

Peg-600 Mediated An Efficient One-Pot Synthesis Of 2-Amino-4-(2-Oxo-2*h*-Chromen-3-Yl)Thiophene-3-Carbonitriles

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Abstract- One-pot synthesis of 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitriles (**4**) has been developed starting from 3-acetyl-2*H*-chromen-2-ones (**1**) by the reaction with equimolar amounts of malononitrile (**2**) and elemental sulfur (**3**) using Gewald reaction. PEG-600 is an efficient reaction media for the synthesis of target compounds. Environmentally benign approach, fast rate of the reaction, convenient work-up procedures and fair yields are the added advantages of this article.

Index Terms- Coumarins, PEG-600, one-pot synthesis, Gewald reaction, thiophene.

1. INTRODUCTION

Coumarin derivatives display diverse biological activities such as anti-tumor¹, anti-HIV², anti-oxidant³ etc. As well, sulfur containing heterocyclic compounds have paved the way for effective research in medicinal and pharmaceutical chemistry. Additionally, thiophene derivatives in combination with other heterocyclic ring systems have been used extensively in pharmaceutical applications such as anti-depressant⁴, analgesic⁵, etc. Hence, it was considered worthwhile to study the preparation of coumarin-thiazole hybrid scaffolds in a single frame work.

Zeng et al. reported the synthesis⁶ of multi substituted-2-aminothiophenes from simple carbonyl compounds, malononitrile and molecular sulfur in presence of imidazole catalyst in DMF at 60 °C for 10-18 h. Silva et al. reported⁷ solvent-free synthesis of 2-aminothiophenes using Gewald reaction under ultrasonic irradiation conditions in presence of morpholine base at RT within 20-80 min. Solid supported synthesis of tetrasubstituted thiophene was reported⁸ by Sutherlin and Castanedo starting from carbonyl compounds, malononitrile and molecular sulfur in presence of morpholine catalyst. Liu et. al. developed⁹ microwave irradiation method for the synthesis of 2-aminothiophene-3-carboxylic acids starting from ketones, cyanoacetamides/cyanoacetates and molecular sulfur using morpholine and Alumina (Al₂O₃). Degani et. al. described¹⁰ microwave accelerated synthesis of 2-aminothiophenes in ionic liquid media via three-component reaction of ketones, ethyl cyanoacetate and molecular sulfur.

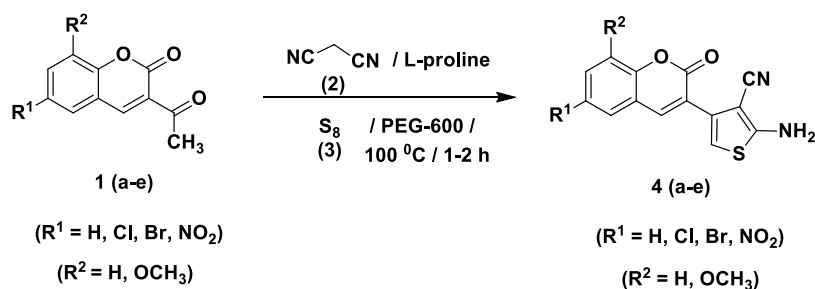
Based on all these observations and in continuation to our previous work¹¹⁻¹², on the synthesis of oxygen-containing heterocycles, it was considered worthwhile to focus on the synthesis of coumarin-1,3 thiazole hybrid scaffolds in a single frame work.

2. RESULTS AND DISCUSSION

Commercially available salicylaldehyde and its derivatives were treated with ethyl acetoacetate in triethanolamine in presence of benign catalyst *L*-proline at RT for 30 min afforded 3-acetyl-2*H*-chromen-2-ones (**1**)¹³. Thus, **1a** (i.e., **1**, R¹=H, R²=H) was treated with active methylene compound malononitrile (**2**) and molecular sulfur (**3**) in green solvent media like PEG-600, Ethanol, Glycerol at RT. The reaction is also performed at 100 °C in the presence of inorganic bases NaHCO₃ and Na₂CO₃ respectively. But the reaction did not proceed and starting materials were recovered as such. From this observation, it is understood that the bases NaHCO₃ and Na₂CO₃ are not suitable to catalyze the Knoevenagel condensation between 3-acetyl-2*H*-chromen-2-one (**1**) and malononitrile (**2**).

When the reaction was carried out using *L*-proline as catalyst at RT, Knoevenagel condensation product is formed, i.e., 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)malononitrile but not the desired title compound **4a**. The same reaction is performed at 100 °C yielded the target compound (**4a**) in high yield. This one-pot reaction was also screened in different green solvents using catalysts like *L*-proline, sulfamic acid and piperidine. These screening results are shown in **Table 1**.

These above screening studies it is proved that The reaction time, yield and physical properties of



Scheme. 1. Step-wise synthesis of 4-hydroxy-2-mercapto-6-phenylpyrimidine-5-carbonitriles (5)

PEG-600 is an efficient solvent and *L*-proline to be the best catalyst for the one-pot synthesis. Thus, this method was explored to the synthesis of other derivatives of **4** starting from **1** (Scheme 1).

compounds **4(a-e)** in one-pot three-component method was shown in Table 2.

Table-1 Optimization results for the one-pot synthesis 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile **4a**

S.No.	Solvent	Catalyst	Time	Temperature	Yield (%)
1	Ethanol	<i>L</i> -proline	2 h	Reflux	76
2	Glycerol	<i>L</i> -proline	3 h	100 °C	65
3	PEG-600	<i>L</i>-proline	1 h	100 °C	89
4	Ethanol	Sulfamic acid	3 h	Reflux	69
5	Glycerol	Sulfamic acid	5 h	100 °C	61
6	PEG-600	Sulfamic acid	1½ h	100 °C	75
7	Ethanol	Piperidine	3½ h	Reflux	68
8	Glycerol	Piperidine	4 h	100 °C	62
9	PEG-600	Piperidine	1½ h	100 °C	77

3.EXPERIMENTAL SECTION:

3.1: One pot synthesis of 4 from 1:

A mixture of **1** (5 mM), malononitrile (5 mM), molecular sulfur (5 mM) and *L*-proline (10 mol%) and PEG-600 (20 ml) was heated to 100 °C for 1-2 h (Table 2). The reaction was preliminarily monitored by TLC analysis. After the completion of reaction, the mixture was cooled to RT and poured into ice-cold water (50 ml). The separated solid was filtered, washed with water (2x50 ml) and dried to obtain crude product **4**. The crude was recrystallized from suitable solvent to obtain pure compound **4**.

3.1.1: Characterization of 4a:

Yield = 1.23 g (92%); recrystallized from: Methanol; IR (KBr): 3307, 2209, 1720; ¹H NMR (400 MHz, *DMSO-d*₆/ TMS): δ 7.18 (s, 2H, -NH₂), 7.37 (t, 1H, Ar-H), 7.45 (d, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.60 (t, 1H, Ar-H), 7.83 (d, 1H, Ar-H), 8.50 (s, 1H, Ar-H); ¹³C NMR (100 MHz, *DMSO-d*₆): 81.8, 110.2, 116.5, 119.3, 121.8, 124.2, 126.5, 129.1, 132.0, 132.5, 145.8, 150.2, 153.2, 159.2; M.⁺+1 =269. HRMS Calculated for the compound C₁₄H₉O₂N₂S [M+H].⁺: 269.03792. Found: 269.03785.

3.1.2: Characterization of 4b:

Yield = 1.28 g (85%); recrystallized from: Ethanol; IR (KBr): 3308, 2213, 1702; ¹H NMR (400 MHz, *DMSO-d*₆/ TMS): δ 6.98 (s, 2H, -NH₂), 7.20 (d, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.83 (d, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 8.54 (s, 1H, Ar-H); ¹³C NMR (100 MHz, *DMSO-d*₆): 81.5, 113.5, 116.5, 119.1, 122.2, 122.5, 129.1, 129.5, 134.5, 140.8, 148.1, 151.0, 151.5, 159.8; Ms: *m/z* 303 [M.⁺+1].

3.1.3: Characterization of 4c:

Yield = 1.51 g (88%); recrystallized from: Chloroform; IR (KBr): 3324, 2213, 1697; ¹H NMR (400 MHz, *DMSO-d*₆/ TMS): δ 6.74 (s, 1H, Ar-H), 7.20 (s, 2H, -NH₂), 7.56 (d, 1H, Ar-H), 7.82 (d, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H); ¹³C NMR (100 MHz, *DMSO-d*₆): 83.3, 114.0, 116.3, 119.6, 121.8, 122.2, 128.4, 128.8, 134.9, 141.3, 149.3, 152.4, 152.7, 158.9; Ms: *m/z* 346 [M.⁺+1]

3.1.4: Characterization of 4d:

Yield = 1.40 g (90%); recrystallized from: Ethanol; IR (KBr): 3265, 2248, 1738; ¹H NMR (400 MHz, *DMSO-d*₆/ TMS): δ 7.22 (s, 2H, -NH₂), 7.46 (s, 1H, Ar-H), 7.61(d, 1H, aryl proton), 8.13 (d, 1H, Ar-H), 8.50 (s, 1H, Ar-H), 8.84 (s, 1H, Ar-H); ¹³C NMR (100 MHz, *DMSO-d*₆): 82.3, 110.6, 115.8, 118.3, 120.6, 120.9,

127.3, 127.7, 132.9, 140.6, 147.9, 151.4, 151.8, 157.9; Ms: m/z 314 [$M.^{+1}$].

3.1.5: Characterization of 4e:

Yield = 1.21 g (81 %); recrystallized from: Acetonitrile; IR (KBr): 3161, 2161, 1734; ^1H NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 3.96 (s, 3H, OCH_3), 7.14 (s, 2H, $-\text{NH}_2$), 7.37 (d, 1H, Ar-H), 7.42 (d, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 8.62 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): 56.6, 84.2, 110.3, 114.7, 116.5, 119.8, 120.3, 121.9, 125.2, 131.8, 141.0, 142.5, 146.8, 158.9, 165.9; Ms: m/z 299 [$M.^{+1}$]

4. CONCLUSION:

In conclusion, we have followed green protocols to carry Gewald reaction. Thus, the title compounds were synthesized in one-pot three-component method. This one-pot method observed to be the better and an efficient method in terms of reaction time, easy workability and yield of the product. Significant enhancement in the rate of the reaction was observed in benign solvent PEG-600 when compared to other solvents. Furthermore, simple reaction conditions, easy purification were added advantages for the synthesis of 2-amino-4-(2-oxo-2H-chromen-3-yl)thiophene-3-carbonitriles (**4**).

Acknowledgements:

The authors are grateful to the authorities of Jawaharlal Nehru Technological University Hyderabad for providing laboratory facilities and technical support. They wish to extend their sincere gratitude toward Department of Science and Technology, Govt. of India, New Delhi, for financial support in the form of **DST INSPIRE Fellowship** to one of them (**D. S**).

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