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Experimental and Theoretical Studies on the Functionalization Reactions of 4-Benzoyl-1,5-Diphenyl-1H-Pyrazole-3-Carboxylic Acid and Acid Chloride with 2,3-Diaminopyridine

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Abstract: The 1*H*-pyrazole-3-carboxylic acid **2** was converted in good yield (69%) into the corresponding 1*H*-pyrazole-3-carboxamide **5** via reaction of the acid chloride **3** with 2,3-diaminopyridine (**4**). A different product, the 3*H*-imidazo[4,5-*b*] pyridine derivative **6,** was formed from the reaction of **3** with **4** and base in benzene for 5 hours. The structures of the synthesized compounds were determined spectroscopically. The mechanism of the reaction between **3** and **4** was examined theoretically.

Keywords: furan-2,3-dione, pyrazole-3-carboxylic acid, pyrazole-3-carboxylic acid chloride, imidazo [4,5-*b*]pyridine, IR and NMR spectra, MO calculations.

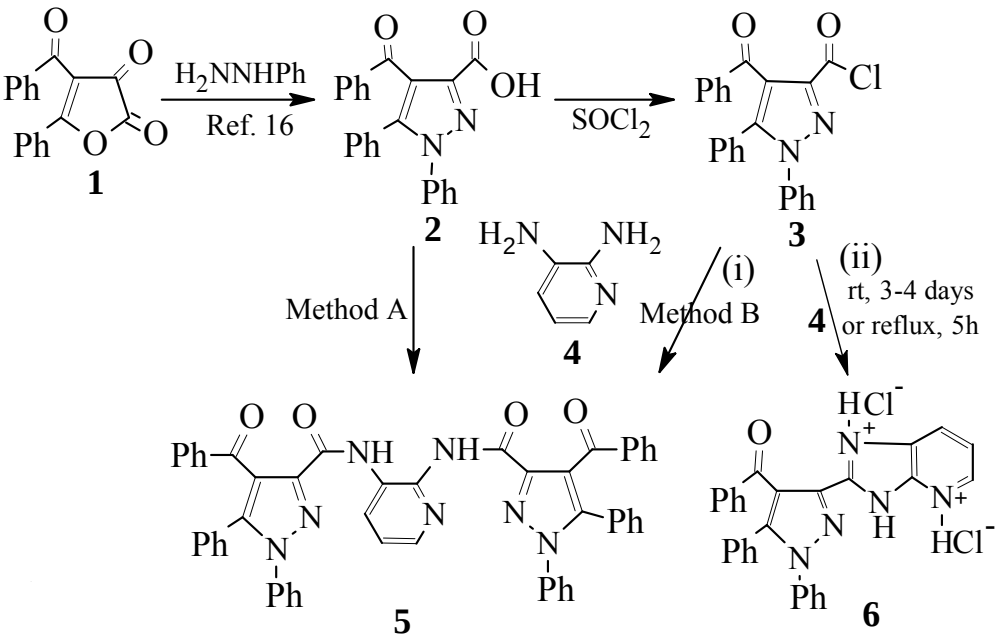
Introduction

The cyclocondensation reaction of 1,3-dicarbonyl compounds with oxalyl chloride represents a convenient synthesis of furan-2,3-dione systems [1-3], which constitute an important group of oxygen-containing heterocyclic starting materials. This synthesis has been widely explored during the last few decades [4-7] and furan-2,3-diones of type **1** have been used successfully for a long time in the syntheses of various heterocycles [8, 9]. Convenient synthetic methods, mechanisms of the reactions, and semi-empirical (AM1 and PM3) and *ab initio* (DFT) calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) with several semicarbazones, ureas, thioureas and anilides

have been reported recently [10-15]. The reaction of furan-2,3-dione with various phenylhydrazones and phenylhydrazine leads to pyrazole-3-carboxylic acid and pyridazinones [16-19].

Pyrazole derivatives are in general well-known nitrogen-containing heterocyclic compounds, and various procedures have been developed for their syntheses [20-23]. The chemistry of pyrazole derivatives have been the subject of much interest due to their importance for various applications and their widespread potential and proven biological and pharmacological activities such as anti-inflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anti-convulsant, antihistaminic, antibiotics, anti-depressant, and CNS regulant activities [24-32]. In view of these important properties, we decided both to prove the reproducibility of the reaction of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (**2**) and acid chloride (**3**) with a diamine binucleophile **4** and to extend our investigations related to the preparation of new heterocycles, which include two pyrazole rings or 3*H*-imidazo[4,5-*b*] pyridine rings in their structure. We are now reporting the reaction mechanism, synthesis and characterization of the 1*H*-pyrazole-3-carboxamide **5** and 3*H*-imidazo[4,5-*b*]pyridine derivative **6** which were formed by the reaction of the pyrazole-3-carboxylic acid **2** or the pyrazole-3-carboxylic acid chloride **3** with 2,3-diaminopyridine (**4**) (see Scheme 1).

Scheme 1.

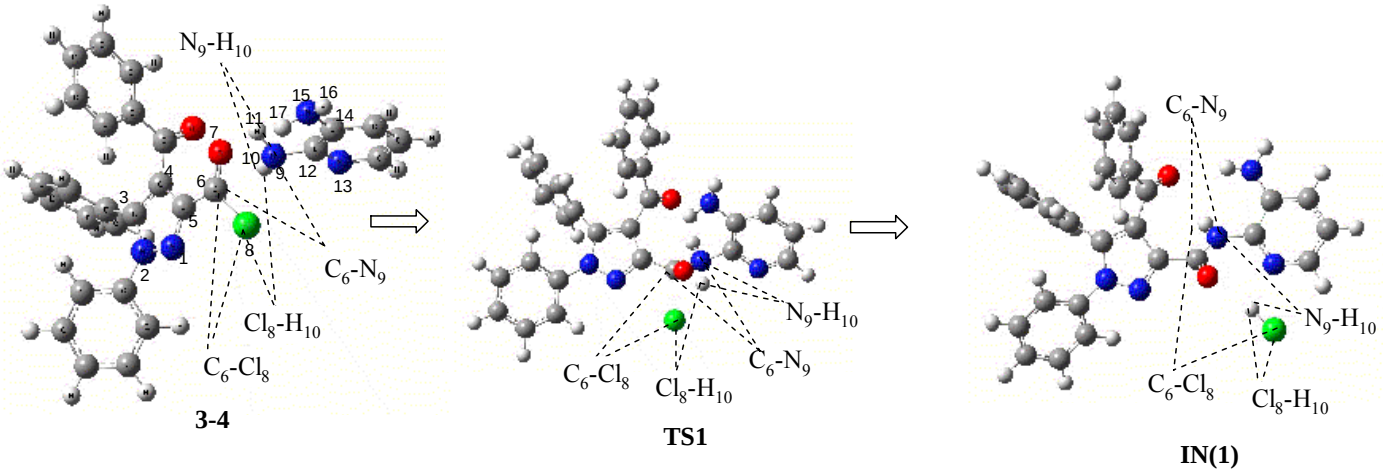


Results and Discussion

Compound **3** reacts with 2,3-diaminopyridine (**4**) in two ways, thus yielding the 1*H*-pyrazole-3-carboxamide derivative **5** or the 3*H*-imidazo[4,5-*b*] pyridine derivative **6**. The substituted 2,3-furandione **1** and 1*H*-pyrazole-3-carboxylic acid **2**, as well as 1*H*-pyrazole-3-carboxylic acid chloride **3**, which are important starting materials in the synthesis of the target heterocycles, were prepared using the literature procedures [1,16,17]. Compound **5** was synthesized in good yield by refluxing 2,3-diaminopyridine (**4**) and a two-fold molar excess of the pyrazole-3-carboxylic acid **2** or the pyrazole-3-carboxylic acid chloride **3** in benzene, without opening of the pyrazole ring (see Scheme 1). The

reactions were performed together with catalytic amounts of an acid (in the case of **2**) or a base (in the case of **3**), for 5-10 hours, by the usual chemical method (for details, see the Experimental section). Addition of binucleophile **4** to the acid **2** or acid chloride **3** usually starts with nucleophilic attack at the acid or acid chloride moieties in these compounds. Therefore, the newly obtained product **5** arises from the sequential attacks of the diamine **4** at the acid chloride moieties of two respective molecules of **3**, followed by elimination of hydrogen chloride (in the case of **2**, by elimination of water). The first step corresponds to the nucleophilic addition of one of 2,3-diaminopyridine's amino groups (N_9) to the electrophilic sp^2-hybridized carbon atom (C_6) of the 1*H*-pyrazole-3-carboxylic acid chloride (See Figure 1).

Figure 1.



The total self-consistent field energy of reacting molecules (**3+4**), which are far from each other (C_6-N_9 = 3.65 Å), is –1931.018 a.u. for RHF/STO-3G method. **TS1** is the result of the C_6-N_9 bond formation for the account of proton transfer to chlorine atom. The C_6-N_9, C_6-Cl_8, and Cl_8-H_{10} bond lengths for **TS1** become 1.61 Å, 2.34 Å, 1.97 Å. (see Table 1.)

Table 1. Conformational and electron characteristics **3-4**, **TS1**, and **IN(1)**.

Atoms/Bonds		3-4			TS1		IN(1)		
		AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	AM1	RHF STO-3G	RHF 3-21G
INTERATOMIC DISTANCES (in Å)	C_6-N_9	3.11	3.65	3.22	1.55	1.61	1.38	1.38	1.35
	C_6- O_7	1.23	1.21	1.19	1.24	1.21	1.24	1.25	1.22
	C_6-Cl_8	1.73	1.82	1.85	2.23	2.34	4.49	3.49	4.12
	N_9-H_{10}	1.00	1.03	1.00	1.07	1.06	3.79	2.68	3.44
	N_{10}-H_{11}	1.00	1.03	1.00	1.02	1.04	1.00	1.04	1.00
	N_9-C_{12}	1.41	1.44	1.38	1.46	1.48	1.42	1.45	1.41
	C_{12}-C_{14}	1.40	1.44	1.39	1.39	1.43	1.40	1.44	1.37
	C_{12}-N_{13}	1.36	1.34	1.31	1.36	1.34	1.36	1.35	1.30

Table 1. Cont.

	N_{15}-H_{16}	1.00	1.03	1.00	1.00	1.03	1.00	1.03	1.00
	N_{15}-H_{17}	1.00	1.03	1.00	1.00	1.03	1.00	1.03	1.00
	C_6-C_5	1.46	1.50	1.45	1.49	1.52	1.49	1.52	1.50
	C_5-C_4	1.45	1.43	1.41	1.45	1.42	1.45	1.44	1.43
	C_5-N_1	1.39	1.33	1.30	1.36	1.33	1.36	1.33	1.30
	Cl_8-H_{10}	4.32	5.37	4.39	2.00	1.97	1.30	1.45	1.33
	Frequencies (cm^{-1})				-351	-281			

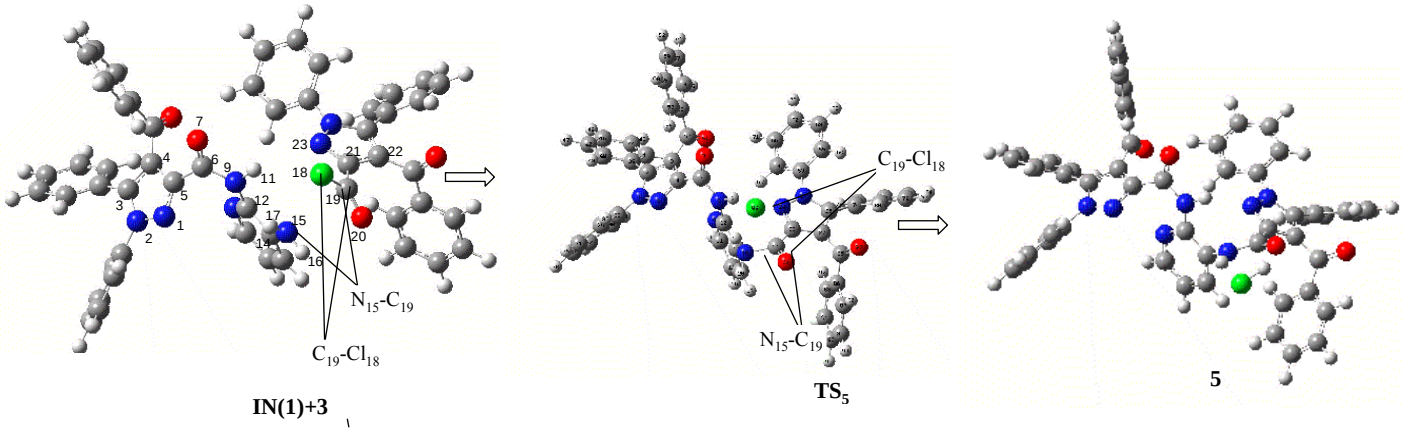
Atoms/Bonds		**3-4**			**TS1**		**IN(1)**		
		AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	AM1	RHF STO-3G	RHF 3-21G
CHARGES (in electronoc units ē)	N_1	-0.01	-0.12	-0.34	-0.01	-0.20	-0.01	-0.12	-0.32
	C_4	-0.17	-0.06	-0.33	-0.24	-0.05	-0.22	-0.07	-0.49
	C_5	-0.16	0.05	0.37	-0.14	0.08	-0.14	0.05	0.35
	C_6	0.34	0.28	0.44	0.41	0.37	0.40	0.36	0.99
	O_7	-0.26	-0.19	-0.53	-0.35	-0.24	-0.32	-0.26	-0.63
	Cl_8	-0.06	-0.18	0.05	-0.56	-0.69	-0.23	-0.53	-0.40
	N_9	-0.31	-0.41	-0.95	-0.10	-0.32	-0.32	-0.38	-1.06
	H_{10}	0.19	0.17	0.33	0.31	0.32	0.23	0.27	0.31
	H_{11}	0.19	0.19	0.37	0.25	0.27	0.26	0.26	0.42
	C_{12}	0.05	0.18	0.74	-0.06	0.17	0.06	0.18	0.78
	N_{13}	-0.18	-0.27	-0.78	-0.10	-0.22	-0.13	-0.24	-0.75
	N_{15}	-0.32	-0.40	-0.96	-0.32	-0.39	-0.32	-0.38	-1.03
	H_{16}	0.20	0.20	0.35	0.21	0.19	0.21	0.18	0.38
	H_{17}	0.17	0.16	0.32	0.19	0.19	0.18	0.18	0.34

The resulting SCF energy value is –1930.967 a.u. for an intermediate product **IN(1)**. In theoretical chemistry, the reaction intermediates and transition states can be strictly distinguished by the use of vibrational analysis. For **TS1** one imaginary frequency was found at –281 cm^{-1}. Molecule **4** approaches the molecular plane of **3** at an angle of 107.1°. Torsion angle of H_9-N_8-C_6-C_4 being equal to -111° is not coplanar. When the bond length of C_6 - N_9 becomes 1.38 Å, **IN(1)** is formed. Torsion angle of H_9-N_8-C_6-C_4 becomes 168° and approximates to the coplanar one. When the bond C_6 - N_9 is formed, new charge redistribution is seen. The negative charge on the N_9 (RHF/STO-3G) decreases from –0.41 to –0.38 ē, positive charge on the C_6 atom and negative charges on the O_7 and Cl_8 atoms increase. In this way, a substantial polarization of bonds formed by the atom C_6 can be observed.

The calculations were done by using semi-empirical AM1 and *ab initio* methods. *Ab initio* calculations were carried out by using two different basis sets that differ in the polarization functions, namely, STO-3G and 3-21G. When the *ab initio* method is used instead of AM1, this causes electron redistribution and changes in bond lengths. The latter are also changed, when the same method but a

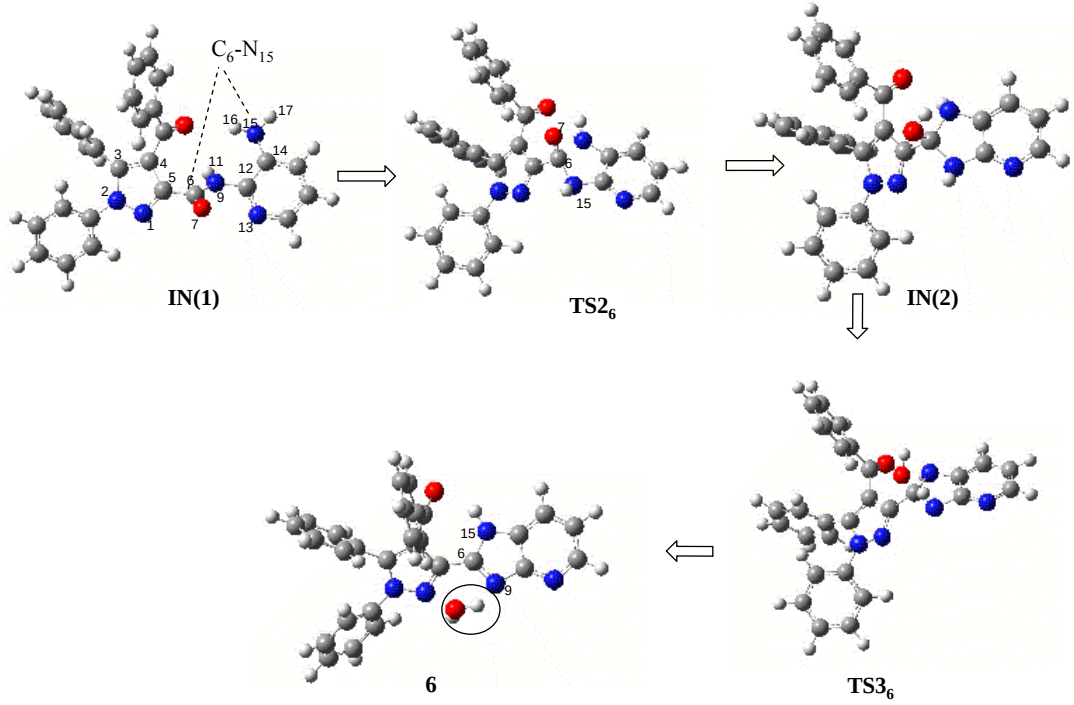
different basis set is used. For example, the C_6-O_7 bond length at **3-4** is 1.23 Å for AM1, 1.21 Å for RHF/ STO-3G, and 1.19 Å for RHF/3-21G.

Figure 2.



The use of different methods and different basis sets displays a little difference in atomic charges calculated. When the number of functions in the basis set grows, the calculations show a considerable redistribution of electron density on bonds. Because of polarization, the negative charge increase on the N_1, N_9, N_{13}, N_{15}, C_4, O_7 atoms, and positive charges increase on the C_{12} and hydrogen atoms.

Figure 3.



In the second step of the reaction, nucleophilic addition of the other amino group (N_{15}) of **IN1** to the sp^2-hybridized carbon atom (C_{19}) of the second electrophilic 1*H*-pyrazole-3-carboxylic acid chloride happens. In this way the compound **5** was obtained. For the transitional state **TS2**, its interatomic distances are determined as $R_{N15\text{-}C19}$ = 1.54 Å, $R_{N15\text{-}H16}$ = 1.10 Å, $R_{C21\text{-}Cl18}$ = 2.40 Å, $R_{C18\text{-}H19}$ = 1.90 Å (see Table 2).

Table 2. Conformational and electron characteristics of **IN(1)**, **TS2$_5$**, and **5**.

	Atoms/Bonds	**IN(1)**	**TS2$_5$**	**5**
INTERATOMIC DISTANCES (in Å)	C_{14}-N_{15}	1.40	1.44	1.41
	N_{15}-H_{17}	1.00	1.02	1.00
	N_{15}-H_{16}	1.00	1.10	3.12
	N_{15}-C_{19}	2.89	1.54	1.38
	C_{19}-O_{20}	1.23	1.23	1.25
	C_{21}-Cl_{18}	1.74	2.40	3.79
	Cl_{18}-H_{19}	3.04	1.90	1.30
	C_{19}-C_{21}	1.46	1.47	1.48
	C_{21}-N_{23}	1.37	1.37	1.36
	C_{21}-C_{22}	1.45	1.45	1.45
	C_{12}-N_9	1.42	1.39	1.40
	N_9- C_6	1.39	1.40	1.39
	N_9-H_{11}	1.00	1.04	1.00
	C_6-O_7	1.24	1.24	1.24
	C_6- C_5	1.48	1.28	1.48
	Frequencies(cm^{-1})		-274	

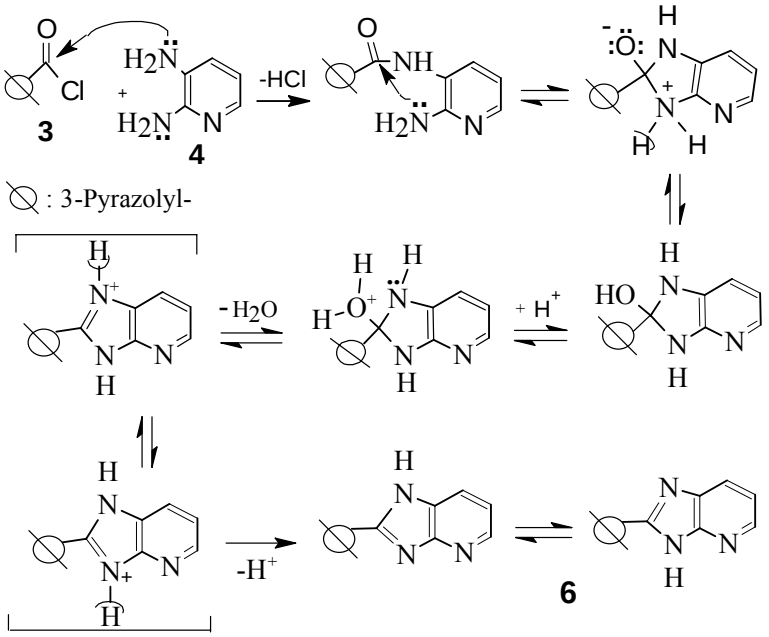
	Atoms/Bonds	5I	TS2	5
CHARGES (in electronoc units ē)	N_1	-0.04	-0.04	-0.03
	N_2	-0.16	-0.07	-0.06
	C_4	-0.20	-0.18	-0.19
	C_5	-0.09	-0.11	-0.10
	C_6	0.46	0.39	0.40
	O_7	-0.37	-0.30	-0.34
	N_9	-0.45	-0.33	-0.30
	H_{11}	0.33	0.32	0.26
	C_{12}	0.12	0.22	0.16
	N_{13}	-0.19	-0.18	-0.17
	C_{14}	0.01	-0.20	-0.05
	N_{15}	-0.47	-0.10	-0.33
	H_{16}	0.26	0.32	0.22
	H_{17}	0.25	0.22	0.26
	Cl_{18}	-0.09	-0.65	-0.22
	C_{19}	0.38	0.40	0.40
	O_{20}	-0.28	-0.28	-0.37
	C_{21}	-0.14	-0.13	-0.13
	C_{22}	-0.20	-0.18	-0.20
	N_{23}	-0.02	-0.01	-0.04

The structure of compound **5** was confirmed, besides elemental analysis, by IR and NMR spectroscopic techniques. These results are in full agreement with similar findings for substituted 1*H*-pyrazole-3-carboxamides [16-18]. The formation of **5** was supported by the results of both analytical and spectroscopic measurements, particularly by the presence of four characteristic absorption bands (FT IR: 1686.93 cm^{-1}, 1670.68 cm^{-1}) for carbonyl (amidic and benzoyl) groups. The broad absorption band of NH≒OH groups was at 3433.64 cm^{-1} [16-18, 37], and the skeleton bands of benzene or pyrazole

rings, together with N-H bending vibrations, were observed at 1596.77, 1581.34, 1518.19, 1499.38, 1448.28 cm^{-1} (C···C, C···N). Important structural information about **5** can be obtained from its ^{13}C-NMR spectrum. The ^{13}C-NMR peaks were found to be at 197.68 (t, ^{3}J = 4.6 Hz, Ph-C=O), 172.20 (s, -NH-C=O), 160.92 (s, -NH-C=O), 158.04 (C-2', pyr.), 147.21, 146.35, 145.65 (C-3, C-3', C-5, C-5' exchangeable), 141.46, 141.03 (N-Ph), 137.18-129.82 (C-Ph), 127.11-124.26 ppm (C-4, C-4'). Final confirmation of structure **5** was derived from its ^{1}H-NMR spectrum: δ is equal to 10.40 ppm (s, OH, tautomeric proton), 9.58 ppm (s, NH) and 8.21-7.18 ppm for a set of signals for aromatic protons [37].

In order to make the reaction selective, we had to determine the parameters, or, in other words, the reaction pathways, that could lead to such results. At this point, the reaction of **3** with **4** in boiling benzene for 5 hours with no catalytic amounts of pyridine or triethylamine gave another product, 2-(4-benzoyl-1,5-diphenyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-1,4-diiumdichloride (**6**), which was also obtained in 49% yield by stirring at room temperature for 3-4 days (see Scheme 1). Thus, compound **3** reacts with 2,3-diaminopyridine (**4**) in two ways and yields either the 1*H*-pyrazole-3-carboxamide derivative **5** or the 3*H*-imidazo[4,5-*b*] pyridine derivative **6**. These results were confirmed by TLC using authentic specimens of **5** or **6** and identified by elemental and spectral data. A Beilstein test gave a green colour for compound **6**. The FT-IR spectra of **6** showed broad bands for the imidazole N-H bond in the ν 3484.56, 3175.22 cm^{-1} region and also for two $^{=}N^{+}$-H groups at 2727.32 cm^{-1}. The characteristic absorption bands for the carbonyl groups of **6** were observed at 1668.15 cm^{-1} [37]. The ^{1}H-NMR peaks were found at δ = 10.12 (broad, NH imidazole and $^{=}N^{+}$-H imidazole or pyridine). The results of MS measurements and other structural data for the compound **6** are given in the Experimental section.

Scheme 2.



The moderate to excellent yield of the reaction can be explained by the chemical behavior of acid chlorides, similar to the behavior of the compound **3** towards *N*-nucleophiles [16-18]. The formation of **6** can easily be explained by a nucleophilic attack on the carbonyl group of the acid chloride **3**. It appears, that this process can be followed by elimination of a molecule of hydrogen chloride, formation of **IN(1)** as mentioned above, and elimination of a molecule of water, to give tautomers of **6**, whose formation is rationalized in Scheme 2.

The elimination of water molecule may occur in two states. First, a new bond C_6-N_{15} is formed, being accompanied by the proton H_{17} transfer to the O_6 atom. Transitional state **TS2** formation happens under C_6-N_{15} = 1.81 Å, C_6-N_9 = 1.52 Å, C_6-O_7 = 1.27 Å, O_7-H_{17} = 1.69 Å for STO-3G basis set. The intermediate product is being formed under C_6-N_{15} = 1.50 Å, C_6-N_9 = 1.47 Å, C_6-O_7 = 1.42 Å, O_7-H_{17} = 0.99 Å (see Table 3). Imaginary frequency for **TS2** is –1854 cm^{-1} that indicates a substantial change in its structure.

Table 3. Conformational and electron characteristics of intermediates, transition states and product.

Atoms/Bonds		IN(1)			$TS2_6$			IN(2)		
		AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	RHF 3-21G
INTERATOMIC DISTANCES (in Å)	C_6-N_9	1.38	1.45	1.36	1.51	1.52	1.46	1.51	1.47	1.44
	C_6- O_7	1.25	1.22	1.21	1.33	1.27	1.33	1.44	1.42	1.42
	N_{10}-H_{11}	0.99	1.03	1.00	1.00	1.03	1.00	1.00	1.03	0.99
	N_9-C_{12}	1.42	1.45	1.42	1.41	1.42	1.36	1.42	1.44	1.38
	C_{12}-N_{13}	1.36	1.35	1.31	1.36	1.35	1.31	1.35	1.33	1.29
	C_{12}-C_{14}	1.45	1.41	1.41	1.46	1.45	1.40	1.46	1.41	1.41
	C_{14}-N_{15}	1.38	1.44	1.37	1.44	1.45	1.44	1.42	1.43	1.38
	N_{15}-H_{16}	0.99	1.03	1.00	1.01	1.03	1.01	1.00	1.03	1.00
	N_{15}-H_{17}	0.99	1.03	0.99	1.10	1.04	1.05	2.40	2.48	1.00
	C_6-C_5	1.49	1.52	1.50	1.51	1.53	1.49	1.52	1.54	1.50
	C_5-C_4	1.45	1.43	1.42	1.45	1.43	1.41	1.45	1.43	1.41
	C_5-N_1	1.36	1.33	1.30	1.36	1.33	1.30	1.36	1.33	1.30
	O_7-H_{17}	3.42	4.06	5.58	1.70	1.69	1.65	0.97	0.99	0.97
	N_{15}-C_6	3.00	3.24	2.81	1.59	1.81	1.63	1.51	1.50	1.45
	Frequencies (cm^{-1})				2031	-1854	-1804			

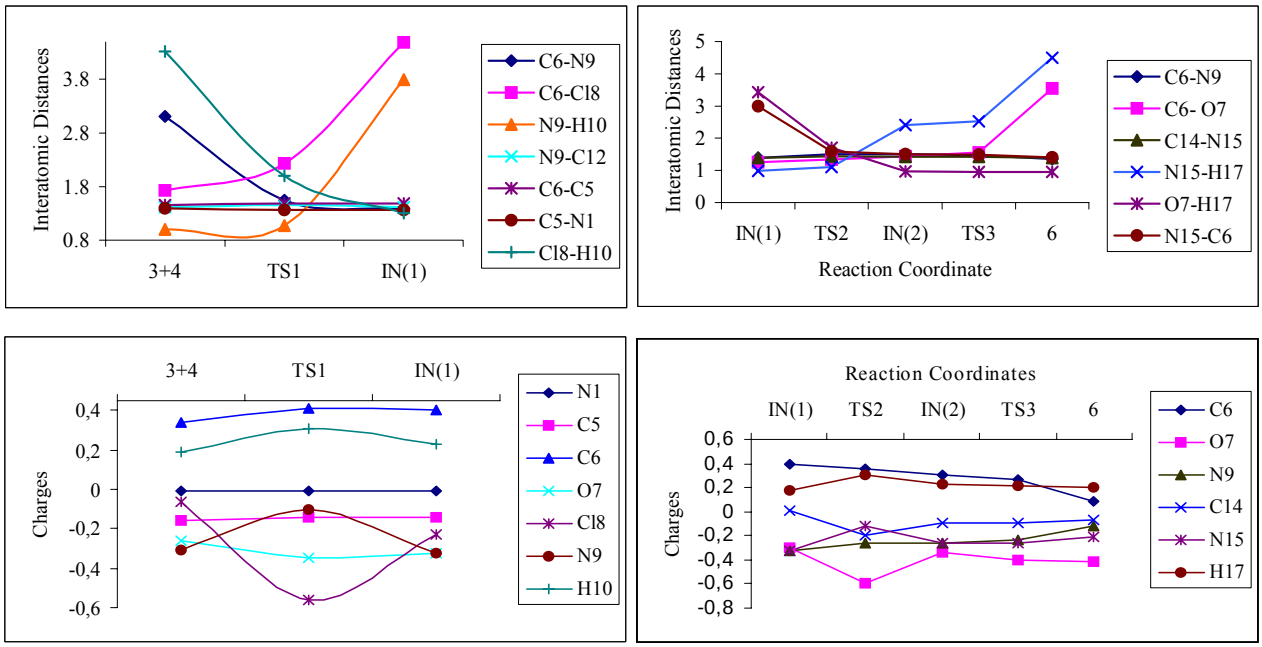
Atoms/Bonds		IN(1)			$TS2_6$			IN(2)		
		AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	RHF 3-21G	AM1	RHF STO-3G	RHF 3-21G
CHARGES (in electronoc units ē)	N_1	-0.01	-0.16	-0.33	-0.02	-0.12	-0.40	-0.01	-0.17	-0.40
	C_4	-0.23	-0.06	-0.41	-0.23	0.08	-0.34	-0.22	-0.22	-0.38
	C_5	-0.13	0.04	0.36	-0.10	0.06	0.46	-0.10	0.06	0.53
	C_6	0.39	0.29	0.91	0.35	0.28	0.76	0.30	0.31	0.76
	O_7	-0.30	-0.24	-0.58	-0.59	-0.30	-0.74	-0.34	-0.30	-0.68
	N_9	-0.33	-0.36	-1.02	-0.26	-0.38	-0.97	-0.26	-0.34	-0.94
	H_{11}	0.26	0.21	0.40	0.23	0.27	0.39	0.23	0.20	0.38
	C_{12}	0.06	0.17	0.73	0.13	0.15	0.89	0.04	0.18	0.79
	N_{13}	-0.11	-0.25	-0.71	-0.16	-0.26	-0.78	-0.14	-0.26	-0.77
	C_{14}	0.01	0.10	0.33	-0.20	0.06	0.17	-0.09	0.07	0.34
	N_{15}	-0.33	-0.38	-1.01	-0.12	-0.38	-1.01	-0.26	-0.36	-1.01
	H_{16}	0.21	0.19	0. 37	0.23	0.23	0.42	0.22	0.20	0.39
	H_{17}	0.18	0.17	0.34	0.30	0.20	0.27	0.23	0.20	0.39

In the second stage of the reaction, final product **6** is obtained. In the transition state **TS3**, bond lengths are 1.60 Å for C_6-O_7, 1.47 Å for N_{15}-C_6 1.26 Å for N_{10}-H_{11}. When the N_{15}-C_6 bond is formed, C_6-O_7 bond is broken simultaneously.

Conclusions

In this study, dicarboxamide derivative **5** was prepared in good yield (69%) without opening the pyrazole ring by the nucleophilic substitution reaction of a two-fold molar excess of compounds **2** or **3** and 2,3-diaminopyridine. The reaction of **3** with **4** in benzene with no catalytic amounts of triethylamine led to the formation of another product **6**, besides **5**. The structures of compounds **5** and **6** were confirmed by elemental analyses and spectroscopic data.

Figure 4.



The changes that occurred in some of the bond lengths during the **IN(1)** and product **6** formation (the lengths were determined by AM1 method) are shown in Figure 4. While **IN(1)** is being formed, C_6-Cl_8 and N_9-H_{10} bonds are broken and C_6-N_9 and Cl_8-H_{10} bonds are formed. In the same way, during the formation of product **6**, C_6-O_7 and N_{15}-H_{17} bonds are broken and N_{15}-C_6 and O_7-H_{17} bonds are formed. As is seen from Figure 4, some important changes in the charges of atoms occur both under the formation and breakage of the bonds, at the time when **IN(1)** and product **6** are being formed. As an example, the charge density on chlorine atom is -0.06ē in **3+4** reactants, -0.56ē in **TS1**, -0.23ē in product. During the formation of product **6**, charge density on carbon atom is 0.39ē in **IN(1)**, 0.35ē in **TS2**, 0.30ē in **IN(2)**, 0.2 ē in **TS3**, and 0.09ē in product **6**. Thus, in this paper we have presented a theoretical and experimental study of the preparation of either product **5** or **6**.

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Experimental

General

Melting points were determined on an Electrothermal 9200 apparatus and are 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 KBr pellets. The ^{1}H- and ^{13}C-NMR spectra were obtained on Varian Gemini 200 instrument with $CDCl_3$ as solvent and 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 F_{254} (Merck) and a 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. All computations were done by the Gaussian 03W program. Quantum chemical calculations were done by means of semi-empirical AM1 and *ab initio* methods. The STO-3G and 3-21G basis sets were used throughout. Geometries were fully optimized with STO-3G and 3-21G basis sets in the frameworks of the methods used. All stationary points were characterized as minima or transition states by vibrational frequency calculations at the same level of theory as geometry optimization. In addition, intrinsic reaction coordinate (IRC) calculations for transition states were also performed.

4-Benzoyl-1,5-diphenyl-N-(2-{[(4-benzoyl-1,5-diphenyl-1H-pyrazol-3-yl)carbonyl]amino}pyridin-3-yl)-1H-pyrazole-3-carboxamide (**5**).

Compound **5** was prepared by two methods as follows:

Method A. From 1H-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, easily obtained from 4-benzoyl-5-phenyl-2,3-dihydrofuran-2,3-dione and phenylhydrazine [1,16,17]) and 2,3-diaminopyridine (**4**) were dissolved in benzene (30 mL) in a molar ratio of 2:1 and heated with stirring under reflux together with catalytic amounts of sulfuric acid for 10 hours. The solution was then cooled to 5 ^{o}C in a refrigerator and a precipitate was formed. After suction filtration, the crude product was recrystallized from methanol and dried over P_2O_5 to give 0.18 g (33%) of **5**; m.p. 250 ^{o}C (white crystals); IR: 3434 (b, NH≒OH), 1687, 1671 (s, C=O), 1597, 1581, 1518, 1499 cm^{-1} (C⎓C, C⎓N, aromatic rings); ^{1}H-NMR: δ 10.40 (s, 1H, OH, tautomeric proton), 9.58 (s, 1H, NH), 8.21-7.18 ppm (m, 33H, Ar-H); ^{13}C-NMR: δ 197.68 (t, ^{3}J = 4.6 Hz, Ph-C=O), 172.20 (s, -NH-C=O), 160.92 (s, -NH-C=O), 158.04 (C-2', pyr.), 147.21, 146.35, 145.65 (C-3, C-3', C-5, C-5' exchangeable), 141.46, 141.03 (N-Ph), 137.18, 136.77, 131.91, 131.72, 131.07, 130.78, 130.40, 130.24, 129.82, (C-Ph), 127.11, 125.39, 125.12 124.83, 124.26 (C-4,

C-4'), 116.94, 114.60, 111.44 ppm; Anal. Calcd. for $C_{51}H_{35}N_7O_4$: C, 75.64; H, 4.36; N, 12.11. Found: C, 75.81; H, 4.41; N, 12.07.

Method B. From 1H-pyrazole-3-carboxylic acid chloride (**3**). Appropriate amounts of the acid chloride **3** (0.50 g, 1.30 mmoles) and 2,3-diaminopyridine (**4**, molar ratio 2:1) were dissolved in benzene (30 mL) and refluxed together with catalytic amounts of triethylamine for 5 hours. The solvent was evaporated and the remaining oily residue was treated with petroleum ether to give a crude product that was recrystallized from methanol and dried over P_2O_5 to yield 0.36 g (69%) of **5**, with an m.p. and TLC identical to those of the product obtained as described above.

2-(4-Benzoyl-1,5-diphenyl-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridine-1,4-diiumdichloride (**6**).

This compound was obtained by method B with a reflux time of 5 hours, and with no catalytic amounts of triethylamine. After cooling the solution to room temperature, the precipitate formed was filtered off and recrystallized from 2-propanol, yield 0.32 g (49%); m.p. 221 ^oC; IR: 3485, 3175 (b, NH ⇌OH), 2727 (b, $^{=}N^+$-H), 1668 (s, C=O), 1624, 1596, 1577, 1515, 1496, 1459 cm^{-1} (C···C, C···N, aromatic rings); ^{1}H-NMR: δ 10.12 (b, 1H, NH imidazole and 2H, $^{=}N^+$-H), 8.42-6.86 ppm (m, 18H, Ar-H); ^{13}C-NMR: δ 196.76 (Ph-C=O), 154.02 (C-2', pyr.), 151.63, 148.92 (C-3', C-5'), 138.32, 137.35, 134.08, 132.97, 132.25, 131.87, 131.20, 130.58 (N-Ph, C-Ph), 127.63, 126.84 (C-4'), 116.04, 115.73 ppm; GC/MS: m/z = 514.3 [M^+], 512.3, 502.4, 501.3, 485.4, 484.3, 470.3, 460.3, 459.3, 442.4, 441.3, 440.3, 431.3, 413.3, 412.3, 368.3, 354.3, 353.3, 352.3, 351.2, 349.2, 334.2, 333.2, 324.3, 323.1, 306.2, 305.2, 295.2, 293.2, 248.2, 247.0, 219.2, 218.2, 216.8, 205.9, 203.8, 190.6, 190.5, 181.2, 180.0, 179.2, 178.2, 177.1, 176.0, 165.1, 160.0, 152.2, 150.2, 147.2, 136.1, 135.1, 120.1, 119.0, 108.1, 107.1, 106.1, 105.0, 93.0, 91.0, 89.1, 81.1, 79.0, 78.1, 77.0, 71.0, 66.1, 64.0, 63.0, 55.1, 53.0, 52.0, 51.0; Anal. Calcd. for $C_{28}H_{21}N_5OCl_2$: C, 65.38; H, 4.11; N, 13.61. Found: C, 65.35; H, 4.09; N, 13.29.

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