Synthesis of Novel Triazole Derivatives Based on 4-methyl-chromene-2-one

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Abstract Synthesis of 1,2,4-triazoles fused to another heterocyclic ring such as pyridine, pyridazine, pyrimidine, pyrazine and triazine are very well known systems with diverse biological application. In this research the 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid ethyl ester was prepared as the key starting material according to the known procedures. Treatment of 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid ethyl ester with hydrazine hydrate afford 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid hydrazide. At the last stage, the prepared 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid hydrazide was reacted in situ with benzaldehyde and their derivatives in the presence of ammonium acetate using acetic acid as solvent. The final triazole products was obtained with excellent yield. The structures of the target compounds confirmed by IR, 1H-NMR, 13C-NMR, and MASS analysis.

Keywords: coumarin, aldehyde, triazole, hydrazide, synthesis


1. Introduction

Coumarin is currently undergoing clinical trials for the treatment of lymphoedema following breast cancer treatment and in the treatment of lung and kidney. Carcinoma having been used both in isolation [1]. Triazole ring system has attracted a continuously growing interest of synthetic organic chemists and those dealing with the medicinal compounds due to its versatile potential to interact with biological systems. The triazole compounds possess a wide range of biological activities and are especially focused for antifungal behavior. The synthesis of compounds containing 1,2,4-triazole ring in their structure has attracted widespread attention, due to their pharmacological properties.

A variety of biological activities such as anti-inflammatory, Analgesic, [2,3] antibacterial, [4,5] have been reported. Synthesis of 1,2,4-triazoles fused to another heterocyclic ring such as pyridine, pyridazine, pyrimidine, pyrazine and triazine are very well known systems with diverse biological application [6-12]. In this research 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid ethyl ester was prepared as the key starting material according to the known procedures. Treatment of 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid ethyl ester with hydrazine hydrate afford 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid hydrazide. At the last stage, the prepared 4-methyl-2-oxo-2H-chromen-7-yl-oxyacetic acid hydrazide was reacted in situ with benzaldehyde and its derivatives in the presence of ammonium acetate using acetic acid as solvent. The final triazole products was obtained with excellent yield.
2. Experimental

All compounds were obtained from Merck chemical company and were used without further purification.

Melting points (m.p.) were determined on an Electrothermal melting point apparatus (Electrothermab 4300) and uncorrected. The progress of the reactions was constantly monitored by the silica-gel G/UV254. IR spectra (wave No./cm⁻¹) were obtained on the Nexus 870 spectrometer using a KBr disk. ¹HNMR were measured on a Bruker Advance DRX 500M in CHCl₃ or DMSO as solvent using TMS as internal standard, and chemical shifts are expressed as ppm. MS Model: 5975C VL MSD with Tripe-Axis Detector.

General procedure for synthesis of 4-methyl-7-(5-aryl-1H-[1,2,4]triazol-3-yl-methoxy)-2H-chromen-2-one

In a 100 ml round bottomed flask equipped with magnetic stirrer, 2 ml of 4-methyl-7-yl-oxyacetohydrazide, 9 ml ammonium acetate and 2 ml of 4-substituted-benzaldehyde was dissolved in 15 ml glacial acetic acid. The reaction mixture was stirred for 48 hours at room temperature. Finally the mixture was poured into a beaker containing 150 gr crushed ice. The product was immediately formed in the ice-water mixture as precipitate. Recrystallization of the solid product from 96% ethanol afforded pure product. Yield 72-81%. IR and NMR techniques were used for characterization of the product.

Synthesis of 4-Methyl-7-[5-(3-nitrophenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one as a typical reaction

In a 100 ml round bottomed flask equipped with magnetic stirrer, 2 ml of 4-methyl-7-yl-oxyacetohydrazide, 9 ml ammonium acetate and 2 ml 4-chlorobenzaldehyde was dissolved in 15 ml glacial acetic acid. The reaction mixture was stirred for 48 hours at room temperature. At the end the mixture was poured into a beaker containing 150 gr crushed ice. The product was immediately formed in the ice-water mixture as precipitate. Recrystallization of the solid product from 96% ethanol afforded pure product. Yield 72-81%. IR and NMR techniques were used for characterization of the product.

White powder, mp 273-275 °C, 0.67 g, yield 88%. ¹HNMR (DMSO): δ 2.4(s, 3H, Me); 5.37 (s, 2H, CH₂); 6.24(s, 1H, H₁ of coumarin ring); 7.75(m, aromatic and other coumarin protons); 11.95(s-broad, 1H, NH). ¹³CNMR (ppm): 18.62 (CH₃), 55.8 (OCH₃), 65.7 (CH₂), 102-164 (coumarin and aromatic carbons), 169 (C=O).

Synthesis of 4-methyl-7-[5-(4-methoxyphenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 274-276 °C, 0.62 g, yield 74%. IR (KBr) (Vmax/cm⁻¹): 3310(NH), 3037(CH- aromatic ring bands), 2850-3000(C-H OCH₃, CH₃ and CH₂), 1631 (C=O), 1691(C=O), 1504-1543(C=C), 1303-1379(C-H), 1018-1253(C-O), 660-959(C-H aromatic ring bands). ¹HNMR (DMSO): δ 2.4(s, 3H, CH₃); 3.8(s, 3H, OCH₃); 5.2(s, 2H, CH₂); 6.2(s, 1H, H₁ of coumarin ring); 6.9-7.74(m, aromatic and other coumarin porotons); 11.7(s-broad, 1H, NH). ¹³CNMR (ppm): 18.6 (CH₃), 55.8 (OCH₃), 65.7 (CH₃), 102-164 (coumarin and aromatic carbons) 168.7 (C=O).

Synthesis of 4-methyl-7-[5-(4-nitrophenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 270-271 °C, 0.67 g, yield 80%. ¹HNMR (DMSO): δ 2.41(s, 3H, CH₃); 5.36(s, 2H, CH₂); 6.23(s, 1H, H₁ of coumarin ring); 7(d, H₂, H₆ of 4-nitrophenyl); 7.68(d, H₃ of coumarin ring); 8(d, H₂, H₃, H₆ of 4-nitrophenyl); 8.3(d, H₆ of coumarin ring); 8.1(s, H₆ of coumarin ring). ¹³CNMR (ppm): 18.6 (CH₃), 65.8 (CH₂), 102-164 (coumarin and aromatic carbons), 169 (C=O).

Synthesis of 4-methyl-7-[5-(4-hydroxyphenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 274-276 °C, 0.59 g, yield 84%. ¹HNMR (DMSO): δ 2.4(s, 3H, CH₃); 5.72(s, 2H, CH₂); 6.23(s, 1H, H₁ of coumarin ring); 6.82-7.75(m, aromatic and other coumarin porotons). ¹³CNMR: 18.66 (CH₃), 65.1 (CH₂), 102-163 (coumarin and aromatic carbons), 168 (C=O).

Synthesis of 4-methyl-7-[5-(4-bromophenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 265-266 °C, 0.62 g, yield 74%. ¹HNMR (DMSO): δ 2.4(s, 3H, CH₃); 5.3(s, 2H, CH₂); 6.23(s, 1H, H₁ of coumarin ring); 6.9-7.75(m, aromatic and other coumarin porotons); 11.92(s-broad, 1H, NH). ¹³CNMR (ppm): 18.6 (CH₃), 65.8 (CH₂), 102-146 (coumarin and aromatic carbons), 169 (C=O).

Synthesis of 4-methyl-7-[5-(4-chlorophenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 280-281 °C, 0.53 g, yield 65%. ¹HNMR (DMSO): δ 2.4(s, 3H, CH₃); 5.31(s, 2H, CH₂); 6.21(s, 1H, H₁ of coumarin ring); 6.9(d, H₂, H₆ of dichlorophenoryl); 7.4(d, H₅ of coumarin ring); 7.7(s, H₆ of dichlorophenoryl and H₂ of coumarin ring); 7.95-8.8(dd, H₅ of coumarin ring); 11.92(s-broad, 1H, NH). ¹³CNMR (ppm): 18.62 (CH₃), 65.8 (CH₂), 102-164 (coumarin and aromatic carbons), 169.2 (C=O).

Synthesis of 4-methyl-7-[5-(4-tert-butyphenyl)-1H-[1,2,4]triazol-3-yl-methoxy]-2H-chromen-2-one: White powder, mp 280-285 °C, 0.42 g, yield 56%. IR (KBr) (Vmax/cm⁻¹): 3120(NH), 3074(CH- aromatic ring bands), 2850-3000(C-H OCH₃, CH₃ and CH₂), 1687-1695(C=O), 1399-1498(C=C), 1017-1270(C-
O), 646-977(C-H aromatic ring bands). $^1$HNMR (DMSO): $\delta$ 2.4 (s, 3H, CH$_3$); 5.31 (s, 2H, CH$_2$); 6.22 (s, 1H, H$_3$ of coumarin ring); 7(d, H$_2$, H$_6$ of chlorophenyl ring); 7.49-7.53 (m, H$_3$, H$_5$ of chlorophenyl ring and H$_5$, H$_6$, H$_8$ of coumarin ring); 11.72 (s, 1H, NH). $^{13}$CNMR (ppm): 18.6 (CH$_3$), 65.7 (CH$_2$), 102-164 (coumarin and aromatic carbons), 169 (C=O). EI-MS (m/z): 367.7, 233, 205, 147, 138, 103,63.

3. Results and discussion

The yield of products and the reaction time depends on the type of aldehyde used as one of the starting materials. For example when the electron withdrawing group is attached to benzaldehyde the yield of product is favored this shows the possible nucleophilic substitution mechanism between the hydrazide NH$_2$ group and the aldehyde.

4. Conclusion

The mild reaction condition, the ease of reaction and the good yield of products are the different for developing this method for synthesis of a series of new products with different substitution. The following proposed mechanism well the synthesis of final product.

References