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Click one pot synthesis, spectral analyses, crystal structures, DFT studies and brine shrimp cytotoxicity assay of two newly synthesized 1,4,5-trisubstituted 1,2,3-triazoles

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ABSTRACT

Methyl-2-(1-benzyl-4-phenyl-1*H*-1,2,3-triazol-5-yl)-2-oxoacetate **(1)** and ethyl-2-(1-benzyl-4-phenyl-1*H*-1,2,3-triazol-5-yl)-2-oxoacetate **(2)** were synthesized by one pot three component strategy, and characterized by FT-IR, NMR (^{1}H and ^{13}C) spectroscopy and TOF-MS spectrometry. Finally, the structures were unequivocally confirmed by single crystal X-ray diffraction analyses. Both compounds, **1** and **2** exist in monoclinic crystal packing having space group $P2_1/n$ and $P2_1/c$, respectively. Crystal structures investigations revealed that the molecular structures of the title compounds are stabilized by weak intermolecular hydrogen bonding interactions to form dimers. Density functional theory (DFT) calculations were performed not only to compare with the experimental spectroscopic results but also to probe structural properties. The molecular electrostatic potential (MEP) mapped over the entire stabilized geometries of the molecules delivered information about the electrophilic and nucleophilic sites. Furthermore, frontier molecular orbital analysis gave the idea about stability and reactivity of compounds. Both compounds were also screened for brine shrimp cytotoxicity assay.

1. Introduction

Click chemistry has recently emerged as an important tool in synthetic chemistry [1]. In recent years, the design and synthesis of pharmacologically relevant heterocyclic molecules by combinatorial techniques is proven as a promising approach in the search for new pharmacological lead structures [2]. Click chemistry is one of the leading reactions to make carbon-heteroatom-carbon (C-X-C) bonds in aqueous environment. Structures bearing C-X-C moiety possess a wide variety of chemical and biological applications in various fields [3–6]. Click reactions require only benign reaction conditions, simple workup including purification procedures, and can still promptly create molecular diversity through the use of reactive modular building blocks. In search for new compounds through these reliable and efficient reactions, click chemistry may accelerate the process of discovery and optimization [3,7].

Importance and applications of triazole chemistry regarding the click reactions is not much hidden, and has been explored by the scientific community extensively [8]. Click chemistry has been successfully applied to synthesize compounds for drug discovery, enzyme inhibition, receptor-ligand binding studies, for DNA labeling and for studying the biological systems [1].

In continuation of our ongoing research regarding the synthesis of 1,4,5-trisubstituted 1,2,3-triazole [9] derivatives via click reaction and density functional theory studies of different classes [10–12], here we are reporting the synthesis, structural investigations and brine shrimp cytotoxic assay of two new 1,4,5-trisubstituted 1,2,3-triazoles. Both compounds were synthesized in good yields, characterized by spectroscopic analysis and finally, the structures were

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confirmed unambiguously by X-ray diffraction studies. The DFT simulations were performed not only to validate the spectroscopic results, but also to investigate other structural properties like frontier molecular orbital (FMOs) analysis, molecular electrostatic potential (MEP). Both compounds were also screened for their brine Shrimp cytotoxicity assay.

2. Materials and methods

2.1. Experimental

Different alkyl and aryl azides were purchased from *J* and *K* chemicals China, and were used without further purification. Phenylacetylides were prepared according to the procedures reported in the literature [13]. Solvents of analytical reagent (AR) grades were purchased from Sigma Aldrich, and used without purification. Melting points were determined on a Yanaco melting point apparatus, and are reported as uncorrected. Thin layer chromatography (TLC) was carried out using pre coated silica gel 60 HF254 aluminum sheets (Merck). IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer, using ATR method. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-ECA 300 spectrometer. TMS was used as an internal reference and *J* values were calculated in Hz. HR-MS were obtained on a Bruker microTOF-QII spectrometer.

2.2. Synthesis

The synthesis of triazole derivatives (**1** and **2**) was carried out by adopting click one pot three component synthetic methodology (for synthetic scheme see Fig. 1).

2.2.1. General procedure for the synthesis of triazoles *1* and *2*

Synthesis of both compounds was accomplished by slight modification of the procedure already described in the literature [9,14].

Methoxalyl chloride for compound **1** and ethoxalyl chloride for compound **2** (0.07 g, 0.5 mmol) was added to a suspension of benzylazide (0.08 g, 0.6 mmol), copper (1) phenylacetylide (0.09 g, 0.5 mmol) and chlorobenzene (2 ml). The resultant mixture was stirred at room temperature for 4 h, and finally subjected to flash column chromatography eluting with 10% ethylacetate in petroleum ether to obtain **1** and **2** as white solids.

*2.2.1.1. Methyl 2-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)-2-oxoacetate **(1)**.* White crystalline solid, m. p. 75–77 °C, Yield = 91%, **IR** (ATR, cm^{-1}): ν_{max} 3031 ($CH_{arom.}$), 2954 (CH), 1739 ($COOCH_3$), 1687 (C=O), 1484 (C=C), 1455 (C=C), 1220 (N=N); **^{1}H-NMR** δ ppm 7.50–7.30 (m, 10H), 5.90 (s, 2H), 3.29 (s, 3H); **^{13}C-NMR** δ ppm 176.9, 161.2, 153.2, 134.2, 129.7, 129.5, 129.0, 128.8, 128.6, 128.5, 128.1, 127.2, 54.2, 52.7. **HRMS** (ESI-TOF) (*m/z*): calculated for $C_{18}H_{15}N_3O_3$, $[M+H]^+$ 322.1186; observed 322.1187.

*2.2.1.2. Ethyl 2-(1-benzyl-4-phenyl-1H-1, 2, 3-triazol-5-yl)-2-oxoacetate **(2)**.* White crystalline solid, m.p. 74–76 °C, Yield = 89%, **IR** (ATR, cm^{-1}): ν_{max} 3057 ($CH_{arom.}$), 2981 (CH), 1741 ($COOCH_3$), 1683 (C=O), 1537 (C=C), 1477 (C=C), 1224 (N=N); **^{1}H-NMR** δ ppm 7.52–7.28 (m, 10H), 5.88 (s, 2H), 3.71 (q, 2H, J = 7.2 Hz), 0.92 (t, 3H, J = 7.2 Hz); **^{13}C-NMR** δ ppm 177.3, 160.8, 152.9, 134.1, 129.6, 128.9, 128.7, 128.6, 128.5, 128.1, 127.2, 62.8, 54.1, 13.2. **HRMS** (ESI-TOF) (*m/z*): calculated for $C_{19}H_{17}N_3O_3$, $[M+H]^+$ 336.1343; observed 336.1345.

2.3. Crystallography

Suitable crystals of both compounds **1** and **2**, having proper size and shape were selected and analyzed by single crystal X-ray diffraction technique. Selected crystal of each compound was coated with paratone 8772 oil and mounted on a glass fiber. All measurements were made on Bruker Kappa *APEX*-IICCD diffractometer with graphite monochromatic M_o-K_α radiation. The structures were solved by direct method and refined by using *SHELXL* 2013 (Sheldrick, 2013) [15]. The figures were plotted with the aid of ORTEP II.

The cif files of both compounds have been assigned CCDC numbers 983913 and 994384 and can be obtained free of charge on application to CCDC 12 Union Road, Cambridge CB21 EZ, UK. (Fax: (+44) 1223 336-033; e-mail: data_request@ccdc.cam.ac.uk).

2.4. Computational details

Computational investigations were performed at density functional theory level by using Gaussian 09 software [16]. The visualization of the results/optimized geometries was achieved through GuassView 5.0 [17]. Optimization of both triazole derivatives **1** and **2** was carried out at B3LYP/6-31G (d, p) level of theory. Frequency simulations were performed at the same level, to confirm the optimized geometries as true minima (no imaginary frequency). Furthermore, frequency output files were used for simulated vibrational analysis. Theoretical nuclear magnetic resonance (^{1}H and ^{13}C NMR) studies were performed at B3LYP/6-311G+(2d,p) level, by adopting GIAO formalism, and the chemical shift were referred with reference to tetramethylsilane. Molecular electrostatic potential (MEP) and frontier molecular orbital (FMOs) were simulated at B3LYP/6-31G (d, p) level of DFT.

2.5. Brine shrimp cytotoxic lethality assay

A 24 h LC_{50} lethality test was performed in a 96 well plate using Brine shrimp (*Artemia salina*) larvae using literature method with some modifications [18]. Six graded concentrations (300, 100, 33.3, 11.1, 3.7, 1.3 μg/ml) in triplicate for test extracts were used.

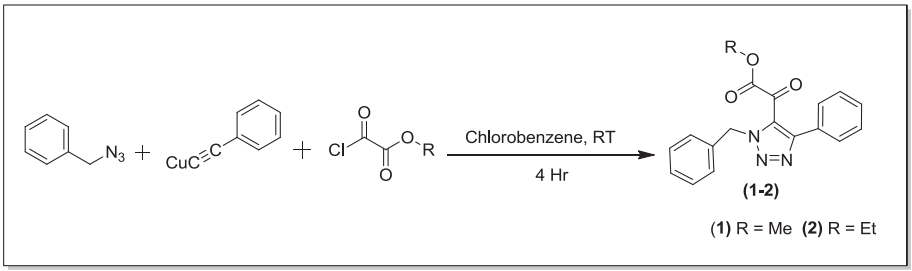

Fig. 1. Synthetic scheme for triazole derivatives **1** and **2**.