Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 77 (4) 407–413 (2012) UDC 546.963'131+547.587.4+547–316:544.4
JSCS–4278 *Original scientific paper*

Synthesis of biscoumarin derivatives by the reaction of aldehydes and 4-hydroxycoumarin using ruthenium(III) chloride hydrate as a versatile homogeneous catalyst

KHALIL TABATABAEIAN*, HANNANEH HEIDARI, ALIREZA KHORSHIDI, MANOUCHEHR MAMAGHANI and NOSRAT O. MAHMOODI

Department of Chemistry, Faculty of Sciences, University of Guilan, P. O. Box 41335-1914, Iran

(Received 27 April, revised 6 October 2011)

Abstract: The one-pot domino Knoevenagel-type condensation/Michael reaction of aromatic, heteroaromatic and aliphatic aldehydes with 4-hydroxycoumarin in aqueous media in the presence of ruthenium salt as homogeneous catalyst was investigated. It was found that 5 mol % of $RuCl_3 \cdot nH_2O$ catalyzes biscoumarin synthesis in high yields (70–95 %) under optimized, mild, green and environmentally benign reaction conditions in short times (25–35min).

Keywords: ruthenium; biscoumarin; aldehyde; 4-hydroxycoumarin; homogeneous catalyst; condensation reaction.

INTRODUCTION

Coumarin derivatives have received considerable attention because of their biological importance and numerous pharmacological activities. Some coumarin derivatives, in general, and biscoumarins, in particular, are known for their antifungal, anti-HIV, anticancer, antithrombotic, anticoagulant, antimicrobial and antioxidant,[1–4] urease inhibitory,[5] cytotoxicity and enzyme inhibitory activities.[6] In addition, their optical and fluorescence emission properties have already been studied.[7,8] Although some types of these compounds could be isolated from plants, for example 7,7'-dihydroxy-6,6'-dimethoxy-3,3'-biscoumarin from *Erycibe obtusifolia*,[9] attempts have been made to use alternative catalysts for biscoumarin synthesis. In 1999, Hagiwara *et al*. reported the use of Et_2AlCl as a Lewis acid for the condensation of 4-hydroxycoumarin and aldehydes in acetonitrile or dichloromethane at room temperature in moderate to good yields (40–80 %).[10] Later, other researchers reported a similar reaction using piperidine,[5] molecular iodine,[11] tetrabutylammonium bromide (TBAB),[12] heteropolyacids,[13] phospho-

* Corresponding author. E-mail: Taba@guilan.ac.ir
doi: 10.2298/JSC110427189T

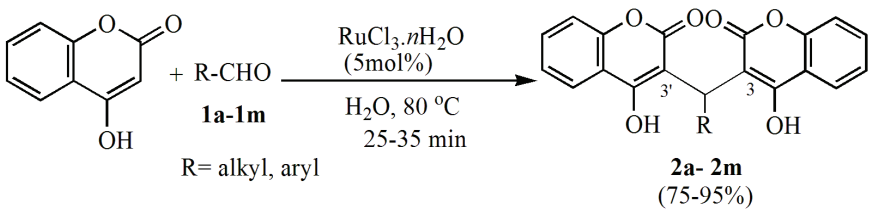
tungstic acid[14] and sodium dodecyl sulfate (SDS)[15] as catalysts. A number of catalyst-free condensation reactions under thermal and microwave irradiation,[1d,16–18] heating in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4)[19] and sonochemical condition[20] were also developed. However, each of the above procedures has its own disadvantages, such as long reaction time, the use of large excess of reagents, low yield and so forth. Due to their wide application, further development of an efficient and useful method for the synthesis of biscoumarin derivatives was considered advantageous.

On the other hand, transition metal and especially ruthenium compounds are favorable materials having useful characteristics, including low redox potential, high electron transfer ability and high coordination ability to heteroatoms. They have been employed as catalyst for various organic syntheses.[21,22] $RuCl_3{\cdot}nH_2O$ has shown suitable homogenous catalytic activity in diverse organic transformations, such as in the generation of hydrogen from isopropanol,[23] deoxygenation of aromatic *N*-oxides,[24] direct arylation of arenes,[25] *etc*. Hence, investigation of ruthenium chemistry has attracted the interest of our group.[26–31]

To the best of our knowledge, Ru(III) salts have never been used as a water-soluble transition metal catalyst for the condensation reaction of 4-hydroxycoumarins with aromatic, heteroaromatic and aliphatic aldehydes for the synthesis of biscoumarin compounds.

RESULTS AND DISCUSSION

Details of the condensation reaction between 4-hydroxycoumarin and various aldehydes are summarized in Scheme 1. In order to optimize the reaction conditions, the effect of various parameters were studied.



Scheme 1. $RuCl_3{\cdot}nH_2O$ catalyzed synthesis of biscoumarins.

Upon treatment of 4-hydroxycoumarin and 3,4-dimethoxybenzaldehyde as a model reaction in the presence of $RuCl_3{\cdot}nH_2O$ (5 mol %) in refluxing EtOH, 3,3'-(3,4-dimethoxybenzylidene)-bis(4-hydroxycoumarin) (**2a**) was formed within 30 min as a white precipitate in 46 % yield (Table I, reaction conditions 2). When water was used as the solvent, surprisingly, the yield improved and the best results were obtained using 5 mol % $RuCl_3{\cdot}nH_2O$ in this solvent; other polar solvents such as EtOH, MeOH and CH_3CN gave lower yields. As is shown in Table II, the temperature had a critical effect on the reaction yield and at room tem-

perature, no reaction occurred even after four hours of stirring the reaction mixture. However, heating the reaction mixture at 80 °C afforded the product in 84 % yield (reaction conditions 3). For yield improvement, the effect of the catalyst loading was also studied (Table III). Increasing the catalyst loading from 5 to 10 mol % did not significantly affect the yield, while the reaction in the absence of $RuCl_3 \cdot nH_2O$ in water at 80 °C, gave the product in only 30 % yield after 10 h.[14]

TABLE I. Optimization of the solvent for the synthesis of 3,3'-(3,4-dimethoxybenzylidene)--bis(4-hydroxycoumarin); reaction conditions: 4-hydroxycoumarin, 2 mmol, 3,4-dimethoxybenzaldehyde, 1 mmol, $RuCl_3 \cdot nH_2O$, 5 mmol, solvent, 5 mL, temperature: 80 °C

Reaction condition	Solvent	τ / min	Yield, %
1	H_2O	30	84
2	EtOH	30	46
3	CH_3OH	30	50
4	CH_3CN	30	30

TABLE II. Optimization of the temperature for the synthesis of 3,3'-(3,4-dimethoxybenzylidene)-bis(4-hydroxycoumarin); reaction conditions: 4-hydroxycoumarin, 2 mmol, 3,4-dimethoxybenzaldehyde, 1 mmol, $RuCl_3 \cdot nH_2O$, 5 mmol, water, 5 mL

Reaction condition	t / °C	τ / min	Yield, %
1	RT	30–240	–
2	50	30	42
3	80	30	84
4	100	30	84

TABLE III. Optimization of the amount of $RuCl_3 \cdot nH_2O$ for the synthesis of 3,3'-(3,4-dimethoxybenzylidene)-bis(4-hydroxycoumarin); reaction conditions: 4-hydroxycoumarin, 2 mmol, 3,4-dimethoxybenzaldehyde, 1 mmol, 80 °C, water, 5 mL

Reaction condition	Amount of catalyst, mol %	τ / min	Yield, %
1	2	30	80
2	5	30	84
3	10	30	82
4	15	30	84

With the optimized conditions in hand, an array of aldehydes were treated with 4-hydroxycoumarin using 5 mol % $RuCl_3 \cdot nH_2O$ at 80 °C whereby the desired products were afforded in good to excellent yields (75–95 %) (Table IV). Aromatic aldehydes, however, provided better yields in comparison with their aliphatic counterparts. With regard to the substituents, both aldehydes with electron withdrawing and electron donating groups participated in the reaction, but the former were better. It should be mentioned that the reaction with amides such as *N*-formylpiperidine failed. Even after several modifications such as a four-fold increase in the catalyst loading, prolonged reaction times and changing solvent,

no traceable amount of the desired product was obtained (Table IV, reaction condition 6).

TABLE IV. Ru(III)-catalyzed synthesis of biscoumarins by condensation of 4-hydroxycoumarin and aldehydes (all products were characterized by ^{1}H-NMR, ^{13}C-NMR and IR data)

Reaction condition	R	τ / min	Product	Yield[a], %	M.p.[b], °C
1	3,4-$(CH_3O)_2C_6H_3$	30	**2a**	84	264–266[c]
2	2-NO_2,CH=CHC_6H_4	30	**2b**	90	190–192
3	2-OH,3-$CH_3OC_6H_3$	33	**2c**	84	268–270
4	3F,4-FC_6H_3	25	**2d**	90	262–264
5	2-Cl,6-FC_6H_3	25	**2e**	92	288–290
6	*N*-Formylpiperidine	60	**2f**	NR[c]	–
7	3-$C_6H_5OC_6H_4$	30	**2g**	90	218–220
8	3-Indolyl	30	**2h**	90	238–240[c]
9	Ph	25	**2i**	84	227–229[c]
10	4-ClC_6H_4	25	**2j**	85	252–254[c]
11	4-$CH_3OC_6H_4$	30	**2k**	92	242–244[c]
12	CH_3CH_2	35	**2l**	75	144–146
13	4-CNC_6H_4	25	**2m**	95	240–242

[a]Isolated yields; [b]m.p. are matched as given in the literature;[25,28] [c]no reaction

The condensation products **2a** and **2h**–**k** (Table IV) are known compounds and their spectroscopic data were consistent with those reported in the literature.[5,14,16,17a] Selected characterization data for the newly synthesized compounds (**2c**–**e**, 2**g** and **2l**–**m**) are given in the Supplementary material to this paper.

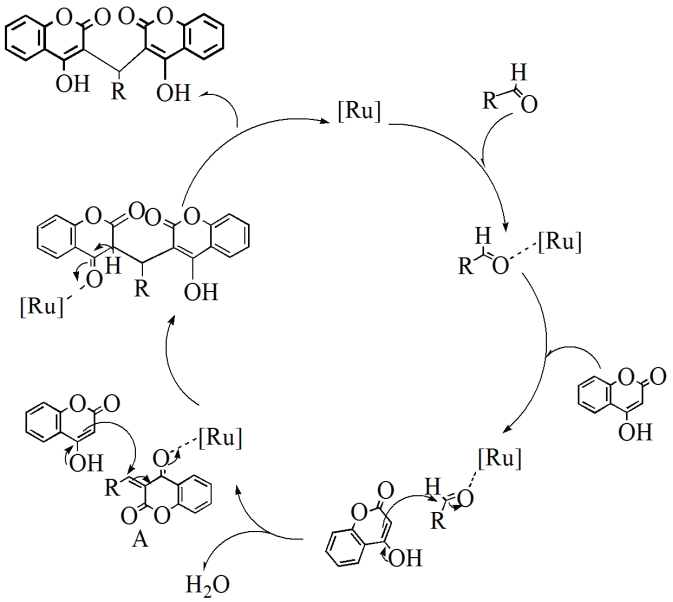
A proposed mechanistic route for the condensation of aldehydes and 4-hydroxycoumarin that rationalizes the formation of the products is exhibited in Scheme 2. As is shown, nucleophilic attack of 4-hydroxycoumarin to the activated aldehyde (by Ru coordination), followed by H_2O elimination provides intermediate "A" that is further activated by Ru. This in turn, undergoes a second nucleophilic attack by another 4-hydroxycoumarin to provide the final product.

In order to evaluate the reusability of the catalyst, after the first run, the product was separated from the reaction mixture by filtration and substrates were added to the filtrate and tested again. It was found that the reused catalyst maintained its activity after successive runs, as is shown in Table V; after six runs, the reused catalyst showed only 8 % decrease in the yield of the biscoumarin product. Thus, the operational simplicity and reusability of the catalyst cover the expensive cost of ruthenium chloride hydrate.

EXPERIMENTAL

All reactions were followed by thin layer chromatography (TLC) with detection by UV light. The IR spectra were obtained in KBr discs on a Shimadzu IR-470 spectrometer. The ^{1}H-NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and the ^{13}C-NMR spectra were obtained on a Bruker DRX-125 or DRX-100 Avance spectrometers. Samples

were analyzed in $CDCl_3$ or DMSO-d_6, and the chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as the internal reference. Melting points were measured on an electrothermal apparatus and are uncorrected. Elemental analyses were realized using a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. The mass spectra of representative compounds were recorded on a HP 5973 network mass selective detector.



Scheme 2. Proposed mechanism for the Ru(III)-catalyzed synthesis of biscoumarins.

TABLE V. Reusability of $RuCl_3 \cdot nH_2O$ in successive runs

Run No.	Yield, %
1	84
2	84
3	82
4	78
5	76
6	76

Materials

4-Hydroxycoumarin, the aldehydes, $RuCl_3 \cdot nH_2O$ and solvents were purchased from Merck and used without further purification.

General procedure for the synthesis of biscoumarins

The catalytic process was performed in a liquid phase. In a typical reaction, 4-hydroxycoumarin (2.0 mmol, 324 mg), the corresponding aldehyde (1.0 mmol), H_2O (5.0 ml) and $RuCl_3 \cdot nH_2O$ (5.0 mmol, 10.7 mg) were taken in a 50 mL round-bottom flask. The reaction mixture was heated at 80 °C in an oil bath and stirred magnetically. After completion of the reaction, as shown by TLC, the mixture was cooled until a solid appeared. The precipitate was

filtered and washed with aqueous ethanol. The crude products were recrystallized from EtOH to yield the pure products. When testing the reusability of the catalyst, hot ethanol was added after completion of the reaction. As the product was insoluble in the cool reaction media, after separation of the solid product, the excess solvent was evaporated from the filtrate. The same substrates were again added to the filtrate including the aqueous medium and catalyst without further purification and reused in the next run.

CONCLUSION

In summary, this study presents a simple experimental procedure under mild reaction conditions, which provides the desired products in short reaction times and high yields. Easy working up, use of water as an eco-friendly solvent, reusability of the catalyst, and availability of the Ru(III) salt are other highlights of this work. This protocol extends the applications of $RuCl_3 \cdot nH_2O$ to clean synthetic methodologies for preparation of pharmaceutically important biscoumarins.

SUPPLEMENTARY MATERIAL

Selected characterization data of the newly synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. The authors thank the Research Council of University of Guilan for the partial support of this study.

ИЗВОД

СИНТЕЗА ДЕРИВАТА БИСКУМАРИНА РЕАКЦИЈОМ АЛДЕХИДА И 4-ХИДРОКСИКУМАРИНА ПОМОЋУ ХИДРАТИСАНОГ РУТЕНИЈУМ(III)-ХЛОРИДА КАО УНИВЕРЗАЛНОГ ХОМОГЕНОГ КАТАЛИЗАТОРА

KHALIL TABATABAEIAN, HANNANEH HEIDARI, ALIREZA KHORSHIDI, MANOUCHEHR MAMAGHANI и NOSRAT O. MAHMOODI

Department of Chemistry, Faculty of Sciences, University of Guilan, P. O. Box 41335-1914, Iran

Испитивана је секвенција домино реакција Knoevenagel-ова кондензација/Michael-ова адиција ароматичних, хетероароматичних и алифатичних алдехида са 4-хидроксикумарином, у воденој средини, у присуству рутенијумових соли као хомогених катализатора. Утврђено је да 5 mol % $RuCl_3 \cdot nH_2O$ катализује синтезу бискумарина у високом приносу (70–95 %) под оптимизованим, благим и еколошки прихватљивим условима, у кратком реакционом времену (25–35 min).

(Примљено 27 априла, ревидирано 6. октобра 2011)

REFERENCES

1. a) F. Borges, F. Roleira, N. Milhazes, L. Santana, E. Uriarte, *Curr. Med. Chem.* **12** (2005) 887; b) I. Manolov, N. Danchev, *Arch. Pharm. Pharm. Med. Chem.* **2** (2003) 83; c) J. C. Jung, O. S. Park, *Molecules* **14** (2009) 4790; (d) I. Manolov, C. Maichle-Moessmer, N. Danchev, *Eur. J. Med. Chem.* **41** (2006) 882
2. a) C. X. Su, J. F. Mouscadet, C. C. Chiang, H. J. Tsai, L. Y. Hsu, *Chem. Pharm. Bull.* **54** (2006) 682; b) H. Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G. W. A. Milne, Y. Pommier, T. R. Burke Jr., *J. Med. Chem.* **40** (1997) 242

3. K. A. Nolan, H. Zhao, P. F. Faulder, A. D. Frenkel, J. D. Timson, D. Siegel, D. Ross, T. R. Burke Jr., I. J. Stratford, A. R. Bryce, *J. Med. Chem.* **5** (2007) 6316
4. a) N. Hamdi, M. C. Puerta, P. Valerga, *Eur. J. Med. Chem.* **43** (2008) 2541; b) V. D. Kancheva, V. P. Boranova, J. Nechev, I. I. Manolov, *Biochimie* **92** (2010) 1138
5. K. M. Khan, S. Iqbal, M. A. Lodhi, G. M. Maharvi, Zia-Ullah, M. I. Choudhary, Atta-ur-Rahman. S. Perveen, *Bioorg. Med. Chem.* **12** (2004) 1963
6. a) M. Choudhary, N. Fatima, K. M. Khan, S. Jalil, S. Iqbal, Atta-ur-Rahman. *Bioorg. Med. Chem.* **14** (2006) 8066; b) I. Kostova, G. Momekov, M. Zaharieva, M. Karaivanova, *Eur. J. Med. Chem.* **40** (2005) 542
7. a) H. Ammar, S. Abid, S. Fery-Forgues, *Dyes Pigm.* **78** (2008) 1; b) A. Chandrasekhar, S. Padmanabhan, S. Seshadri, *Dyes Pigm.* **7** (1986) 13
8. B. D. Wagner, *Molecules* **14** (2009) 210
9. J. Liu, Z. Feng, J. Xu, Y. Wang, Z. Peicheng, *Phytochemistry* **68** (2007) 1775
10. H. Hagiwara, S. Miya, T. Suzuki, M. Ando, I. Yamamoto, M. Kato, *Heterocycles* **51** (1999) 493
11. M. Kidwai, V. Bansal, P. Mothsra, S. Saxena, R. K. Somvanshi, S. Dey, T. P. Singh, *J. Mol. Catal., A* **268** (2007) 76
12. J. M. Khurana, S. Kumar, *Tetrahedron Lett.* **50** (2009) 4125
13. M. M. Heravi, S. Sadjadi, N. Mokhtari Haj, H. Oskooie, F. F. Bamoharram, *Catal. Commun*. **10** (2009) 1643
14. P. Singh, P. Kumar, A. Katyal, R. Karla, S. K. Dass, S. Prakash, R. Chandra, *Catal. Lett.* **134** (2010) 303
15. H. Mehrabi, H. Abusaidi, *J. Iran. Chem. Soc*. **7** (2010) 890
16. S. Kadir, A. A. Dar, K. Z. Khan, *Synth. Commun.* **38** (2008) 3490
17. a) G. X. Gong, J. F. Zhou, L. T. An, X. L. Duan, S. J. Ji, *Synth. Commun.* **39** (2009) 497; b) J. F. Zhou, G. X. Gong, L. An, X. Sun, F. Zhu, *Chin. J. Org. Chem*. **29** (2009) 1988
18. H. Shaterian, M. Honarmand, *Chin. J. Chem.* **27** (2009) 1795
19. J. M. Khurana , S. Kumar, *Monatsh. Chem.* **141** (2010) 561
20. G. Cravotto, G. M. Nano, G. Palmisano, S. Tagliapietra, *Synthesis* (2003) 1286
21. S. I. Murahashi, *Ruthenium in Organic Synthesis*, Wiley-VCH, New York, 2004
22. C. Bruneau, P. H. Dixneuf, *Ruthenium Catalysts and Fine Chemistry*, Springer, Berlin, 2004
23. H. Junge, M. Beller, *Tetrahedron Lett.* **46** (2005) 1031
24. S. Kumar, A. Saini, J. S. Sandhu, *Tetrahedron Lett.* **46** (2005) 8737
25. N. Luo, Z. Yu, *Chem. Eur. J.* **16** (2010) 787
26. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *Synth. Commun.* **40** (2010) 1677
27. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *Can. J. Chem.* **87** (2009) 1213
28. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *Tetrahedron Lett*. **49** (2008) 1450
29. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *Catal. Commun*. **9** (2008) 416
30. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *J. Mol. Catal., A* **270** (2007) 112
31. K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, A. Khorshidi, *Can. J. Chem*. **84** (2006) 1541.