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ORIGINAL PAPER

Experimental and theoretical studies on the functionalization reactions of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid and-acid chloride with various aminophenols

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Abstract The 1*H*-pyrazole-3-carboxylic acid **1** was converted via reactions of its acid chloride **2** with various aminophenol derivatives **3a–d** into the corresponding *N*-(hydroxyphenyl)-1*H*-pyrazole-3-carboxamides **4a–d**, respectively, in good yields (34–53%). The reactions of **1** or **2** with **3** in benzene or toluene for 5–7 h with no catalytic amounts of base lead to the formation of the products **4**. The structures of all new synthesized compounds were established by the ^{13}C NMR,^{1}H NMR, IR, masss spectroscopic data and elemental analyses. The reaction mechanism of **2** with **3** was studied by means of the RHF/3-21G and RHF/6-31G method.

Keywords Nitrogen heterocycles · Pyrazole-3-carboxylic acid · NH_2 group versus OH group of aminophenol · IR and NMR spectra · MO calculations

Introduction

The cyclocondensation reaction of 1,3-diones (diaroylmethanes) with oxalyl chloride represents a convenient synthesis of furan-2,3-dione systems [1, 2] belonging to an important group of oxygen-containing heterocyclic starting materials that has in general been widely explored during the last few decades [3, 4]. On the other hand, 2,3-dihydrofuran-2,3-diones have been used successfully in the syntheses of various heterocycles for a long time [5]. A convenient method for their synthesis, the mechanism of 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 with several semicarbazones, ureas, thioureas and anilides have been reported recently [6–10]. The reaction of the furan-2,3-dione with various phenylhydrazones and phenylhydrazine leads to pyrazole-3-carboxylic acid and pyridazinones [11–14].

Pyrazole derivatives are generally well-known nitrogen-containing heterocycles, and various procedures have been developed for their syntheses [15–19]. The chemistry of pyrazole derivatives have been the subject of much research due to their importance in various applications and their widespread potential biological and pharmacological activities (antiinflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anticonvulsant, CNS regulating, antihistaminic, antibiotics, antidepressant, antibacterial etc. [13, 14, 20–22]). In view of these important properties, we decided both to prove reproducibility of the reaction of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (**1**) and -acid chloride (**2**) with some aminophenol derivatives **3** and to extend our investigations related to preparing new heterocycles which include the pyrazole ring in their structure. We are now reporting the reaction mechanism, synthesis and characterization of *N*-(hydroxyphenyl)-1*H*-pyrazole-3-carboxamides **4** by the reaction of the pyrazole-3-carboxylic acid **1** or the acid chloride **2** with the corresponding aminophenol derivatives **3a–d** (see Scheme 1). No theoretical study has yet been reported on the subject. Therefore, the mechanisms of these

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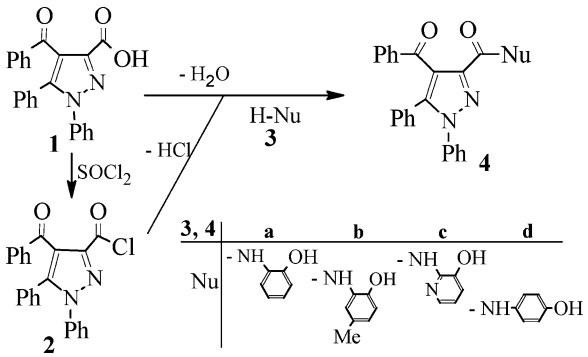

Scheme 1

reactions are of interest for theoretical so as for practical considerations.

Thus, as seen from Scheme 1, the compounds **4a–d** have been first synthesized from these reactions, and the results obtained from the experiment and theoretical calculations are discussed in this study.

Experimental

Materials and physical measurements

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 at 200 and 50 MHz, respectively, using TMS as internal standard. Mass spectra were measured on Shimadzu GC/MS-QP 5050A spectrometer, using DI method with EI. Melting points (uncorrected) were determined on an Electrothermal 9200 apparatus. After completion of the reactions, solvents were evaporated with rotary evaporator (Buchi RE model 111). All experiments were followed by using DC Alufolien Kieselgel 60 F_{254} Merck and Camag TLC lamp (254/366 nm). Solvents were dried by refluxing with the appropriate drying agents and distilled before use. All other reagents were purchased from Merck, Fluka, Aldrich, Sigma and Acros Chemical Co. and used directly without further purification.

Calculation methods

Ab initio (RHF/3-21G) calculations by means of the GAUSSIAN 98W program package (Version 5.4 Rev A.9) were performed with full geometry optimization for reactants, intermediates and products to clear up the mechanism of the reactions of 1*H*-pyrazole-3-carboxylic acid **2** with aminophenol derivatives **4a–d**. Vibrational calculations for all calculated molecules were performed and negative imaginary frequencies were found for transitional states (TS). This means that their structures are true TS, so we can determine the structures that connect correct reactants and products by examining the imaginary frequencies obtained from the intrinsic reaction coordinate (IRC) calculations [23].

Preparation of the *N*-hydroxyphenyl-1*H*-pyrazole-3-carboxamides **4a–d** general procedures

*Method I: From 1H-pyrazole-3-carboxylic acid (**1**)*

Appropriate amounts of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid **1** (0.50 g, 1.80 mmol) and the corresponding aminophenol derivatives **3** (molar ratio 1:1) were dissolved in benzene or toluene and heated by stirring under reflux together with catalytic amounts of sulfuric acid for 7 h. Then the solution was cooled to 5°C in a refrigerator and the corresponding reaction products **4** were either precipitated or obtained after evaporation of the solvent and triturating with diethyl ether or petroleum ether. After suction filtration the crude products were recrystallized from the proper solvent (methanol) or washed with petroleum ether and cyclohexan for several times and dried on P_2O_5.

*Method II: From 1H-pyrazole-3-carboxylic acid chloride (**2**)*

Appropriate amounts of the acid chloride **2** (0.50 g, 1.30 mmol) and the corresponding aminophenol derivatives **3** (molar ratio 1:1) were dissolved in benzene or toluene and refluxed with no catalytic amounts of pyridine for 5–7 h. Then the solution was cooled to room temperature and the corresponding reaction products **4** were obtained after evaporation of the solvent and triturating with diethyl ether or petroleum ether. After suction filtration the crude products **4** either were recrystallized from the suitable alcohol or washed carefully with nonpolar solvents and dried.

4-Benzoyl-*N*-(2-hydroxyphenyl)-1,5-diphenyl-1*H*-pyrazole-3-carboxamide (**4a**)

By the method I with a reflux time of 7 h (2-aminophenol) resulting in a yield of 53% (0.33 g) or by the method II with a reflux time of 5 h (2-aminophenol) resulting in a yield of 34% (0.21 g). M.p. = 237–238°C (washed with petroleum ether and than cyclohexane). Calc. for $C_{29}H_{21}N_3O_3$ (459.50): C, 75.80; H, 4.61; N, 9.14%. Found: C, 75.79; H, 4.50; N, 9.11%. Selected IR data (cm^{-1}): $\nu = 3383$ (NH), 3500-3000 (b, peak max. 3194, OH, hydrogen bonded), 1685, 1638 (s, C=O), 1609, 1597, 1577, 1537, 1499 (C···C, C···N, aromatic rings, NH bend).^{1}H NMR ($CDCl_3$, ppm): $\delta = 9.62$ (b, 1H, OH), 8.74 (b, 1H, NH), 7.78-6.92 (m, 19H, Ph-H).^{13}C NMR ($CDCl_3$, ppm): $\delta = 193.82$ (Ph-C=O), 162.07 (-NH-C=O),

148.76, 147.19, 146.53 (C-3, C-5 exchangeable), 140.92, 139.85 (N-Ph), 135.11, 132.68, 131.94, 131.38, 131.12, 130.83, 130.46, 130.12, 129.78, 129.62, 127.91, 126.82 (C-Ph), 124.46, 124.02, 123.65 (C-4). GC/MS: $m/z = 459.3$ [M^+], 427.2, 383.2, 381.9, 365.2, 351.2, 350.2, 349.2, 323.2, 321.1, 306.2, 305.1, 295.2, 275.0, 245.0, 219.1, 218.1, 217.1, 190.1, 180.0, 175.1, 166.5, 165.1, 161.0, 146.4, 133.0, 129.0, 106.1, 105.0, 91.0, 89.0, 78.0, 77.0, 59.0, 51.0.

4-Benzoyl-*N*-(2-hydroxy-5-methylphenyl)-1, 5-diphenyl-1*H*-pyrazole-3-carboxamide (**4b**)

By method II with a reflux time of 7 h (2-amino-4-methylphenol) resulting in a yield of 41% (0.25 g). M.p. = 254°C (1-butanol). Calc. for $C_{30}H_{23}N_3O_3$: C, 76.09; H, 4.90; N, 8.87%. Found: C, 76.18; H, 5.02; N, 9.01%. Selected IR data (cm^{-1}): $\nu = 3379$ (NH), 3500-3000 (b, peak max. 3218 cm^{-1}, OH, hydrogen bonded), 1686, 1633 (s, overlap C=O, NH bend), 1602, 1591, 1575, 1547, 1504, 1488 (C···C, C···N, aromatic rings).^{1}H NMR ($CDCl_3$, ppm): $\delta = 9.56$ (b, 1H, OH), 8.53 (b, 1H, NH), 7.83-6.89 (m, 18H, Ph-H), 2.26 (b s, 3H, CH_3).^{13}C NMR ($CDCl_3$, ppm): $\delta = 193.78$ (Ph-C=O), 161.74 (-NH-C=O), 148.63, 146.81, 146.38 (C-3, C-5 exchangeable), 140.78, 139.96 (N-Ph), 135.19, 131.96, 131.88, 131.77, 131.48, 131.10, 130.74, 130.52, 130.27, 129.82, 129.75, 127.51, 126.90 (C-Ph), 124.75, 124.14, 121.60, 114.63 (C-4), 22.25 (CH_3).

4-Benzoyl-*N*-(3-hydroxypyridin-2-yl)-1,5-diphenyl-1 *H*-pyrazole-3-carboxamide (**4c**)

By method II with a reflux time of 7 h (2-amino-3-hydroxypyridine) resulting in a yield of 48% (0.28 g). M.p. = 227°C (methanol). Calc. for $C_{28}H_{20}N_4O_3$: C, 73.03; H, 4.38; N, 12.17%. Found: C, 73.15; H, 4.24; N, 12.23%. Selected IR data (cm^{-1}): $\nu = 3391$ (NH), 3600-3200 (b, peak max. 3275 cm^{-1}, OH, hydrogen bonded), 1718, 1663 (s, C=O), 1596, 1581, 1498, 1472 (C···C, C···N, aromatic rings, NH bend).^{1}H NMR ($CDCl_3$, ppm): $\delta = 9.36$ (b, 1H, OH), 8.28 (q, 1H, NH), 7.84-7.04 (m, 18H, Ph-H).^{13}C NMR ($CDCl_3$, ppm) $\delta = 193.28$ (Ph-C=O), 160.74 (-NH-C=O), 159.72 (C-2′, pyr.), 147.60, 146.74, 145.35, 145.24 (C-3, C-5 exchangeable), 140.98, 140.56, 139.87, 139.54 (N-Ph), 135.25, 135.02, 134.06, 132.02, 131.61, 131.31, 131.25, 131.01, 130.90, 130.59, 130.49, 130.37, 130.09, 127.77, 127.18 (C-Ph), 124.79, 122.96 (C-4).

4-Benzoyl-*N*-(4-hydroxyphenyl)-1,5-diphenyl-1 *H*-pyrazole-3-carboxamide (**4d**)

By method II with a reflux time of 6 h (4-aminophenol) resulting in a yield of 37% (0.22 g). M.p. = 255°C (methanol). Calc. for $C_{29}H_{21}N_3O_3$ (459.50): C, 75.80; H, 4.61; N, 9.14%. Found: C, 75.65; H, 4.48; N, 8.92%. Selected IR data (cm^{-1}): $\nu = 3550$-2900 (s, b, NH and OH, hydrogen bonded), 1657 (s, b, C=O), 1616, 1597, 1561, 1516, 1497, 1479 (C···C, C···N, aromatic rings, NH bend);^{1}H NMR (DMSO-d_6, ppm): $\delta = 10.23$ (b, 1H, OH), 9.25 (b, 1H, NH), 7.82-6.66 (m, 19H, Ph-H).^{13}C NMR (DMSO-d_6, ppm): $\delta = 192.52$ (Ph-C=O), 160.35 (-NH-C=O), 155.57 (O-Ph), 147.82, 145.06 (C-3, C-5 exchangeable), 140.40, 139.55 (N-Ph), 134.96, 131.70, 131.39, 131.01, 130.87, 130.74, 130.54, 130.25, 129.68, 127.83, 123.85, 123.34 (C-Ph), 116.70 (C-4). GC/MS: m/z = 459.3 [M^+], 441.4, 382.2, 380.2, 367.1, 353.2, 352.2, 351.2, 349.2, 323.2, 321.3, 307.2, 306.2, 305.2, 295.2, 293.2, 272.2, 248.2, 247.1, 219.2, 218.2, 204.2, 191.8, 190.8, 181.1, 180.2, 175.8, 165.1, 152.2, 135.1, 108.1, 107.1, 106.1, 105.0, 91.0, 89.1, 81.1, 79.0, 78.1, 77.0, 71.1, 65.1, 64.0, 63.0, 55.1, 53.0, 52.0, 51.0.

Results and discussion

Synthesis and structure determination of the compounds **4**

Our approach to obtaining the particular heterocyclic systems uses the synthesis of the 1*H*-pyrazole-3-carboxylic acid **1** from 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione [1] and phenylhydrazine or phenylhydrazones, respectively [11, 16]. The compound **1** can easily be transformed into the corresponding 1*H*-pyrazole-3-carboxylic acid chloride **2** by usual chemical procedures [12]. Substituted 2,3-furandione, acid **1** and acid chloride **2**, which are used as an important initial materials in the synthesis of the target heterocycles, were prepared using the literature procedures [1, 11, 12, 16]. The reaction of the compound **1** or **2** with some aminophenols led to the formation of the corresponding carboxamide derivatives **4** under reflux for 5–7 h, without opening the pyrazole ring. In order to make the reaction selective, we had to determine the parameters in other words the reaction pathways, leading to such results. The compounds **1** or **2** treatment with various aminophenol derivatives **3a–d** in boiling benzene or toluene gave the corresponding *N*-(hydroxyphenyl)-1*H*-pyrazole-3-carboxamides **4** as main product. The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **4a–d** were obtained in moderate yields (37–53%) after evaporation of the organic solvents and recrystallization from proper solvent (like ethanol or methanol, see Scheme 1). A thin layer chromatographic analysis of the mother liquors still revealed the presence of more **4a–d** and, in the cases of 2-aminophenol or 2-amino-3-hydroxypyridine **3a**,**c** as starting materials, small amounts of by-products (probably 1*H*-pyrazole-3-carboxylate esters) were also determined. Although we have not studied this issue further,

we assume that the reaction occurs under thermodynamic control. It is worth mentioning that **4a–d** can be acquired in the reaction mixtures by monitoring the progress of each reaction and, therefore, are not the result of an improper isolation and/or purification of the esters formed in the above mentioned nucleophilic substitution reactions. The selectivity of the reaction is controlled by the reaction conditions and the basicity/nucleophilicity balance of the NH groups versus OH groups of **3a–d** By employing 2-aminophenol in reaction with **1** or **2**, the compound **4a** was obtained, exclusively. The formation of this adduct **4a**, which is synthesized from **1** and 3-amino-4-hydroxybenzenesulphonic acid in boiling xylene for 9 hours in yield (40%), is strongly supported by the results of all analytical and spectroscopic measurements, in particular by the presence of carbonyl characteristic bands of **4a** (FT IR: 1685 s, 1637 s. cm^{-1}). The broad absorption bands of NH and OH groups were observed between 3500-3000 cm^{-1} (peak max. 3383 and 3193, hydrogen bonded) [11–14, 24, 25], and the skeleton bands of benzene or pyrazole rings with together NH bending vibrations were observed at 1609-1449 cm^{-1} (C···C, C···N). Important structural information about **4a** can be obtained from its ^{13}C NMR spectrum. The ^{13}C NMR peaks were found to be at 193.82 (t,$^{3}J = 4.3$ Hz, Ph-CO), 162.07 (s, N-CO), 148.76, 147.19, 146.53 (C-3, C-5 exchangeable), 140.92, 139.85 (N-Ph), 135.11-126.82 (C-Ph) and 124.46, 124.02, 123.65 ppm (s, C-4). Final confirmation of structure **4a** was derived from its ^{1}H NMR spectrum: $\delta = 9.62$ ppm (broad, OH), 8.74 (broad, NH) and 7.78-6.92 for a set of signals for aromatic protons [24, 25]. In addition, the structure of **4a** was revealed by its GC/MS analysis, too, for details see Experimental part.

Theoretical calculations and results

To support the reaction mechanism, we have investigated it as quantum chemical calculations as well. Carbonyl groups are well known to be hard centres, responsive to the basicity of the nucleophile. However, carbonyl groups are responsible for the terms of frontier orbitals as well. Hard nucleophiles are generally those which are negatively charged and have relatively low-energy HOMOs. HOMO energies of aminophenol derivatives **3a–d** are -0.27121, -0.26843, -0.28663, -0.26759 a.u., respectively. LUMO energy of the 1*H*-pyrazole-3-carboxylic acid **1** is 0.08689 a.u. Mulliken charges of nitrogen atoms of aminophenols **3a–d** are -0.97, -0.98, -0.99, -1.02 ē, respectively. That is why aminophenols are hard nucleophiles. Aminophenols can be reacted with hard electrophiles. Charge of C_6 atom of 1*H*-pyrazole-3-carboxylic acid is 0.98 ē. Therefore charges control plays an essential role in this interaction and in the compounds' chemical reactivity.

One imaginary frequency found for $\mathbf{TS_{a–d}}$ indicates the structure being a true transition state. The main geometric

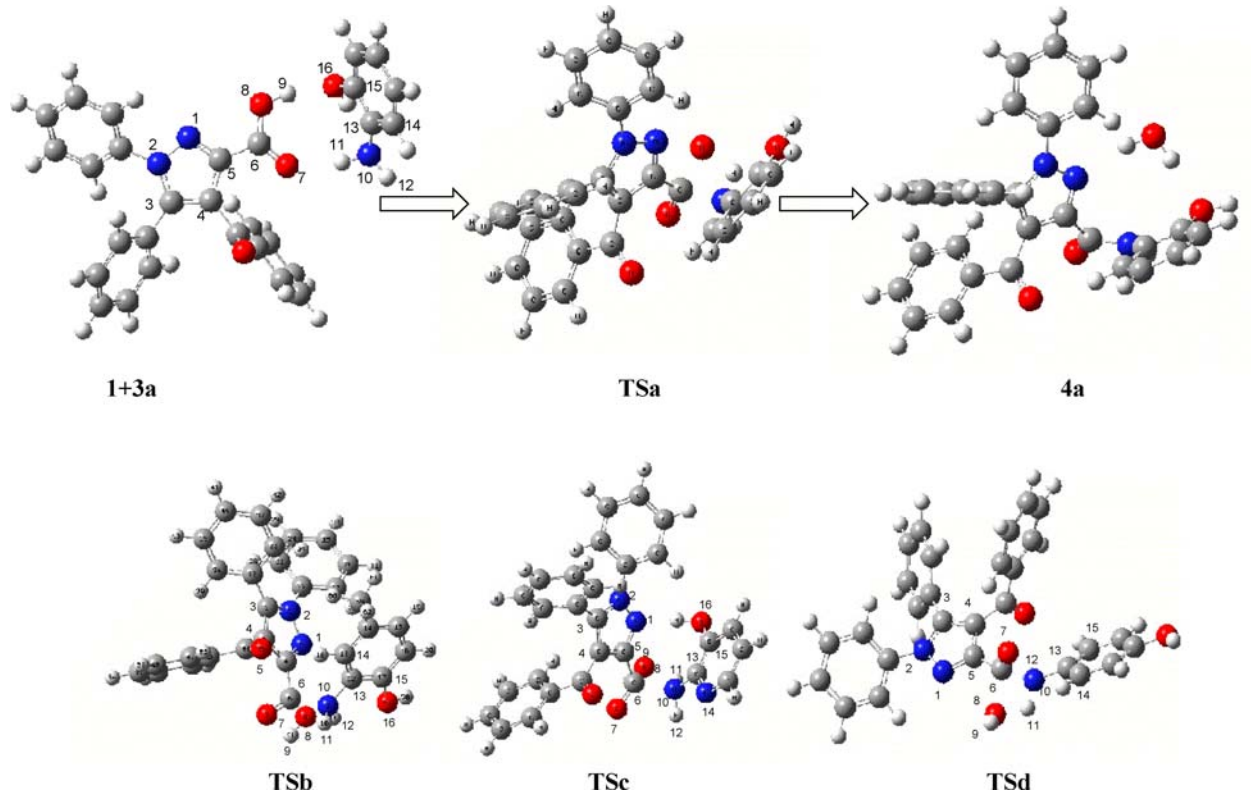

Fig. 1 Structures of **1** + **3a**, **4a** and transition states ($\mathbf{TS_{a–d}}$)

Table 1 The geometric and electronic parameters of $\mathbf{1}+\mathbf{3}_{\mathbf{a–d}}$, $\mathbf{TS1}_{\mathbf{(a–d)}}$, $\mathbf{4}_{\mathbf{(a–d)}}$ (RHF-3-21G)

	1 + 3				**TS1**				**4**			
	a	**b**	**c**	**d**	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**
Bond length												
C_5-C_6	1.46	1.46	1.46	1.46	1.48	1.48	1.48	1.49	1.48	1.48	1.50	1.49
C_6-O_7	1.22	1.22	1.22	1.21	1.24	1.24	1.23	1.24	1.21	1.23	1.22	1.22
C_6-O_8	1.32	1.32	1.32	1.34	1.64	1.65	1.69	1.66	4.04	3.12	3.34	3.83
O_8-H_{11}	3.45	3.41	3.32	4.26	1.48	1.48	1.49	1.47	0.97	0.97	0.97	0.97
N_{10}-C_{13}	1.40	1.39	1.38	1.38	1.44	1.44	1.43	1.44	1.42	1.41	1.39	1.42
C_6- N_{10}	3.90	3.90	1.33	4.13	1.60	1.60	1.62	1.61	1.36	1.34	1.36	1.34
C_{15}-O_{16}	1.40	1.41	1.40	–	1.37	1.38	1.37	–	1.39	1.38	1.38	–
N_{10}-H_{11}	1.01	1.01	1.00	1.00	1.07	1.07	1.06	1.01	3.24	3.28	4.92	4.78
Total energy (a.u)	− 1565, 6081	− 1604, 4290	− 1581, 5114	− 1565, 5840	− 1565, 5099	− 1604, 3307	− 1581, 4162	− 1564, 9997	− 1565, 5816	− 1604, 4049	− 1581, 4811	− 1565, 0880
Frequency (cm^{-1})					− 1635	− 1634	− 1577	− 1599				
Bond angles												
N_1-C_5-C_4	79	111.79	110.24	111.71	111.94	111.92	1.9.89	111.45	110.24	111.96	110.43	110.73
N_1-C_5-C_6	123.84	123.85	125.18	123.34	126.75	126.70	124.27	122.88	122.72	123.48	122.76	117.48
C_5-C_6-O_8	114.57	114.65	115.43	113.29	105.00	104.88	108.80	102.72	170.75	172.11	101.09	136.70
C_5-C_6-N_{10}	120.36	150.43	113.59	27.01	151.40	110.28	114.48	116.66	110.36	118.50	121.21	125.42
O_7-C_6-N_{10}	33.16	33.81	75.44	138.04	114.31	114.44	113.49	118.34	119.28	122.92	117.66	128.39
C_6-N_{10}-C_{13}	97.50	100.05	134.43	121.79	123.24	122.94	119.46	120.52	126.52	126.82	128.12	116.13
N_{10}-C_{13}-C_{14}	124.79	124.10	120.19	121.02	122.62	122.34	119.87	119.87	122.18	122.06	121.03	124.88
N_{10}-C_{13}-C_{15}	117.20	118.12	119.76	105.31	117.03	117.16	118.47	107.42	118.68	118.17	118.48	114.20
Dihedral angles												
C_4-C_5 C_6-O_8	179.74	179.84	141.86	176.61	159.46	159.28	144.29	− 153.31	− 177.38	136.84	83.77	170.06
N_1-C_5-C_6-O_8	178.24	− 1.70	37.19	− 6.01	− 153.32	− 20.53	− 33.34	35.96	7.01	− 36.78	− 93.55	− 7.77
C_4-C_5-C_6-O_7	− 0.22	− 0.16	36.94	− 3.80	26.10	25.93	22.23	74.32	54.34	52.10	86.56	151.48
N_1-C_5-C_6-O_7	178.24	178.29	− 144.00	173.57	− 153.33	− 153.88	− 155.41	− 96.40	− 121.26	− 121.51	− 90.76	− 26.36
C_5-C_6-O_8-H_{11}	179.22	179.42	171.88	178.62	− 123.17	− 123.65	− 129.26	− 120.35	142.45	− 96.72	− 128.84	− 6.64
C_5-C_6-N_{10}- C_{13}	− 77.91	− 88.39	− 78.97	178	8.04	8.84	15.70	136	− 3.91	− 4.27	− 13.57	170
C_6-N_{10}-C_{13}-C_{14}	137.54	140.71	149.39	153.31	63.28	62.88	96.31	52.84	38.38	43.43	− 12.32	− 163.13
C_6-N_{10}-C_{13}-C_{15}	− 44.72	− 41.61	− 26.37	− 27.08	− 116.84	− 116.73	− 85.11	− 128.71	− 144.78	− 139.74	168.41	17.87

Table 2 The geometric and electronic parameters of $\mathbf{1}+\mathbf{3_a}$, $\mathbf{TS1_a}$, $\mathbf{4_a}$ (RHF/3 − 21G and RHF/6 − 31G)

	1 + 3a		TS1a		4a	
Bond Length (Å)	(3-21G)*	6-31G	(3-21G)*	(6-31)	(3-21G)*	6-31
C_5-C_6	1.45	1.46	1.48	1.47	1.48	1.48
C_6-O_7	1.32	1.23	1.24	1.21	1.21	1.23
C_6-O_8	1.32	1.32	1.64	2.09	4.04	4.08
O_8-H_{11}	3.45	3.38	1.48	1.21	0.97	0.95
N_{10}-C_{13}	1.46	1.38	1.44	1.45	1.42	1.41
C_6-N_{10}	2.00	3.94	1.60	1.49	1.36	1.36
C_{15}-O_{16}	1.41	1.40	1.37	1.37	1.39	1.38
N_{10}-H_{11}	1.02	0.99	1.07	1.28	3.24	3.49
Total energy (a.u.)	− 1565, 9706	− 1573, 7228	− 1565, 9508	− 1573, 6725	− 1565, 9893	− 1573, 7542

*Catalytic effect was taken into account

parameters of the reactants ($\mathbf{1}+\mathbf{3_{a–d}}$), $\mathbf{TS_{a–d}}$ and $\mathbf{4_{a–d}}$ calculated by RHF/3-21G method are given in Table 1 and optimized structures of them are shown in Fig. 1.

Inspection of the data given in Table 1 reveals in $\mathbf{TS_a}$, C_6–N_{10} and C_6–O_8 lengths are 1.60 Å, and 1.64 Å, respectively. This fact indicates that we have a concerted reaction in which bonds are broken and formed simultaneously, and thus, no intermediates occur. The two reactants approach each other in gauche mode with the dihedral angle C_5–C_6–N_{10}–C_{13} (− 77.91°) formation. The Mulliken charges of C_6 at $\mathbf{1}+\mathbf{3_a}$, $\mathbf{TS_a}$ and $\mathbf{4_a}$ are respectively 0.98, 0.79, 0.88 ē, charges of N_{10} at $\mathbf{1}+\mathbf{3_a}$, $\mathbf{TS_a}$ and $\mathbf{4_a}$ are − 0.97, − 1.00, − 1.00 ē, and those of O_7 at $\mathbf{1}+\mathbf{3a}$, $\mathbf{TS_a}$ and $\mathbf{4_a}$ are respectively − 0.67, − 0.73, − 0.59 ē. So, the Mulliken population values on atoms show that the electronic density redistribution happens due to the nature of bonds that are formed as a result of different orbitals overlapping. As a consequence of the charge redistribution, the bonds' lengths change as well (see Table 1).

The energetic features were studied by RHF/3-21G, RHF/6-31G (see their values given in Tables 1 and 2). Calculated from Table 1 values of activation barriers for reactions **a–d** are 37.09, 44.92, 32.47 and 39.25 kcal/mol respectively for RHF/3-21G. Calculated activation barrier for reaction **a** is 33.81 kcal/mol with RHF/6-31G. The compound **1** becomes meta-stable with the catalytic effect and charges of C6, O7 and O8 atoms increases to 1.005, 0.62 and 0.71 ē respectively and bonds between C6 and O atoms is weaken so the leaving of water and because of the increasing charge of C6 atom C6–N9 bond occurs easily.

A second general mechanism is an acid-catalyzed mechanism. As calculations were done by taking into account catalytical effect, it was observed activation energy decreases from 37.09 to 13.31 kcal/mol. In the first step the acid attacks an electron pair of the carbonyl oxygen atom. The resulting protonated carbonyl compound is highly reactive because the carbonyl carbon carries more positive charge (−1.02 ē) than it does in the unprotonated compound (−0.97 ē). Therefore the activation energy for the uncatalyzed reaction is 23.78 kcal/mol larger than the activation energy for the catalyzed reaction.

Conclusions

N-(Hydroxyphenyl)-1*H*-pyrazole-3-carboxamides **4** have been synthesized from the nucleophilic substitution reaction of the pyrazole-3-carboxylic acid **1** or the -acid chloride **2** with the corresponding aminophenols **3a–d** without opening the pyrazole ring. Quantum-chemistry calculations were performed for reactants, **TS**s and products to understand the reaction mechanism. Electronic parameters of the reactants and products were calculated. This study and the proceeding reports in this series disclose only a few aspects of the scope of this chemistry. Other applications are under investigation.

In this reaction, charges control plays an essential role, as to the compounds' chemical reactivity, and reaction proceeds through one TS. At the beginning, the electron density on the reacting atoms is 0.98 ē, but because of while new bonds that have been formed in the TS, the electron density decreases to 0.79 ē, while in the product it increases to 0.88 ē. Electron density of C_6. As the result decreasing electron density on the C_6–O_8 bond, the length of this bond increases.

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