One pot multicoponent synthesis of 4-hydroxy-6-methyl-3-(3 phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-ones

Bade Thirupaiah, Kodam Sujatha & Vedula Rajeswar Rao*
Department of Chemistry, National Institute of Technology, Warangal 506 004, India
E-mail: vrajesw@yahoo.com

Received 6 June 2017; accepted (revised) 16 November 2017

An efficient one pot multicomponent reaction for the synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-ones with good to excellent yields have been described. Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one 1, thiosemicarbazide 2 and various aromatic carboxylic acids 3a-j in dry toluene and POCl3 afford 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-ones. All the synthesized compounds have been characterized from their analytical and spectral data.

Keywords: Dehydroacetic acid, benzoic acid, thiosemicarbazide, thiazole, thiazolo triazole, multicomponent reaction

Multi component reactions are the reactions in which two or more starting materials sequentially combine to form the final compound in a single reaction vessel. MCRs are efficient, atom economic and selective reactions because of less number of steps, shorter reaction times, good yields, and play an important role in modern organic chemistry.

The thiazole ring system is an important structural moiety found in a number of biologically active molecules. In recent years thiazoles have received much attention in the field of medicinal chemistry because of their pharmacological activities like anti-fungal4, anti- microbial5, anti-bacterial6, anti-inflammatory7, anti-cancer8 and anti-HIV activity9. On the other hand, synthesis of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one and its derivatives has attracted considerable attention from organic and medicinal chemists10 for many years due to their wide range of applications in medical field in the form of fungicidal11, complexing agent12, anti-microbial13, good cosmetic14, herbicidal15 and insecticidal activities16. Thiazolo triazoles are an important class of heterocyclic molecules in which two fused rings of thiazole and triazole exist in isomeric forms and possess good biological activities17-21.

In view of the pharmacological significance of thiazolo triazol pyrans and in continuation of our earlier research work in the field of multi component synthesis of biologically active heterocyclic compounds, herein we report the synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4] triazol-5-yl)-2H-pyran-2-ones 4 via a multi component approach.

Results and Discussion

Previously triazolo-thiazoles were synthesized by Rao et al.27 by two methods. These methods have limitations like harsh reaction conditions, suffer from many step synthesis, has longer reaction times, application of expensive metal catalyst and provided only low yields. In the present method we have developed a new synthetic route for the title compounds via a multi component approach. This method gives greater yield of the products, a single step process, has shorter reaction duration and does not require any metal catalyst.

Two methods of synthesis of 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-one derivatives 4 are given. Method I is a one-pot multi component synthesis. Reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one 1, thiosemicarbazide 2 and various aromatic carboxylic acids 3 in dry toluene and POCl3 under reflux gave a fused system 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-one 4 (Scheme I). Method II is a two-step procedure. Reaction of bromo dehydroacetic acid 1 with thiosemicarbazide 2 in acetic acid under reflux gave the corresponding 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one 5. This intermediate, on reactions with substituted benzoic acids 3a-j in the presence...
POCl₃ gave 4-hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-one derivatives 4a-j (Scheme II). The products obtained by both methods were found to be identical by mixed melting point measurements, co-TLC and their analytical and spectral data.

A plausible mechanism for the formation of title compounds 4 is proposed in Scheme III. The initial step is the formation of 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one 5 from 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one 1 and thiosemicarbazide 2. Intermediate 5 reacts with various aromatic acids 3 to give corresponding title compounds 4.

In the IR spectrum of 4a, the OH functional group appeared at 3389 cm⁻¹, lactone –C=O group at 1724 cm⁻¹ and –C=N at 1599 cm⁻¹ respectively. ¹H NMR spectrum of compound 3a exhibited characteristic peaks –CH₃ of pyran as singlet at δ 2.22, pyran proton as singlet at δ 6.15, thiazole proton as singlet at δ 7.27, aromatic protons appears as multiplets in the region of δ 7.46-7.50, 7.90-7.98 and -OH proton appeared as singlet at δ 12.68 respectively. ¹³C NMR spectrum exhibited characteristic lactone carbonyl carbon at δ 193.5. The mass spectrum of the compound 4a shows [M+H]⁺ ion peak at m/z 326. From the spectral data we assigned the structure 4 for the synthesized molecules.

**Experimental Section**

**General procedure for preparation of compounds 4a-j**

A mixture of substituted 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1 mmol), thiosemicarbazide (1 mmol) and aromatic carboxylic acid (1 mmol) was taken in a round bottom flask containing 15 mL of dry toluene and 5 mL of POCl₃, and refluxed for about 3-4 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled to RT and poured onto crushed ice. The resulting solid product was filtered, washed with NaHCO₃ solution (5%), followed by cold water. It was dried and purified by recrystallization from ethanol.

**4-Hydroxy-6-methyl-3-(3-phenylthiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-one, 4a**: Yellow solid. Yield 89%. m.p.173-75°C. IR (KBr): 3389 (OH), 1724 (lactone –C=O), 1599 (–C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.22 (s, 3H, CH₃ of pyran), 6.15 (s, 1H, pyran), 7.27 (s, 1H, CH of thiazole), 7.46-7.50 (m, 2H, ArH), 7.90-7.98 (m, 3H, ArH), 12.68 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.2, 98.6, 103.3, 121.1, 127.9, 129.1, 131.8, 133.2, 136.2, 146.6, 151.9, 153.5, 163.1, 193.5; ESI-MS: m/z (%) 326 (M+H)⁺. Anal. Calcd for C₁₅H₁₅N₃O₄S: C, 59.07; H, 3.41; N, 12.92. Found: C, 59.00; H, 3.37; N, 12.87%.
3-(3-(2-Chlorophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4b: Yellow solid. Yield 89%. m.p. 203-205°C. IR (KBr): 3398 (OH), 1717 (lactone C=O), 1599 cm⁻¹ (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.23 (3H, CH₃ of pyran), 6.17 (1H, pyran), 7.32-7.56 (m, 1H thiazole, 4H ArH), 12.72 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.3, 98.9, 109.5, 111.9, 127.3, 128.4, 129.3, 130.7, 133.5, 134.2, 138.6, 146.0, 151.7, 155.4, 163.2, 192.3; ESI-MS: m/z (%) 340 (M+H)⁺. Anal. Calcd for C₁₆H₁₂N₂O₇S: C, 53.41; H, 2.80; N, 16.81%. Found: C, 53.37; H, 2.73; N, 16.63%.

4-Hydroxy-6-methyl-3-(3-(p-tolyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-2H-pyran-2-one, 4c: Yellow solid. Yield 85%. m.p.151-53°C. IR (KBr): 3406 (OH), 1727 (lactone C=O), 1599 cm⁻¹ (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.21 (3H, CH₃ of pyran), 2.36 (3H, CH₃ of pyran), 6.15 (1H, pyran), 7.31 (1H, CH of thiazole), 7.66 (d, J = 8.8Hz, 2H, ArH), 8.36 (d, J = 9.2, 3H, ArH), 12.74 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.2, 23.1, 98.8, 104.1, 119.6, 125.5, 128.5, 130.7, 133.1, 135.2, 144.9, 152.1, 154.8, 162.9, 193.0; ESI-MS: m/z (%) 340 (M+H)⁺. Anal. Calcd for C₁₆H₁₂N₂O₇S: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.50; H, 3.39; N, 16.40%.

3-(3-(2-Aminophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4d: Yellow solid. Yield 88%. m.p.147-49°C. IR (KBr): 3434 (OH), 1720 (lactone C=O), 1600 cm⁻¹ (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.22 (s, 3H, CH₃ of pyran), 6.13 (s, 1H, pyran), 7.28 (s, 1H, CH of thiazole), 8.60-8.75 (m, 3H, ArH), 12.83 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.2, 100.4, 105.5, 118.2, 119.7, 128.6, 129.5, 132.5, 144.1, 149.3, 152.5, 155.1, 163.5, 192.5. Anal. Calcd for C₁₆H₁₂N₂O₇S: C, 46.27; H, 2.18; N, 16.86. Found: C, 46.19; H, 2.13; N, 16.81%.

3-(3-(2-Aminophenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-4-hydroxy-6-methyl-2H-pyran-2-one, 4e: Yellow solid. Yield 82%. m.p.216-18°C. IR (KBr): 3417 (OH), 1722 (lactone C=O), 1612 cm⁻¹ (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.21 (s, 3H, CH₃ of pyran), 3.82 (s, 2H, NH₂), 6.18 (1H, pyran), 6.72-6.80 (m, 2H, ArH), 7.29-7.34 (m, 1H thiazole, 2H ArH), 12.61 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.2, 99.1, 105.4, 110.5, 117.1, 119.8, 121.6, 128.0, 131.2, 132.9, 144.7, 147.2, 152.4, 155.1, 164.3, 192.8. Anal. Calcd for C₁₆H₁₂N₂O₇S: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.50; H, 3.49; N, 16.40%.

4-Hydroxy-3-(3-(4-hydroxyphenyl)thiazolo[2,3-c][1,2,4]triazol-5-yl)-6-methyl-2H-pyran-2-one, 4f: Yellow solid. Yield 80%. m.p.188-90°C. IR (KBr): 3413 (OH), 1727 (lactone C=O), 1602 cm⁻¹ (C=N); ¹H NMR (400 MHz, DMSO-d₆): δ 2.23 (s, 3H, CH₃), 6.17 (s, 1H, pyran), 7.19 (s, 1H thiazole), 7.49 (d, J = 8.0, 2H ArH), 8.03 (d, 2H, ArH); ¹³C NMR (100 MHz, DMSO-d₆): δ 22.2, 99.1, 105.4, 110.5, 117.1, 119.8, 121.6, 128.0, 131.2, 132.9, 144.7, 147.2, 152.4, 155.1, 164.3, 192.8. Anal. Calcd for C₁₆H₁₁N₂O₈S: C, 52.14; H, 2.88; N, 16.14%. Found: C, 52.00; H, 2.80; N, 16.14%.

Scheme III — Generation of the target molecule 3-(2-hydrazinylthiazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one

---

Indian J. Chem., Sec B, July 2018
General procedure for synthesis of compound 5 from 4

A mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one (1 mmol) and thiosemicarbazide was refluxed with 5 mL of acetic acid for about 1 h. The reaction mixture was cooled and the solid product separated was filtered and washed with water. It was dried and purified by recrystallization from acetic acid.

General procedure for synthesis of compound 4a-j

In conclusion, we have described the synthesis of thiazolo-triazolyl derivatives. The reaction proceeded by two methods. The first method is a multi-component reaction and the second method is a two-step reaction. The advantages of this synthetic protocol are mild reaction conditions, shorter reaction times, easy work-up and excellent yields.

Acknowledgments

The authors are very much thankful to the Director of the National Institute of Technology, Warangal, T.S., India, for providing financial support and facilities.

References