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Synthesis and Structure Elucidation of 4-(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-methylene)-2-phenyl-1*H*-imidazol-5(4*H*)-one

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Abstract: 4-(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl-methylen)-2-phenyl-1(3*H*)-imidazol-5-one **(5)** was synthesized in four steps in high yield. Benzimidinium chloride **(1)** reacted with dimethyl acetylenedicarboxylate to afford 2-phenyl-4-methoxycarbonylmethylen-1(3*H*)-imidazol-5-one **(2)** which was converted to 2-phenyl-4-hydrazinecarbonylmethylen-1(3*H*)-imidazol-5-one **(3)** using hydrazine hydrate in methanol. Furthermore, the reaction of **(3)** with carbon disulfide afforded compound **(4)** which can be used without further purification to achieve compound **(5)** using hydrazine hydrate.

Keywords*:* Dimethyl acetylenedicarboxylate (DMAD), Structure elucidation, Benzimidinium chloride, Imidazole derivative.

Introduction

Heterocyclic compounds particularly five and six member ring derivatives have occupied a prominent place among various classes of organic compounds for their diverse biological activities[1]. Substituted imidazoles have been reported to act as anti-inflammatory[2a], analgesic[2b], antibacterial[3a], antifungal[3b], antituberculosis[3c] and anticonvulsant[3d]. Also, imidazoles derivatives have for years been targets for the search of compounds that can modulate *e.g.* blood pressure, heart rate, CNS diseases and drugs like clonidine and phentolamine have been marketed for the treatment of hypertension[4-6]. Recently, the interest in this heterocyclic system has widened as it is a precursor to a class compounds called room temperature ionic liquids[7]. They have become ubiquitous ligands in organometallic chemistry and catalysis[8-11].

Triazoles and condensed triazole system were reported to possess diverse types of biological activities including antifungal, antibacterial, antiparasitic, hypocholesteremic, hypotensive and anti-inflammatory properties[12-13]. In continuation of our work on the synthesis of heterocyclic systems containing nitrogen and sulfur[14], we describe here the synthesis of new imidazole and triazole derivative.

Experimental

The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (the samples as KBr disks for the range 400-4000 cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H, 300.134 MHz; ^{13}C, 75.469 MHz) using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The C, H, N analyses were performed by the microanalytical service of the N.I.O.C. Research Institute of Petroleum Industry.

*2-Phenyl-4-methoxycarbonylmethylen-1(3H)-imidazol-5-one (**2**)*

A solution of benzimidinium chlorid (1.57 g, 10 mmol) and DMAD (1.42 g, 10 mmol) in 15 mL of MeOH was heated at reflux for 3 h. The solution was cooled and the reaction vessel set aside overnight. The crystals formed were separated. Yield 92%, mp 156-157 ^{o}C; MS: *m/z* 230 (M^{+}); FT-IR: NH_2 3082, CO 1748, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H, OMe), 7.05 (s, 1H, =CH), 7.58 (m, 3H, Ar-H), 8.08 (m, 2H, Ar-H), 11.66 (s, 3H, NH). ^{13}C NMR (DMSO-d_6) δ 51.7 (OMe), 115.9 (=CH), 126.1 (C-Ar), 128.5 (C-Ar), 129.5 (C-Ar), 132.9 (C-Ar), 151.9 (C=C), 167.5 (C=N), 168.9 (C=O), 187.4 (C=O). *Anal*. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.17. Found: C, 62.59; H, 4.33; N, 12.18.

*2-Phenyl-4-hydrazinecarbonylmethylen-1(3H)-imidazol-5-one (**3**)*

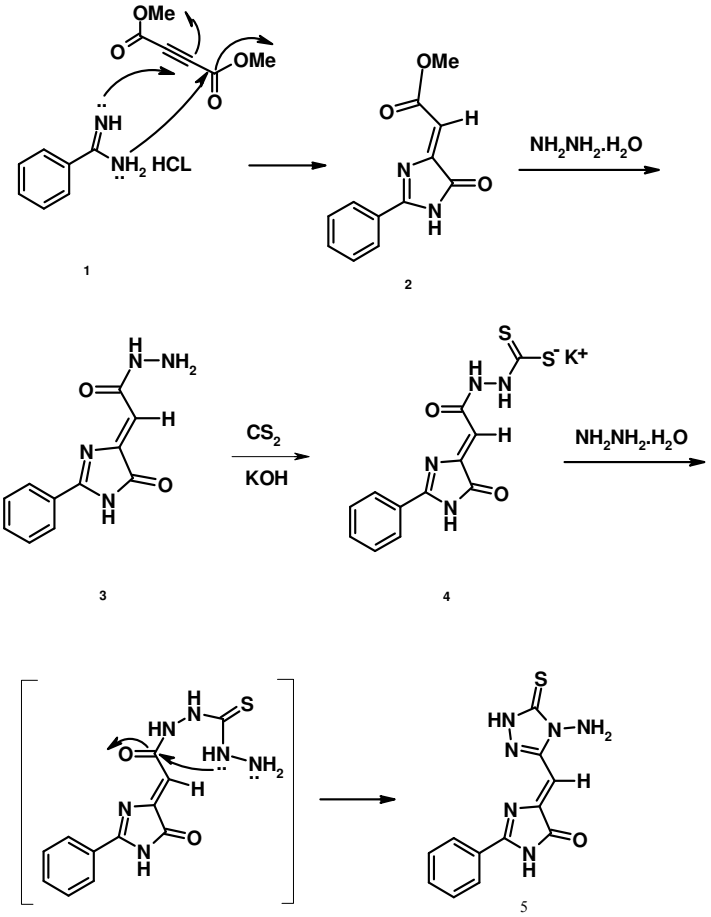
A mixture of **2** (2.30 g, 10 mmol) and hydrazine hydrate (0.85 mL, 15 mmol, 85%) in 30 mL of methanol was heated at reflux for 1 h. The methanol, water and excess hydrazine hydrate were removed in vacuo, and the residual solid recrystallized from ethanol. Yield 88%, mp > 300 ^{o}C; MS: *m/z* 231 (M^{+}); FT-IR: NH_2 3294, CO 1688, 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.90 (s, 2H, NH_2), 6.79 (s, 1H, =CH), 7.55 (m, 3H, Ar-H), 7.72 (m, 2H, Ar-H), 8.41 (br, 1H, NH), 10.17 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 119.5 (=CH), 126.0 (C-Ar), 128.4 (C-Ar), 129.1 (C-Ar), 131.2 (C-Ar), 149.5 (=C), 158.7 (C=N), 162.9 (C=O), 165.3 (C=O). *Anal*. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.14; H, 4.33; N, 24.24. Found: C, 57.15; H, 4.31; N, 24.22.

4-(4-*Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-ylmethylen)-2-phenyl-1(3H)-imidazol-5-one (**5**)*

Carbon disulfide (0.85 mL, 14 mmol) was added drop wise to an ice-cold solution of potassium hydroxide (0.84 g, 15 mmol) and **3** (2.08 g, 9 mmol) in 30 mL absolute ethanol. The mixture was stirred at room temperature for 14 h. Dry ether 20 mL was then added and the separated solid was filtered and washed with ether (2x5 mL). The product **4** obtained in nearly quantitative yields was employed in the next reaction without further purification. A suspension of **4** (about 2.75 g, 8 mmol) and hydrazine hydrate (0.91 mL, 16 mmol, 85%) in 20 mL of water refluxed while stirring for 4 h. Hydrogen sulfide was evolved. On dilution with 100 mL of cold water and acidification with concentrated HCl, the solid was precipitated. The product was filtered, washed with water and recrystallized from ethanol. Yield 85%, mp 213 ^{o}C; MS: *m/z* 286 (M^{+}); FT-IR: NH_2 3440, CO 1678 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 6.05 (s, 2H, NH_2), 7.15 (s, 1H, =CH), 7.64 (m, 3H, Ar-H), 8.20 (m, 2H, Ar-H), 13.07 (br, 1H, NH), 14.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 121.1 (=CH), 125.7 (C-Ar), 127.6 (C-Ar), 128.3 (C-Ar), 132.1 (C-Ar), 151.3 (=C), 153.2 (C=N), 156.5 (C=N), 166.2 (C=O), 180.2 (C=S). *Anal*. Calcd. for $C_{12}H_{10}N_6OS$: C, 50.35; H, 3.50; N, 29.37. Found: C, 50.33; H, 3.51; N, 29.35.

Results and Discussion

2-Phenyl-4-methoxycarbonylmethylen-1(3*H*)-imidazol-5-one (**2**) was obtained when benzimidinium chloride **(1)** is heated at reflux with DMAD (dimethyl acetylenedicarboxylate) in methanol. It's ^{1}H NMR spectrum exhibits signals corresponding to =CH and NH groups at δ 7.05 and 11.66 ppm, respectively. The reaction of **2** with hydrazine hydrate in methanol afforded 2-phenyl-4-hydrazinecarbonylmethylen-1(3*H*)-imidazol-5-one **3**. The IR spectra of **3** exhibited the absorption bond of NH_2 at 3294 cm^{-1}. The ^{1}H NMR spectra showed two broad lines δ 4.90 and 8.41 ppm arising from NH_2 and NH, respectively. The OMe was not observed in the ^{1}H and ^{13}C NMR spectra of compound **3**. These can be assigned for the exchange of OMe with $NH_2NH_2.H_2O$ and are in agreement with carbonylhydrazine functional group in compound **3**. Carbon disulfide was then added to a solution of **3** in potassium hydroxide / ethanol to give potassium *N*-[(2-phenyl-1(3*H*)-imidazol-5-one-4-yliden)acetyl] hydrazinecarbodithiolate **4**. A suspension of **4,** without further purification, and hydrazine hydrate in water refluxed while stirring to furnish 4-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-ylmethylen)-2-phenyl-1(3*H*)-imidazol-5-one **5**. The structure of compound **5** was deduced from its elemental analyses and its IR, ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR of compound **5** exhibited two broad lines δ 13.07 and 14.24 ppm arising from NH protons along with a broad signal from NH_2 protons at about δ 6.05 ppm.



Scheme 1

Conclusion

In conclusion, a general and convenient synthesis of functionalized C=S and NH_2 has been developed. The main advantages of these reactions are mild reaction conditions and high yields. The new compounds could be of interest in pharmacology, biology and as building blocks for cyclocondensations[1-14].

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