EFFICIENT CATALYSTS FOR THE RAPID SYNTHESIS OF BENZYLIDENE BIS(4-HYDROXYCOUMARIN) DERIVATIVES IN AQUEOUS MEDIA

Zahed Karimi-Jaberi[a]* and Mohammad Reza Nazarifar[a]

Keywords: 4-hydroxycoumarin, biscoumarin, trichloroacetic acid, ceric sulfate.

Trichloroacetic acid, CCl_3COOH, efficiently catalyzed the reaction of an aromatic aldehydes and 4-hydroxycoumarin in aqueous media under mild conditions to afford the corresponding α,α′-benzylidene bis(4-hydroxycoumarin) derivatives in high yields. Ceric sulfate, $(Ce(SO_4)2.4H_2O)$, has also been used as another solid catalyst for this reaction.

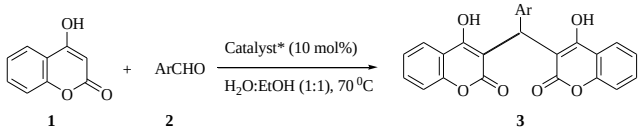
* Corresponding Authors
Fax: +98 7126224402
E-Mail: zahed.karimi@yahoo.com
[a] Department of Chemistry, Firoozabad Branch, Islamic Azad University, P.O. Box 74715-117 Firoozabad, Fars, Iran

Introduction

It is well known that coumarin derivatives exhibit a wide range of biological activities, pharmaceutical and therapeutic properties, such as, antitumour, anticoagulant, antihelminthic, hypnotic, antifungal and antibacterial activities.[1-5] Recently, the synthesis of biscoumarin derivatives have attracted great interest due to their biological and pharmacological activities. The condensation of 4-hydroxycoumarin with aldehydes is the most convenient methods for the synthesis of biscoumarins. Various new techniques,[6-16] such as microwave-assisted synthesis technique,[6] ionic liquids,[10,17] solvent-free techniques[11] and acid catalysts,[7,12,13] were used to improve this reaction. In spite of their potential utility, many of these methods involve expensive reagents, harsh reaction conditions, high temperatures, long reaction times and unsatisfactory yields. Thus, the introduction of milder, faster and more eco-friendly methods is still in great demand.

From the environmental acceptability, recently inorganic acidic salts have widely used in organic synthesis because of minimized wastes, simplicity in handling and decreased reactor corrosion problems.[18] Trichloroacetic acid has been used by our group for the synthesis of enaminones,[19] dihydropyrano[2,3-c]pyrazoles,[20] and xanthenes.[21]

With our continuous investigation on the methodology of green synthesis,[19-22] we report the results that led to an extremely convenient method for the preparation α,α′-benzylidene bis(4-hydroxycoumarins) from aromatic aldehydes and 4-hydroxycoumarin in the presence of trichloroacetic acid or ceric sulfate in excellent yield (Scheme 1).



Catalyst: A: 10 Mol % trichloroacetic acid
B: 10 Mol % ceric sulfate 4.H_2O

Scheme 1. Synthesis of benzylidene bis(4-hydroxycoumarin)

Experimental

Typical procedure for the synthesis of α,α′-benzylidene bis(4-hydroxycoumarin) Derivatives

A solution of aromatic aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol), and CCl_3COOH or $Ce(SO_4)_2.4H_2O$ (10 mol %) in 5.0 mL aqueous ethanol (50%) was stirred at 70 °C for the appropriate times (Table 1). Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water (2 × 10 ml) and purified by recrystalization from ethanol.

Selected spectral data

3,3′-(3-Nitrobenzylidene)-bis-(4-hydroxycoumarin) (**3c**) :IR(KBr): 3424, 2925, 1655, 1616, 1564, 1494, 1450, 1347, 762 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6):δ 6.39 (s, 1H, CH), 7.28-8.04 (m, 12H, ArH), 8.04-9.52 (m, 2H, OH).

3,3′-(4-Cholorobenzylidene)-bis-(4-hydroxycoumarin) (**3f**): IR(KBr): 3420, 2923, 1668, 1606, 1563, 1490, 1451, 1351, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6):δ 6.63 (s, 1H, CH), 7.16-7.90 (m, 12H, ArH), 7.90-9 (m, 2H, OH).

3,3′-(4-Methoxybenzylidene)-bis-(4-hydroxycoumarin) (**3h**): IR(KBr): 3443, 2926, 1668, 1606, 1563, 1510, 1452, 1352, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6):δ 3.71 (s, 3H, CH3O), 6.31 (s, 1H, CH), 6.80-7.93 (m, 12H, ArH), 8.16-8.78 (m, 2H, OH).

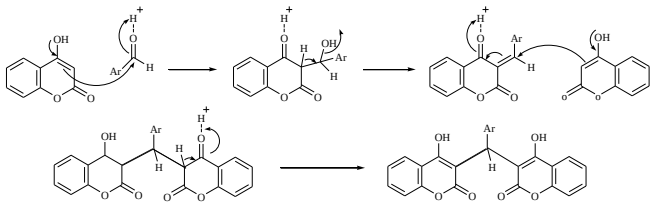
3,3′-(4-Chloro-3-nitrobenzylidene)-bis-(4-hydroxycoumarin) (**3k**): IR(KBr): 3423, 2920, 1665, 1613, 1558, 1536, 1450, 1348, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6):δ 6.28 (s, 1H, CH), 7.26-7.85 (m, 11H, ArH), 8.15-8.56 (m, 2H, OH); 13C NMR (DMSO-d6):δ 36.42, 103.23, 116.24, 119.31, 121.99, 123.81, 124.03, 124.51, 131.39, 132.07, 132.89, 143.87, 147.94, 152.90, 164.70, 167.34. Anal. Calcd. for $C_{25}H_{14}ClNO_8$: C, 60.80; H, 3.27; N, 2.84; Found: C, 60.89; H, 3.25; N, 2.90.

Results and Discussion

To optimize the amount of catalyst, effect of solvent and effect of temperature, reaction of benzaldehyde and 4-hydroxycoumarin was selected as the model reaction to afford α,α′-(benzylidene)-bis-(4-hydroxycoumarin). The optimized reactant ratios were found to be 1.0 equiv. benzaldehyde and 2.0 equiv. 4-hydroxycoumarin in the presence of catalysts (10 mol %) in 5 ml aqueous ethanol (1:1, H_2O–EtOH). The expected α,α′-benzylidene bis(4-hydroxycoumarin) was produced in 88 % yield after 5 min at 70 °C, for trichloroacetic acid and 86 % yield after 7 min at 70 °C for ceric sulfate. With respect to the quantity of the catalyst, there was no significant enhancement in yields when the concentration was increased from 10 mol % to 20 mol %.

After optimizing the reaction conditions, different aldehydes, both with electron donating and electron withdrawing groups were investigated for the present protocol. It was found that all the reactions proceeded well and produced the corresponding products in good yields and in very short reaction times (Table 1). No significant change in yield was observed when either substituted aromatic aldehydes were used. However, the synthesis could not be achieved in the absence of the catalyst.

The reaction proceeds via condensation of 1 equiv. of aldehyde with 2 equiv. of 4-hydroxycoumarin to form the corresponding product as has been suggested earlier.13 The reaction pathway is shown in Scheme 2.



Scheme 2. Proposed mechanism

As shown in Table 2, we compared results of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [$MIM(CH_2)_4SO_3H$],[10] sodium dodecyl sulfate (SDS),[12] phosphotungstic acid,[13] $H_{14}[NaP_5W_{30}O_{110}]$-$SiO_2$,[7] piperidine,[8] HBF_4 and tetrabutylammoniumbromide (TBAB),[9] [bmim]BF_4,[11] in the synthesis of α,α′-(enzylidene bis(4-hydroxycoumarin) derivatives with present method and demonstrated that CCl_3COOH or $(Ce(SO_4)_2.4H_2O)$ can act as effective catalysts. Thus, the present work using CCl_3COOH or $(Ce(SO_4)_2.4H_2O)$ as catalysts is an efficient route for production of α,α′-benzylidene bis(4-hydroxycoumarin) derivatives.

All products were identified by ^1H-NMR, ^{13}C NMR and IR spectroscopic methods and the results were confirmed by comparison with those available in the literature.

Table 1. Synthesis of benzylidene bis(4-hydroxycoumarin) derivatives

Entry	Aldehyde	Product	Method A[a]		Method B[b]		M.p. (°C)[ref.]
			Time, min	Yield, %	Time, min	Yield, %	
1	Benzaldehyde	**3a**	5	88	7	86	230-232[6]
2	4-Nitrobenzaldehyde	**3b**	3	98	5	97	232-234[6]
3	3-Nitrobenzaldehyde	**3c**	3	87	5	85	229-231[12]
4	4-Cyanobenzaldehyde	**3d**	4	89	5	82	242-244[16]
5	4-Fluorobenzaldehyde	**3e**	4	90	6	84	211-212[12]
6	4-Chlorobenzaldehyde	**3f**	3	94	5	88	256-258[6]
7	3-Methoxybenzaldehyde	**3g**	3	84	6	81	238-240[9]
8	4-Methoxybenzaldehyde	**3h**	4	83	7	80	246-248[6]
9	4-Bromobenzaldehyde	**3i**	3	95	5	91	264-266[12]
10	4-Methylbenzaldehyde	**3j**	5	86	6	84	266-268[6]
11	4-Chloro-3-nitrobenzaldehyde	**3k**	3	90	5	88	269-270

[a]Method A: Trichloroacetic acid; [b] Method B: Ceric sulfate

Table 2. Comparison results of CCl_3COOH and $(Ce(SO_4)_2.4H_2O)$ with other catalysts reported in the literature.

Entry	Conditions	Catalyst	Time (min)	Yield (%)
1	Solvent-free, 80 °C	$[MIM(CH_2)_4SO_3H]$ (20mol%)	25-30	86-96
2	H_2O, 60 °C	SDS (20mol%)	2.5-3 h	80-96
3	H_2O, 80 °C	Phosphotungstic acid (15mol%)	14-25	90-98
4	EtOH, 25 °C	$H_{14}[NaP_5W_{30}O_{110}]$-$SiO_2$ (0.3 mol%)	20-30	90-98
5	EtOH, r.t.	Piperidine	4 h	89-97
6	H_2O, 25 °C	HBF_4 (10 mol%)	10-12h	55-70
7	H_2O, reflux	TBAB (10 mol %)	25-40	82-95
8	Solvent-free, 60-70 °C	[bmim]BF_4 (4 mmol)	2-3h	77-91
9	H_2O: EtOH (1:1), 70 °C	CCl_3COOH (10 mol %)	3-5	83-98
10	H_2O: EtOH (1:1), 70 °C	$(Ce(SO_4)_2.4H_2O)$(10 mol %)	5-7	80-97

 DOI: 10.17628/ECB.2014.3.512

Conclusion

In conclusion, we have demonstrated that CCl_3COOH and $Ce(SO_4)_2.4H_2O$ are efficient catalysts for synthesis of α,α′-benzylidenebis(4-hydroxycoumarin). Simple reaction procedures, inexpensive catalysts and single product formation make this an attractive protocol over the existing procedures.

References

[1]Manian, R. D. R. S., Jayashankaran, J., Raghunathan, R., *Tetrahedron Lett.*, **2007**, *48*, 1385.

[2]Kostova, I., Momekov, G., Zaharieva, M., Karaivanova, M., *Eur. J. Med. Chem*., **2005**, 40, 542.

[3]Lee, J. H., Bang, H. B., Han, S. Y., Jun, J. G., *Tetrahedron Lett*., **2007**, *48*, 2889.

[4]Zhao, H., Neamati, N., Hong, H., Mazumder, A., Wang, S., Sunder, S., Milne, G. W. A., Pommier, Y., Burke, T. R., *J. Med. Chem.*, **1997**, *40*, 242.

[5]Maria, G. K., Marian, E. J., *Med. Pharm. Chem*. **1961**, *3*, 583.

[6]Gui-Xia, G., Jian-Feng, Z., Li-Tao, A., Xiu-Li, D., Shun-Jun, J., *Synth. Commun*., **2009**, *39*, 497.

[7]Heravi, M. M., Nahavandi, F., Sadjadi, S., Oskooie, H. A., Bamoharram, F. F., *Synth. Commun*., **2010**, *40*, 498.

[8]Khan, K. M., Iqbal, S., Lodhi, A. M., Maharvi, G. M., Ullah, Z., Choudhary, M. I., Rahman, A. U., Perveen, S., *Bioorg. Med. Chem.*, **2004**, *12*, 1963.

[9]Khurana, J. M., Kumar, S., *Tetrahedron Lett.*, **2009**, *50*, 4125.

[10]Tavakoli-Hoseini, N., Heravi, M. M., Bamoharram, F. F., Davoodnia, A., Ghassemzadeh, M., *J. Mol. Liq*., **2011**, *163*, 122.

[11]Khurana, J. M., Kumar, S., *Monatsh. Chem*., **2010**, *141*, 561.

[12]Mehrabi, H., Abusaidi, H., *J. Iran. Chem. Soc*., **2010**, *7*, 890.

[13]Singh, P., Kumar, P., Katyal, A., Karla, R., Dass, S. K., Prakash, S., Chandra, R., *Catal. Lett*., **2010**, *134*, 303.

[14]Wang, J., Shi, D. Q., Zhuang, Q. Y., Wang X. S., Tu, S. J., *Chin. J. Org. Chem*., **2005**, *25*, 926.

[15]Mazaahir, K., Bansal, V., Mothsra, P., Saxena, S., Somvanshi, R. K., Dey, S., Singh, T. P., *J. Mol. Catal. A: Chem*., **2007**, *268*, 76.

[16]Tabatabaeian, K., Heidari, H., Khorshidi, A., Mamaghani, M., Mahmoodi, N. O., *J. Serb. Chem. Soc*., **2011**, *76*, 1.

[17]Yadav, U. N., Shankarling, G. S., *J. Mol. Liq*., **2014**, *191*, 137.

[18]Salehi, P., Zolfigol, M. A., Shirini, F., Baghbanzadeh, M., *Curr. Org. Chem*., **2006**, *10*, 2171.

[19]Karimi-Jaberi, Z., Takmilifard, Z., *Eur. Chem Bull.*, **2013**, *2*, 211.

[20]Karimi-Jaberi, Z., ReyazoShams, M. M., *Heterocycl. Commun.* **2011**, *17*, 177.

[21]Karimi-Jaberi, Z., Abbasi, S. Z., Pooladian, B., Jokar, M. *E-J. Chem.*, **2011**, *8*, 1895-1899.

[22]Karimi-Jaberi, Z., Nazarifar, M. R., Pooladian, B., *Chin. Chem. Lett.* **2012**, *23*, 781.

Received:. 13.03.2024.
Accepted: 15.04.2014.