆O₅: C, 75.54; H, 4.23; N, 10.36. Found: C, 75.67; H, 4.41; N, 10.35.

Conclusions

The compounds 5a-i were obtained as a result of the reaction of the 1*H*-pyrazole-3-carboxylic acid **2** or its acid chloride **3** with various binucleophiles diamine derivatives 4a-i. Semi-empirical method AM1 was used to determine the electronic structure and study the reaction mechanism. Each amine group of *o*-phenylenediamine reacts with 1*H*-pyrazole-3-carboxylic acid **2a** without opening the pyrazole ring, according to theoretical calculations. Total energy of transition states for 5a, 5b, 5d, 5e are 1.28234948, 0.27847431, 0.36402526, 0.27847431 hartree

The absorption band observed at 1684 cm⁻¹ for **5b** belongs to benzoyl carbonyl groups. The distance R_{C6=O7} for both benzoyl carbonyl groups is 1.2388 Å. The absorption bands observed at 1652 and 1640 cm⁻¹ belong to carbonyl groups and their distances are 1.246 Å and 1.251 Å. The broad N-H absorption bands were observed at 3233 and 3445 cm⁻¹.

Acknowledgements

The authors wish to express their gratitude to Prof. Dr. Y. Akçamur for helpful and encouraging discussions. This study was financially supported by *Research Center of Erciyes University*.

References

- (1) E. Ziegler, M. Eder, C. Belegatis, E. Prewedourakis, *Monatsh. Chem.* **98**, 2249 (1967).
- (2) E. Ziegler, G. Kollenz, M. Eder, H. Igel, *Monatsh. Chem.* **102**, 1769 (1971).
- (3) G. Kollenz, C.O. Kappe, H.A.A El-Nabi, *Heterocycles*. **32**(4), 669 (1991).
- (4) T.Hökelek, E. Sarıpinar, I. Yıldırım, M. Akkurt, Y. Akçamur, *Acta Cryst.* **E58**, 30 (2002).
- (5) S. Murai, K. Hasegawa, N. Sonoda, *Angew. Chem. Int. Ed. Engl.* **14**, 636 (1975).
- (6) R.W. Saalfrank, T. Lutz, B. Hörner, J. Gündel, K. Peters, H.G. von Schnering, *Chem. Ber.* **124**, 2289 (1991).

- (7) E. Ziegler, G. Kollenz, W. Ott, *Synthesis*, **11**, 679 (1973).
- (8) E. Ziegler, G. Kollenz, G. Kriewitz W. Ott, *Liebigs Ann. Chem*, 1751 (1977).
- (9) C. Wentrup, H.W. Winter, G. Gross, K.P. Netch, G. Kollenz, W. Ott, A.G. Biedermann, *Angew. Chem. Int. Ed. Engl* (1984).
- (10) C.O. Kappe, G. Farber, C. Wentrup, G. Kollenz, *J. Org. Chem.* **57**, 7078 (1992).
- (11) B. Fulloon, H.A.A. El-Nabi, G. Kollenz, C. Wentrup, *Tetrahedron Lett.* **36**, 6547 (1995).
- (12) H.A.A. El-Nabi, G. Kollenz, *Monatsh. Chem*, **128**, 381 (1997).
- (13) G. Kollenz, G. Penn, G. Dolenz, Y. Akçamur, K. Peters, E.-M. Peters, H.G. von Schnering, *Chem. Ber.* **117**, 1299 (1984).
- (14) E. Terpetschnig, W. Ott, G. Kollenz, K. Peters, H.G. von Schnering, *Monatsh. Chem.* **119**, 367 (1988).
- (15) G. Kollenz, H. Sterk, G.J.Hutter, *Org. Chem*, **56**, 235 (1991).
- [16] R.L. Toung, C. Wentrup, *Tetrahedron Let.* **48**, 7641 ()
- (17) I. Yildirim, I.O. Ilhan, *J. Heterocyclic Chem.* **34**, 1047 (1997).
- (18) H.A.A. El-Nabi, *Tetrahedron* **53**, 1813 (1997.)
- (19) A. Stadler, K. Zangger, F. Belaj, G. Kollenz, *Tetrahedron* **57**, 6757 (2001).
- (20) Review: G. Kollenz, W. Heilmayer, *Trends in Heterocycl. Chem.* **3**, 379 (1993).
- (21) G. Kollenz, E. Ziegler, W. Ott, H.Z. Igel, *Naturforschg* **31b**, 1511 (1976).
- (22) W. Ott, E. Ziegler, G. Kollenz, *Synthesis* **7**, 477 (1976).
- (23) Y. Akçamur, G. Kollenz, *Org. Prep. Proced. Int.* **19**, 52 (1987).
- (24) B. Altural, Y. Akçamur, E. Sarıpinar, I. Yildirim, G. Kollenz, *Monatsh. Chem.* **120**, 1015 (1989).
- (25) I. Yildirim, E. Sarıpinar, Y. Güzel, Ş. Patat, Y. Akçamur, *J. Mol. Struct.* **334**, 165 (1995).
- (26) I. Yildirim, M. Tezcan, Y. Güzel, E. Sarıpinar, Y. Akçamur, *Tr. J. Chem*, **20**, 27 (1996).
- (27) E. Sarıpinar, I. Yildirim, Y. Güzel, Y. Akçamur, *Monatsh. Chem.*, **127**, 505 (1996).
- (28) I. Yildirim and F. Kandemirli, *Heteroat. Chem.*, **15**(1), 9 (2004).
- (29) Y. Akçamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E.-M. Peters, H.G. von Schnering, *Monatsh. Chem.* **117** 231 (1986).
- (30) Y. Akçamur, A. Sener, A.M. Ipekoglu, G. Kollenz, *Heterocycl. Chem.* **34**, 221 (1997).
- (31) A. Sener, R. Kasımoğulları, M.K. Sener, I. Bildirici, Y. Akçamur, *J. Heterocycl. Chem.* **39**, 869 (2002).
- (32) J.A. Joule, K. Mills, G.F. Smith, *Heterocyclic Chemistry*, 3rd Ed., Chapman & Hall, London, UK 1995.
- (33) A. Weissberger, *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings* (R.H. Wiley, Ed.), *The Chemistry of Heterocyclic Compounds*, Interscience Publishers, New York, 1967.
- (34) J. Elguero, in *Comprehensive Heterocyclic Chemistry* (Ed): A.R. Katritzky, C.W. Rees), Pergamon, Oxford, 1984.
- (35) G. Daidone, D. Raffa, F. Plescia, B. Maggio, A. Rocco, *ARKIVOC* (XI), 227 (2002).
- (36) R.N. Mahajan, F.H. Havaladar, and P.S. Fernandes, *J. Indian Chem. Soc.* **68**, 245 (1991).
- (37) P.G. Baraldi, S. Manfredini, R. Romagnoli, L. Stevanato, A.N. Zaid and R. Manservigi, *Nucleosides and Nucleotides* **17**, 2165 (1998).

- (38) G.J. Hatheway, C. Hansch, K.H. Kim, S.R. Milstein, C.L. Schmidt, R.N. Smith and F.R. Quin, *J. Med. Chem.* **21** 563 (1978).
- (39) R. Riedel, *Von Arzneim. Forsch./Drug Res.* **31**, 655 (1981).
- (40) P.D. Mishra, S. Wahidullah, S.Y. Kamat, *Indian J. Chem. Sec. B*, **37**, 199 (1998).
- (41) M. Londershausen, *Pestic. Sci.* **48** 269 (1996).
- (42) H.S. Chen and Z. M. Li, *Chem. J. Chinese Univ.* **19**, 572 (1998).
- (43) F. Lepage, B. Hublot, *Eur. Pat. Appl.*, EP 459, 887; *Chem. Abstr.* **116**, 128917 (1992).
- (44) M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A., Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E.J. Stratmann Jr, C. Burant, S. Dapprich, J. M. Millam, A.D. Daniels, K.N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G., Baboul, B.B., Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M.P. Challacombe, M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A., Pople, Gaussian, Inc., Pittsburgh PA, Gaussian 98, Revision A.9 (1998).
- (45) G.C. Bassler, T.C. Morrill, *Spectrometric Identification of Organic Compounds* (R.M. Silverstein, Ed.), John Wiley and Sons, New York, NY (1991).
- (46) C. Gonzalez, H.B. Schelegel, *J. Chem. Phys.* **90**, 2154 (1989).
- (47) C. Gonzalez, H.B. Schelegel, *J. Phys. Chem.* **94**, 5523 (1990).

Received on November 15, 2004.