Res Chem Intermed
DOI 10.1007/s11164-014-1810-7

Molybdate sulfuric acid-catalyzed one-pot synthesis of substituted coumarins under solvent-free conditions

Saeed Khodabakhshi · Bahador Karami · Khalil Eskandari

Received: 23 June 2014 / Accepted: 11 September 2014
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Abstract An efficient method for the synthesis of new aryloylamido coumarins via a one-pot, three-component reaction of an aryl glyoxal, benzamide, and a 4-hydroxycoumarin in the presence of molybdate sulfuric acid under solvent-free conditions is reported. This high yielding reaction is in accordance with green chemistry aspects.

Keywords Aryloylamido coumarins · Aryl glyoxal · Benzamide · 4-Hydroxycoumarin

Introduction

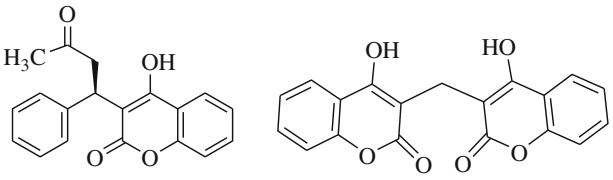
Coumarin and its derivatives have become well known because of their interesting biological and photodynamic properties [1, 2]. The development of efficient and concise strategies that allow access to functionalized coumarins is an important task in modern organic chemistry [3–5]. For example, some substituted 4-hydroxycoumarins at the 3-position have been found in a fascinating array of bioactive natural products and pharmaceutical compounds. Dicoumarol and warfarin are vitamin K antagonists which play an anticoagulant role in the treatment of thromboembolic disorders (Fig. 1) [6, 7].

S. Khodabakhshi (✉)
Young Researchers and Elite Club, Gachsaran Branch, Islamic Azad University, Gachsaran, Iran
e-mail: saeidkhm@yahoo.com

B. Karami
Department of Chemistry, Yasouj University, P.O. Box 353, 75918-74831 Yasouj, Iran

K. Eskandari
Young Researchers and Elite Club, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran

Published online: 01 October 2014



Warfarin Dicoumarol

Fig. 1 Coumarin derivatives as vitamin K antagonists

To date, some multicomponent synthetic methodologies have been reported for the preparation of arylamino/amido coumarins [8, 9]. One-pot and multicomponent reactions (MCRs) have drawn special attention due to the advent of high-throughput screening techniques that have enabled rapid identification of potential new medicines among large collections of organic compounds [10, 11]. In addition, the continual insistence on development of facile, convenient, and nonpolluting synthetic procedures has persuaded chemists to update their science and increase their potency with respect to green chemistry factors. In relation to this, solid-phase reactions have attracted remarkable attention in the synthetic community and have proved to be promising conditions in organic synthesis due to their economic and environmentally friendly nature. In addition, if the catalyst is recyclable, this would improve both the environmental impact and the economic profile of the method [12–14]. In this paper, we wish to report the one-pot synthesis of some aryloylamido coumarins using molybdate sulfuric acid (MSA) as a recyclable catalyst under solvent-free conditions.

Experimental

General

Commercially available reagents were purchased from Merck. Aryl glyoxals were prepared in accordance with previous literature [15]. MSA was prepared based on our previous report [16]. Melting points were measured on an elecrtothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in DMSO-*d*6 as solvent. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. TLC was performed on TLC-Grade silica gel-G/UV 254 nm plates.

General procedure for the synthesis of **4**

A mixture of aryl glyoxal (1 mmol), benzamide (1.1 mmol), and MSA (5 mol%) was stirred and heated at 80 °C for 30 min. Then, the 4-hydroxycoumarin was

added and the reaction stirred until completion. The reaction progress was monitored by TLC (EtOAc/Hexane, 1:1). After completion, the mixture was washed with MeOH. The precipitate was dissolved in hot EtOH:THF (3/1) and the catalyst was separated. The purification by silica gel column chromatography using n-hexane–EtOAc (1:1) as an eluent is needed to obtain pure product.

Spectral data

*Compound **4a***

Mp. 220–224 °C. IR (KBr): 3,347, 2,924, 1,687, 1,613, 1,565, 1,492, 1,344, 1,260 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 8.55$ (s, 1H), 7.90 (d, 1H, $J = 7.6$ Hz), 7.84–7.78 (m, 4H), 7.42 (t, 1H, J = 7.6 Hz), 7.50–7.38 (m, 6H), 7.29 (t, 2H, $J = 7.6$ Hz), 6.64 (d, 1H, $J = 6.4$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 196.4$, 165.3, 162.3, 160.5, 151.34, 134.2, 132.3, 131.8, 130.5, 130.4, 127.4, 127.2, 127.1, 126.3, 123.0, 122.7, 115.3, 114.8, 101.0, 52.2. Anal. Calcd for $C_{24}H_{17}NO_5$: C, 72.17; H, 4.29; N, 3.51. Found: C, 72.28; H, 4.10; N, 3.58.

*Compound **4b***

Mp. 248–250 °C. IR (KBr) $\tilde{\nu} = 3{,}373$, 3,064, 2,926, 1,688, 1,614, 1,599, 1,566, 1,345, 1,227, 1,159 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 8.79$ (d, 1H, $J = 6.8$ Hz), 8.03 (d, 1H, $J = 7.2$ Hz), 7.97–7.91 (m, 4H), 7.67 (t, 1H, $J = 7.2$ Hz), 7.58 (t, 1H, $J = 7.2$ Hz), 7.49 (t, 2H, $J = 7.6$ Hz), 7.40 (t, 2H, $J = 8.0$ Hz), 7.32 (t, 2H, $J = 8.8$ Hz), 6.67 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 193.5$, 167.0, 166.9, 163.8, 162.0, 152.9, 133.9 (d, $J = 3.1$ Hz), 133.5, 132.5, 132.1, 130.8 (d, $J = 9.3$ Hz), 128.8, 128.0, 124.6, 124.3, 116.99, 116.1 (d, $J = 22.3$ Hz), 102.6, 52.8. Anal. Calcd for $C_{24}H_{16}FNO_5$: C, 69.06; H, 3.86; N, 3.36. Found: C, 69.33; H, 3.76; N, 3.30.

*Compound **4c***

Mp. 243–245 °C. IR (KBr) $\tilde{\nu} = 3{,}350$, 3,061, 1,696, 1,615, 1,587, 1,565, 1,347, 1,222, 620 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 8.81$ (d, 1H, $J = 6.8$ Hz), 8.03 (d, 1H, $J = 7.6$ Hz), 7.92 (d, 2H, $J = 7.2$ Hz), 7.80 (d, 2H, $J = 8.4$ Hz), 7.71–7.66 (m, 3H), 7.57 (t, 1H, $J = 7.2$ Hz), 7.49 (t, 2H, $J = 7.6$ Hz), 7.40 (t, 2H, $J = 7.6$ Hz), 6.65 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 196.9$, 167.1, 163.9, 162.1, 153.0, 134.9, 133.8, 133.5, 132.1, 129.9, 128.8, 128.0, 127.3, 124.7, 124.3, 116.9, 116.2, 102.7, 52.9. Anal. Calcd for $C_{24}H_{16}BrNO_5$: C, 60.27; H, 3.37; N, 2.93. Found: C, 60.39; H, 3.32; N, 2.70.

*Compound **4d***

Mp. 243–245 °C. IR (KBr) $\tilde{\nu} = 3{,}377$, 3,074, 1,701, 1,673, 1,613, 1,565, 1,523, 1,344, 1,222 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): $\delta = 8.85$ (s, 1H), 8.30 (d, 2H, $J = 8.8$ Hz), 8.09-7.92 (m, 5H), 7.66 (t, 1H, $J = 7.6$ Hz), 7.56 (t, 1H, $J = 7.2$ Hz),

7.48 (t, 2H, $J = 7.2$ Hz), 7.39 (t, 2H, $J = 7.2$ Hz), 6.69 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 197.5$, 167.1, 133.8, 133.6, 132.1, 129.2, 128.7, 128.0, 124.7, 124.2, 117.0, 101.9, 67.48. Anal. Calcd for $C_{24}H_{16}N_2O_7$: C, 64.87; H, 3.63; N, 6.30. Found: C, 65.07; H, 3.70; N, 6.26.

*Compound **4e***

Mp. 218–220 °C. IR (KBr) $\tilde{\nu} = 3{,}343$, 3,069, 2,960, 1,692, 1,616, 1,600, 1,566, 1,261 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 8.73$ (d, 1H, $J = 7.2$ Hz), 8.04 (dd, 1H, $J_1 = 8.4$, $J_2 = 1.6$ Hz), 7.92–7.86 (m, 4H), 7.69–7.65 (m, 1H), 760–7.56 (m, 1H), 7.50 (t, 2H, $J = 7.6$ Hz),7.42–7.38 (m, 2H), 7.01 (d, 2H), $J = 8.8$ Hz), 6.66 (m, 1H), 3.79 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 193.6$, 167.0, 166.9, 163.5, 163.4, 162.0, 152.9, 133.9, 133.4, 132.1, 130.3, 128.8, 128.2, 127.9, 124.7, 124.3, 116.9, 116.2, 114.3, 103.2, 55.9, 52.5. Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92; H, 4.46; N, 3.26. Found: C, 70.02; H, 4.40; N, 3.29.

*Compound **4f***

Mp. >280 °C. IR (KBr) $\tilde{\nu} = 3{,}412$, 3,069, 2,938, 1,695, 1,626, 1,600, 1,536, 1,360, 1,267 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 8.48$ (d, 1H, $J = 8.4$ Hz), 7.90–7.85 (m, 3H), 7.71 (s, 1H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.59–7.55 (m, 1H), 7.53–7.49 (m, 2H), 7.42–7.38 (m, 1H), 7.31 (t, 1H, $J = 8.0$ Hz), 7.16–7.12 (m, 1H), 7.09–7.05 (m, 2H), 6.75–6.72 (m, 1H), 3.78 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 196.3$, 172.8, 166.5, 164.1, 159.3, 154.0, 137.3, 134.6, 132.0, 131.1, 129.7, 128.9, 127.6, 125.4, 122.8, 122.7, 120.7, 119.1, 116.1, 113.1, 96.0, 55.6, 53.4. Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92; H, 4.46; N, 3.26. Found: C, 69.98; H, 4.43; N, 3.20.

*Compound **4g***

Mp. 225–227 °C. IR (KBr) $\tilde{\nu} = 3{,}230$, 3,061, 2,938, 1,717, 1,673, 1,632, 1,602, 1,554, 1,225 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 8.78$ (d, 1H, $J = 6.8$ Hz), 8.50 (d, 1H, $J = 8.4$ Hz), 8.04 (d, 1H, $J = 8.4$ Hz), 8.01–7.98 (m, 2H), 7.96–7.93 (m, 3H), 7.64–7.56 (m, 4H), 7.54–7.49 (m, 3H), 7.35 (t, 1H, $J = 7.6$ Hz), 7.29 (d, 1H, $J = 8.4$ Hz), 6.96 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 197.6$, 167.3, 167.2, 163.6, 162.5, 152.7, 134.3, 133.9, 133.3, 132.6, 132.2, 130.4, 128.9, 128.7, 128.0, 127.8, 126.8, 126.4, 126.4, 124.8, 124.6, 124.3, 116.8, 116.1, 102.8, 53.9. Anal. Calcd for $C_{28}H_{19}NO_5$: C, 74.82; H, 4.26; N, 3.12. Found: C, 75.12; H, 4.15; N, 3.01.

*Compound **4h***

Mp. 242–244 °C. IR (KBr) $\tilde{\nu} = 3{,}329$, 1,695, 1,671, 1,617, 1,568, 1,349, 1,041 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 8.85$ (d, 1H, $J = 6.8$ Hz), 8.52 (s, 1H), 8.05–7.98 (m, 3H), 7.96-7.94 (m, 4H), 7.64 (t, 2H, $J = 6.8$ Hz), 7.60–7.56

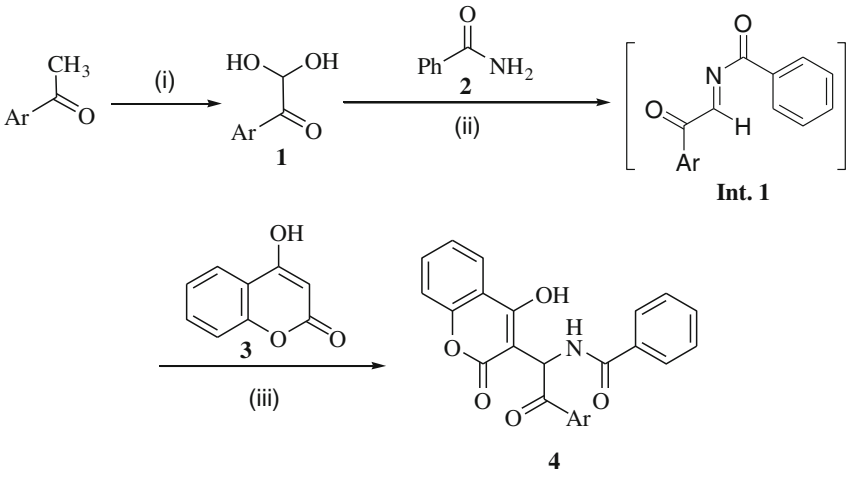
(m, 2H), 7.50 (t, 2H, $J = 7.6$ Hz), 7.39–7.34 (m, 2H), 6.86 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 195.5$, 167.1, 163.7, 162.1, 152.9, 135.3, 133.9, 133.9, 133.4, 133.3, 132.3, 132.1, 129.8, 128.9, 128.8, 128.6, 128.1, 128.0, 127.5, 124.6, 124.3, 124.2, 116.9, 116.2, 102.8, 53.0. Anal. Calcd for $C_{28}H_{19}NO_5$: C, 74.82; H, 4.26; N, 3.12. Found: C, 74.95; H, 4.17; N, 3.05.

Results and discussions

As part of an ongoing research program aiming to find novel methods within organic chemistry, we have synthesized a small library consisting of some heterocyclic compounds containing coumarin nucleus [17–19]. We report a simple and facile procedure for the synthesis of aryloylamido coumarins **4** from the reaction of aryl glyoxals **2**, which in turn are obtained by selenium dioxide oxidation of the corresponding aryl ketones **1** [20], with benzamide **2** and 4-hydroxycoumarin **3** under solvent-free conditions (Scheme 1).

It should be noted that the intermediate **1** was in situ-generated and the reactions were performed efficiently via a one-pot method. In fact, in the first designation, we were concerned about some limitations including the formation of probable dicoumarols as the side product [21].

At the outset, to determine suitable reaction conditions, the reaction of phenyl glyoxal with **2** and **3** was carried out as a model. In all cases, the reaction was performed under solvent-free conditions. To find the best amount of catalyst, we



(i): SeO_2, 1,4-Dioxan/H_2O
(ii): Solvent-free, MSA (5 mol%), 60 °C
(iii): Solvent-free, MSA (5 mol%), 80 °C

Scheme 1 Synthesis of aryloylamido coumarins using MSA

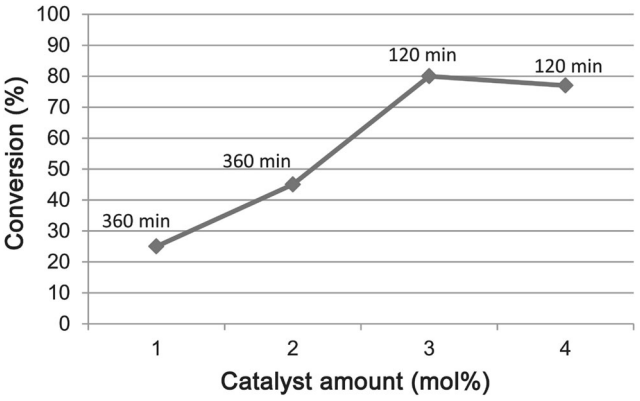


Fig. 2 Optimization of the catalyst amount in synthesis of **4a** at 80 °C under solvent-free conditions

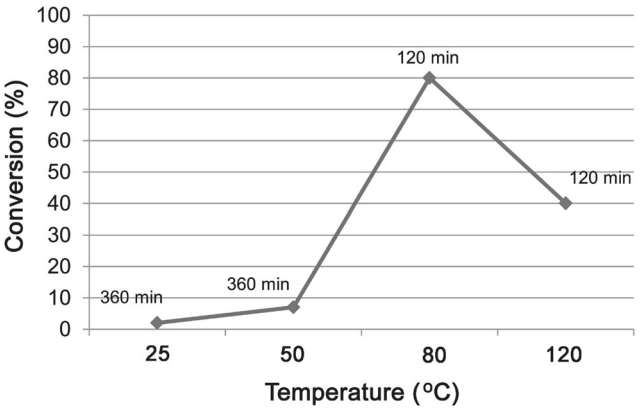


Fig. 3 Optimization of temperature in synthesis of **4a**

screened the model reaction in the absence and presence of several amounts of MSA. In the absence of the MSA, the model reaction could be carried out but the product was obtained in very low yield after a long period of time. In the presence of MSA, however, it was found that 5 mol% of MSA is optimal to carry out the reaction in a short duration. Increasing the amount of catalyst did not markedly affect the progress of the reaction (Fig. 2).

In another variation, various temperatures were investigated (Fig. 3). It was observed that the reaction did not proceed at room temperature. The best result was obtained when the temperature increased to 80 °C. Further increasing the temperature led to undesired products and the yield was dramatically decreased.

After optimization of the reaction conditions, we employed different aryl glyoxals to show the generality of the present method (Table 1).

Table 1 Synthesis of **4** using MSA as catalyst under solvent-free conditions

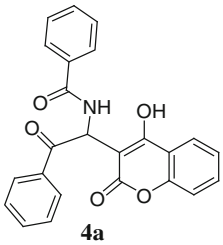
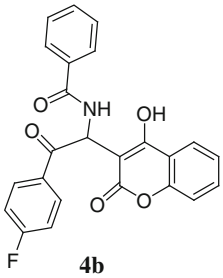
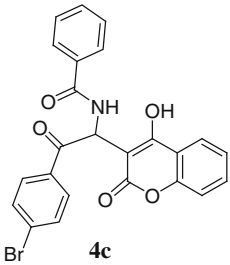
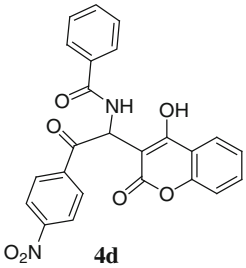
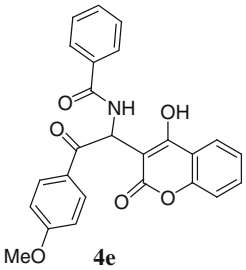
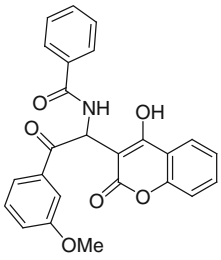
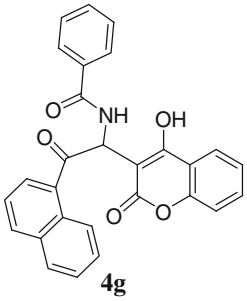
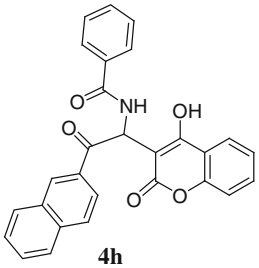
Entry	Ar	Product	Time (min)	Yield (%)[a]
1	C_6H_5	 **4a**	120	80
2	4-F-C_6H_4	 **4b**	100	75
3	4-Br-C_6H_4	 **4c**	110	80
4	4-NO_2-C_6H_4	 **4d**	120	77
5	4-MeO-C_6H_4	 **4e**	90	80

Table 1 continued

Entry	Ar	Product	Time (min)	Yield (%)[a]
6	3-MeO-C_6H_4	 **4f**	135	70
7	1-Naphthyl	 **4g**	120	85
8	2-Naphthyl	 **4h**	90	87

[a] Isolated yield

All synthesized compounds (**4a**–**h**) were characterized by ^{1}H and ^{13}C NMR, elemental analysis, and IR spectrometry. In these reactions, electron-rich and -deficient aryl glyoxals worked well.

Chemical reactions in the absence of organic solvents, defined as solvent-free reactions, obviously reduce pollution and cost due to simplification of experimental procedure, work-up technique, and saving of labor [22]. The used catalyst (MSA) is also safe and separable from the reaction mixture and is reusable for further reactions [23–25]. Therefore, the efficiency of this strategy under environmentally friendly conditions will clearly be in accordance with green chemistry principles. In order to enhance the catalytic efficiency of the MSA and reduce waste, the recyclability of the catalyst was also investigated. As shown in Fig. 4, it could be seen that the catalyst remained active through at least 3 runs. After the product was

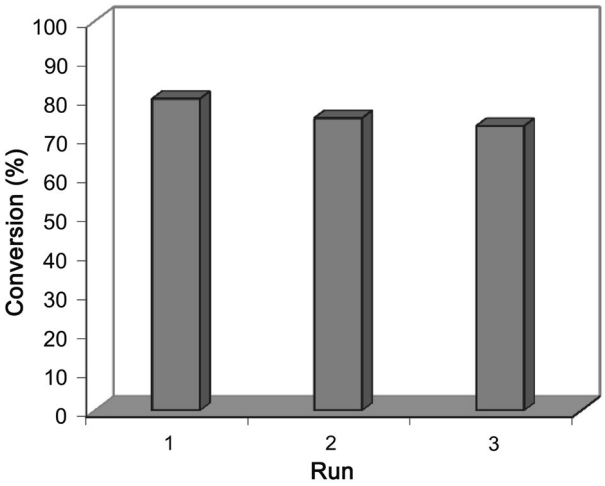


Fig. 4 Recyclability of MSA in synthesis of **4a** under optimized conditions. Reaction time: 120 min

removed from the catalyst using an organic solvent, the catalyst was reused directly for the next time without further purification.

Conclusion

In summary, we have successfully developed a green, cost-effective and facile method for the one-pot synthesis of some new substituted coumarins using MSA as a safe and recyclable solid acid catalyst under solvent-free conditions. Some interesting features are highlighted: high yields of products, operational simplicity, avoidance of organic solvents, and novelty. It is important to mention that the presence of transformable functionalities in the products makes them potentially valuable for further synthetic manipulations.

Acknowledgments Financial support for this work by the research affairs, Yasouj University (Iran), is gratefully acknowledged.

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