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Reaction of (chloro carbonyl) phenyl ketene with 5-amino pyrazolones: Synthesis, characterization and theoretical studies of 7-hydroxy-6-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidine-2,5(1*H*,4*H*)-dione derivatives

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ABSTRACT

New 7-hydroxy-6-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidine-2,5(1*H*,4*H*)-dione derivatives were synthesized from the reaction of (chlorocarbonyl)phenyl ketene and 5-amino pyrazolones in high to excellent yields and short reaction times. Structures of the new compounds were fully characterized by their spectral data IR, ^{1}H NMR, and ^{13}C NMR and by the theoretical results. Density Functional Theory (DFT) was used to optimize the structures, compute the energies and vibrational frequencies IR and ^{1}H NMR shielding tensors of the desired products. The theoretical results excellent are compared with the experimental data.

1. Introduction

(Chlorocarbonyl)ketenes are versatile bifunctional reagents for the synthesis of numerous heterocyclic compounds. The reactions of bisnucleophiles with these ketenes leads to cyclic compounds, which have been reported in several papers [1,2]. (Chlorocarbonyl) phenyl ketene has been used mainly for the synthesis of five and six membered heterocycles functionalized with oxo and hydroxyl groups in 1,3-positions. The reactions of binucleophiles with this ketene lead to the synthesis of heterocyclic compounds [3,4]. Structures containing such units often play an essential role due to their biological activity, predominantly in cancer and virus research [5,6]. Pyrazole derivatives are one of the important class of heterocyclic compounds. This compounds can be used as the intermediate in organic synthesis and possess a range of interesting biological and antimicrobial properties [7–10]. a massive search for new anticancer agents has been fueled by various academics and industries to unveil the new molecular targets and mechanisms based on the lead candidates of different classes of compounds. A large number of pyrazolo[1,5-*a*]pyrimidine derivatives are reported to exhibit a broad spectrum of biological activities such as antitumor [11,12], anxiolytic [13]and antimicrobial [14]. But pyrazolo [1,5-*a*]pyrimidine derivatives are widely used as inhibitors of cyclin-dependent kinases (CDKs), that are involved in mediating the transmission of mitogenic signals and numerous other cellular events [15–18] including cell proliferation, migration, differentiation, metabolism and immune response. Some their fused pyrimidine derivatives are used as dyes [19–23]. Due to the biological activities of pyrazolo[1,5-*a*]pyrimidine derivatives new ways for the synthesis of these compounds have been of interest. So in order to access analogs of pyrimidine fused to pyrazole rings, the reaction of (chlorocarbonyl)phenyl ketene with 5-aminopyrazole-3-one derivatives was investigated in this paper.

2. Experimental

Phenyl malonic acid, aniline derivatives, ethyl cyanoacetate and hydrazine hydrate were obtained from Merck Chemical Co. and were used without further purification. (Chlorocarbonyl)phenyl ketenes **4** were prepared according to the literature procedure [24]. The 5-amino-1,2-dihydro-3*H*-pyrazol-3-one derivatives **3a–e** were known and prepared according to the general procedure reported

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in the literature [25]. THF was dried over sodium and distilled prior to use. Melting points were measured on an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. The proton and carbon NMR spectra were recorded with Bruker DRX-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, internal standard TMS. Elemental analyses were carried out using a Heraeus CHN-O-Rapid analyzer.

2.1. Theoretical method

All geometry optimizations and quantum chemical calculations were performed through Gaussian 09 software [26] using density functional theory (DFT) with B3LYP/6-311G quantum level. The B3LYP(Becke's hybrid 3-parameter functional with Lee-Yang-Parr correlation)functional was selected for the calculations. B3LYP has been introduced as one of the most accurate methods for energy calculation. Structure parameters have been calculated by optimizing type job in Gaussian package. For Thermodynamic properties (ΔG) and IR spectrum, frequency type job at Gaussian package has been done and NMR data have obtained by NMR type job with the same method.

2.2. Typical procedure for the preparation of compounds (**5a**–**c**)

To a stirred solution of corresponding 5-amino-1,2-dihydro-3*H*-pyrazol-3-one derivatives **3** (2 mmol) in 20 mL boiling dry THF was added a mixture of (chlorocarbonyl)phenyl ketene **4** (2 mmol) in 5 ml dry THF dropwise over 2 min. The product was formed after 5 min as a colored precipitate. Stirring was then continued for an additional 15 min. The solid product was collected and recrystallized from dry ethyl acetate and hexane (2:3).

2.3. 7-Hydroxy-6-phenyl-3-(phenyldiazenyl)pyrazolo [1,5-a] pyrimidine-2,5(1H,4H)-dione (**5a**)

The 0.29 g (85%) red crystals, IR (KBr): 3200-2900 (NH, OH), 1657 (C=O), 1625, 1550, 1481 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.01 (1H, s, NH), 9.32 (1H, s, OH), 8.17–6.97(10H, m, arom, NH)[8.16 (2H, d, $^3J_{H-H}$ = 8 Hz), 8.87 (2H, d, $^3J_{H-H}$ = 8 Hz), 7.46–7.43 (3H, m), 7.29–7.23 (3H, m), 7.98 (1H, t, $^3J_{H-H}$ = 8 Hz)]. ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm): 160.04, 159.80, 151.36, 145.94, 143.69, 134.35, 129.22, 127.51, 126.88, 123.31, 123.01, 117.76, 84.32, 67.93. Anal. Calcd for. $C_{17}H_{13}NO_3S$: C, 62.24; H, 3.77; N, 20.16; O, 13.82%. Found: C, 62.02; H. 3.59; N; 20.01%.

2.4. 7-Hydroxy-3-((4-methoxyphenyl)diazenyl)-6-phenylpyrazolo [1,5-a]pyrimidine-2,5(1H,4H)-dione (**5b**)

The 034 g (90%) dark violet crystals, IR (KBr): 3200-2900 (NH, OH), 1668 (C=O), 1628, 1554, 1491 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.79 (1H, s, NH), 9.09 (1H, s, OH), 8.16–6.95(10H, m, arom, NH) [8.16 (2H, d, $^3J_{H-H}$ = 4 Hz), 7.83 (2H, d, $^3J_{H-H}$ = 8 Hz), 7.73–7.21 (3H, m), 7.01 (2H, d, $^3J_{H-H}$ = 8 Hz), 6.97 (1H, t, $^3J_{H-H}$ = 8 Hz)], 3.38 (3H, s, methoxy). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm): 160.58, 160.48, 158.78, 150.49, 146.20, 134.59, 129.26, 126.48, 123.32, 119.88, 118.51, 114.70, 84.26, 66.30, 55.46. Anal. Calcd for. $C_{19}H_{15}N_5O_4$: C, 60.48; H, 4.01; N, 18.56; O, 16.96%. Found: C, 60.31; H. 4.16; N; 18.39%.

2.5. 3-((4-Chlorophenyl)diazenyl)-7-hydroxy-6-phenylpyrazolo [1,5-a]pyrimidine-2,5(1H,4H)-dione (**5c**)

The 0.34 g (90%) dark violet crystals, IR (KBr): 3200-2900 (NH, OH), 1672 (C=O), 1593, 1549, 1484 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm): 9.77 (1H, s, NH), 9.06 (1H, s, OH), 8.15–6.96(10H, m, arom, NH) [8.14 (2H, d, $^3J_{H-H}$ = 8 Hz), 7,85 (2H, s), 7.48 (2H, d, $^3J_{H-H}$ = 8 Hz), 7.33–7.22 (2H, m), 6.96 (2H, s)]. ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm): 161.13, 160.35, 151.36, 145.54, 134.50, 131.10, 130.39, 129.54, 127.48, 123.26, 120.23, 116.85, 84.27, 67.64. Anal. Calcd for. $C_{18}H_{12}ClN_5O_3$: C, 56.63; H, 3.17; Cl, 9.29; N, 18.34; O, 12.57%. Found: C, 56.51; H. 3.02; N; 18.25%.

2.6. 7-Hydroxy-6-phenyl-3-(p-tolyldiazenyl)pyrazolo [1,5-a] pyrimidine-2,5(1H,4H)-dione (**5d**)

The 0.31 g (88%) violet crystals, IR (KBr): 3200-2900 (NH, OH), 1672 (C=O), 1628, 1552, 1492 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 9.96 (1H, s, NH), 9.25 (1H, s, OH), 8.17–6.97(10H, m, arom, NH) [7.16 (2H, d, $^3J_{H-H}$ = 8 Hz), 7.76 (2H, d, $^3J_{H-H}$ = 8 Hz), 7.24 (4H, t, $^3J_{H-H}$ = 8 Hz), 6.98 (2H, t, $^3J_{H-H}$ = 4 Hz), 2.49 (3H, s, methyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 160.08, 159.85, 151.31, 146.12, 141.10, 136.81, 134.47, 129.80, 127.61, 123.40, 123.10, 117.77, 84.40, 64.85, 20.62. Anal. Calcd for. $C_{19}H_{15}N_5O_3$: C, 63.15; H, 4.18; N, 19.38; O, 13.28%. Found: C, 63.01; H. 4.10; N; 19.29%.

2.7. 4-((7-Hydroxy-2,5-dioxo-6-phenyl-1,2,4,5-tetrahydropyrazolo [1,5-a]pyrimidin-3-yl)diazenyl) benzenesulfonamide (**5e**)

The 0.35 (82%) dark violet crystals, IR (KBr): 3639, 3547 (NH_2), 3300-2800 (NH, OH), 1688 (C=O), 1630, 1596, 1486 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm): 10.08 (1H, s, NH), 9.32 (1H, s, OH), 8.16–6.96 (12H, m, arom, NH, NH_2) [8.16 (2H, d, $^3J_{H-H}$ = 4 Hz), 8.00 (2H, d, $^3J_{H-H}$ = 4 Hz), 8.87 (2H, d, $^3J_{H-H}$ = 4 Hz), 7.41 (2H, s, NH_2), 7.29–7.22 (3H, m), 6.98 (1H, t, $^3J_{H-H}$ = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm): 160.52, 160.43, 153.78, 145.48, 141.66, 134.48, 130.52, 129.82, 128.29, 127.60, 123.42, 118.41, 84.48, 67.02. Anal. Calcd for. $C_{18}H_{14}N_6O_5S$: C, 50.70; H, 3.31; N, 19.71; O, 18.76; S, 7.52%. Found: C, 50.54; H. 3.16; N; 19.88%.

3. Result and discussion

Synthesis of 5-aminopyrazoles **3** is readily available by diazotization of aniline derivatives **1a**–**e** followed by coupling with ethyl cyanoacetate, affording the corresponding hydrazones **2a**–**e**. Reaction of compounds **2** with hydrazine hydrate undergoes corresponding 5-aminopyrazoles **3a**–**e** [25] in good yields, Scheme 1.

In connection with our ongoing work on the development of new synthetic routes to heterocyclic compounds by condensation of (chlorocarbonyl)ketenes **4** with 1,3-dinucleophiles [1,3,4], we report herein the reaction of (chlorocarbonyl)ketenes **4** with 5-aminopyrazoles **3** for the synthesis of 7-hydroxy-6-phenyl-3-(phenyldiazenyl)pyrazolo[1,5-*a*]pyrimidine-2,5(1*H*,4*H*)-dione derivatives **5a**–**e**, Scheme 2.

A literature survey indicates that only a few references are available on the synthesis and chemistry of pyrazolo [1,5-*a*]pyrimidine derivatives [27]. In this method, 7-hydroxy-6-phenyl-3-(aryldiazenyl)pyrazolo[1,5-*a*]pyrimidine-2,5(1*H*,4*H*)-dione derivatives **5a**–**e** have been produced from the one-pot cyclocondensation of (chlorocarbonyl)phenyl ketene **4** and 5-amino-4-(aryldiazenyl)-1,2-dihydro-3*H*-pyrazol-3-one derivatives **3**. The simplicity and efficient one-pot procedure is one aspect of particular interest, in comparison to the other multi-step methods. On the other hand, readily available starting materials such as (chlorocarbonyl)phenyl ketene, shorten experimental time, and high yield of the final products are the other advantages of this method. When (chlorocarbonyl)phenyl ketenes **4** were added to a solution of the 5-aminopyrazolone derivatives **3** at boiling solvent, precipitate of the product was formed immediately.

A plausible mechanism for the formation of the product **5** is