Tetrahedron Letters 54 (2013) 3892–3895

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective synthesis of pyrano[3,2-*c*]coumarins via Cu(II)-catalyzed tandem reaction

Avik Kumar Bagdi, Adinath Majee, Alakananda Hajra *

Department of Chemistry, Visva-Bharati (A Central University), Santiniketan 731235, India

ARTICLE INFO

Article history:
Received 28 February 2013
Revised 11 May 2013
Accepted 14 May 2013
Available online 21 May 2013

Keywords:
Pyrano[3,2-*c*]coumarins
Tandem reaction
Copper triflate
Regioselectivity
Solvent-free

ABSTRACT

Efficient synthesis of pyrano[3,2-*c*]coumarins has been achieved via copper(II) triflate catalyzed tandem reaction of 4-hydroxycoumarin with α,β-unsaturated carbonyl compounds in high yields. The catalytic reaction proceeded very smoothly under solvent-free conditions and showed high regioselectivity. The synthetic potential of this methodology was explored to 4-hydroxy-6-methyl-2-pyrone successfully.

Pyranocoumarins are privileged structural motifs in naturally occurring oxygen-ring compounds which are ubiquitous to a variety of biologically active products and have been shown to a wide range of biological activities such as antifungal, insecticidal, anticancer, anti-HIV, anti-inflammatory, antioxidants, and antibacterial activities.[1] Recently, they have been receiving special attention in medicinal chemistry for the treatment of skin disorder.[2] A large number of pyranocoumarin derivatives having several structural arrays between the coumarin and the pyran rings have been isolated from nature. Notably a few important pyranocoumarins are xanthyletin (predominantly isolated from *Zanthoxylum americanum*), khellactone (isolated from *Ligusticum elatum*), arisugacins, and pyripyropenes (Fig. 1).[3]

Due to their wide occurrence in nature and associated broad ranges of pharmacological activities, the synthesis of pyranocoumarins is of extremely attractive domain in bioorganic chemistry. However, synthesis of pyrano[3,2-*c*]coumarins among various pyranocoumarin derivatives has gained special interest as they are being synthesized from 4-hydroxycoumarin, a commercially available and inexpensive starting material (Scheme 1).

The usual strategy is the reaction of 4-hydroxycoumarin with various types of electrophiles such as 1,3-diarylallylic compounds,[4a] propargylic alcohols,[4b,c] and α,β-unsaturated aldehydes[4d–f] or ketones.[4g,h] Pyranocoumarins have also been synthesized using multicomponent reaction.[5] Reagents as well as catalysts used for tandem reaction between 4-hydroxycoumarin and α,β-unsaturated carbonyl compounds are $POCl_3$,[4g] Bronsted acid,[4e] $AuCl_3/3AgOTf$,[4h] etc. But these methods have many limitations such as, $POCl_3$ is not environmentally friendly, Bronsted acid is not easily available and $AuCl_3/3AgOTf$ is highly expensive. In addition, regioselectivity is also a major issue for these cyclizations.[4d] In consideration of these limitations, the search for finding a cost-effective, simple and selective protocol for the synthesis of pyrano[3,2-*c*]coumarins is highly desirable.

During the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically feasible.

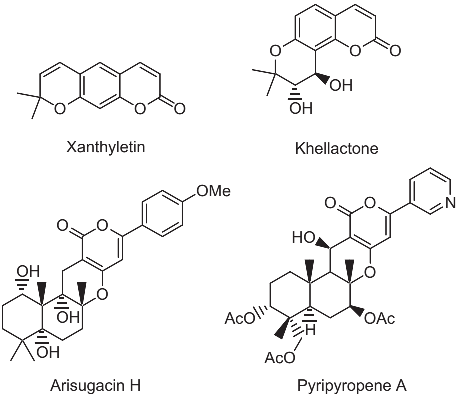
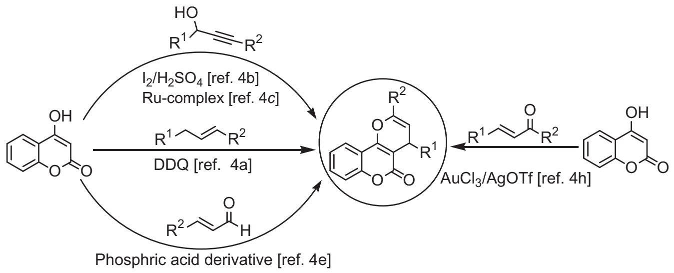


Figure 1. Natural products containing pyranocoumarin moieties.

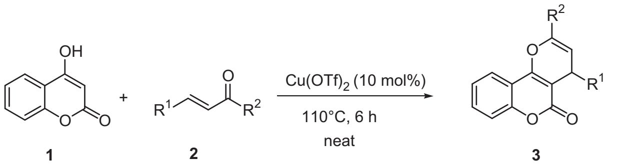
---

* Corresponding author. Tel./fax: +91 3463 261526.
E-mail address: alakananda.hajra@visva-bharati.ac.in (A. Hajra).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.061



Scheme 1. Synthetic methods for the formation of pyranocoumarin.



Scheme 2. The tandem coupling of 4-hydroxycoumarin with enones.

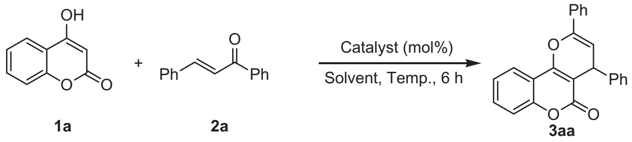
In this context, design of solvent-free catalytic reaction has drawn considerable attention in the area of green synthesis.[6] As a part of our research to provide a greener methodology,[7] here we report an efficient synthesis of pyrano[3,2-*c*]coumarin derivatives using copper triflate as the catalyst under solvent-free conditions (Scheme 2).

Reaction conditions were optimized using various catalysts, solvents, and temperatures employing 4-hydroxycoumarin and 1,3-diphenylpropenone as the model substrates (Table 1). Initially the reaction was carried out using copper triflate (10 mol %) as the catalyst and toluene as the solvent under reflux conditions (entry 1). Under these conditions 70% desired product was isolated. Other solvents such as 1,2-DCE, THF, EtOH, dioxane were also screened, but no further improvement was observed (20–60%). Surprisingly when the reaction was carried out under neat conditions at 110 °C, the yield was obtained in 84% (entry 6). Inferior yield (63%) was obtained at low temperature (entry 7). Increasing the amount of catalyst did not improve the yield significantly (entry 9) while decreasing the amount of catalyst decreased the yield (entry 8). Other copper salts (CuI, $CuCl_2$, $Cu(OAc)_2$) were found to be less effective for this tandem reaction. Other metal triflates such as $In(OTf)_3$, $Zn(OTf)_2$, $La(OTf)_3$ were not so effective as $Cu(OTf)_2$. Finally optimized yield was obtained using 10 mol % copper triflate under neat conditions at 110 °C (entry 6).

After optimizing the reaction conditions, different types of α,β-unsaturated ketones were studied with 4-hydroxycoumarin to verify the general applicability of the present methodology and the results are summarized in Table 2. It was observed that a wide range of α,β-unsaturated ketones were converted into the corresponding pyranocoumarins in high yields. Chalcones bearing electron-donating groups such as –Me and –OMe (**3ab**, **3ac**, **3ah**) and electron-withdrawing groups such as $-NO_2$, –Cl (**3ad**, **3ae**, **3ai**, **3aj**) afforded the desired products with high yields. Acid sensitive chalcone was also unaffected under these reaction conditions (**3af**). In general, the reaction is clean and proceeded smoothly. However, under the present reaction conditions cinnamaldehyde produced a mixture of unidentified products. We next turned our attention to extend our present methodology to other structural analogue of 4-hydroxycoumarin. Gratifyingly, 4-hydroxy-6-methyl-2-pyrone reacted well with chalcones to give the corresponding products (**3ba**, **3bb**, **3bc**, **3bf)** without any difficulty. All these reactions were carried out in open atmosphere and are not sensitive to air and moisture. In addition, the reaction is highly regioselective. No other regio-isomer was isolated under the present reaction conditions.

A proposed mechanism for the tandem reaction is shown in Scheme 3. Probably the first step is the Michael addition of 4-hydroxycoumarin to the α,β-unsaturated ketone which gave the intermediate **4**.[4h] Copper(II) catalyzed the Michael reaction by increasing the electrophilicity of the chalcone **2**. The intermediate

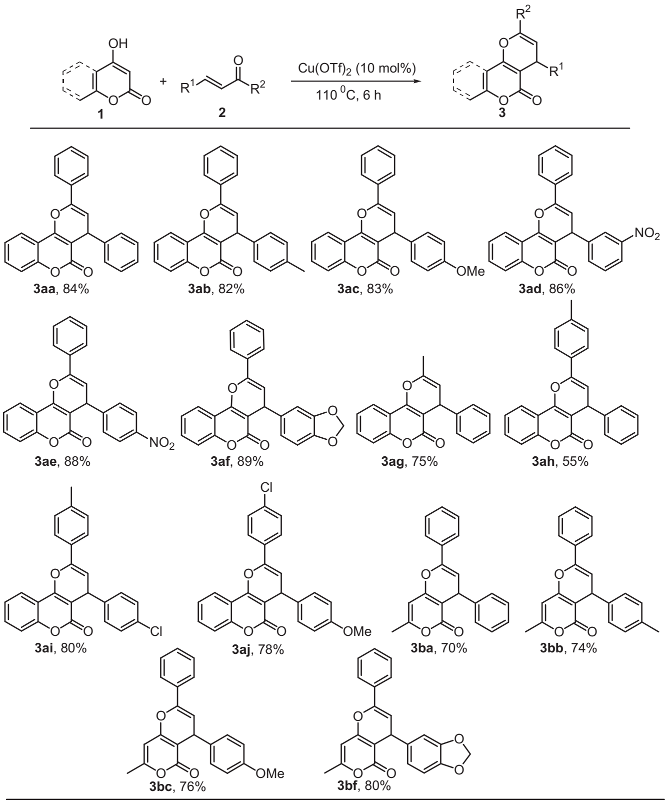
Table 1
Optimization of the reaction conditions[a]



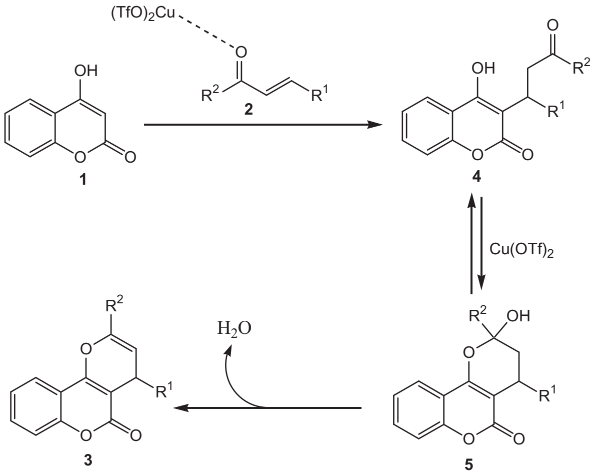
Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Yield[b] (%)
1	$Cu(OTf)_2$ (10)	Tolune	Reflux[c]	70
2	$Cu(OTf)_2$ (10)	DCE	Reflux[c]	60
3	$Cu(OTf)_2$ (10)	Ethanol	Reflux[c]	55
4	$Cu(OTf)_2$ (10)	THF	Reflux[c]	20
5	$Cu(OTf)_2$ (10)	Dioxane	Reflux[c]	57
6	**$Cu(OTf)_2$ (10)**	**Neat**	**110**	**84**
7	$Cu(OTf)_2$ (10)	Neat	80	63
8	$Cu(OTf)_2$ (5)	Neat	110	72
9	$Cu(OTf)_2$ (15)	Neat	110	85
10	CuI (10)	Neat	110	<10
11	$CuCl_2$ (10)	Neat	110	30
12	$Cu(OAc)_2$ (10)	Neat	110	<10
13	$Zn(OTf)_2$ (10)	Neat	110	80
14	$In(OTf)_3$ (10)	Neat	110	70
15	$La(OTf)_3$ (10)	Neat	110	68
16	—	Neat	110	<5

[a] Carried out with 1 mmol of **1a** and 1 mmol of **2a** in the presence of catalyst for 6 h.
[b] Isolated yields.
[c] Solvent (2 mL) under reflux.

Table 2
Substrate scope for the reaction[a]



[a] Reactions conditions: 1 mmol of **1** and 1 mmol of **2** in the presence of $Cu(OTf)_2$ (10 mol %) at 110 °C for 6 h; isolated yields.



Scheme 3. Proposed mechanism for the formation of pyranocoumarins **3**.

4 afforded the desired pyranocoumarin through intramolecular cyclization by removal of H_2O.

In summary, copper triflate was found to be a novel and highly efficient Lewis acid catalyst for the synthesis of pyranocoumarins via Michael addition followed by intramolecular cyclization. The reaction is highly regioselective and water is produced as the sole byproduct only. Operational simplicity, environmentally friendly reaction conditions avoiding toxic reagents and volatile solvents, the compatibility with various functional groups are the advantages of the present procedure. Further studies on the application of the present methodology to the synthesis of biologically active compounds are under investigation in our laboratory.

Acknowledgments

A.H. and A.M. acknowledge the financial support from DST, Govt. of India (Grant No. SR/S5/GC-05/2010). We are thankful to DST-FIST and UGC-SAP. A.K.B. thanks CSIR for his fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.061.

References and notes

1. (a) Mali, R. S.; Joshi, P. P.; Sandhu, P. K.; Manekar-Tilve, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 371; (b) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Mc Phail, A. T.; Lee, K. H. *J. Med. Chem.* **2001**, *44*, 664; (c) Nicolaides, D. N.; Gautam, D. R.; Litinas, K. E.; Hadjipavlou-Litina, D. J.; Flyakakidou, K. C. *Eur. J. Med. Chem.* **2004**, *39*, 323; (d) Meliou, E.; Magiatis, P.; Mitaku, S.; Skalsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78; (e) Galinis, D. L.; Fuller, R. W.; Mc Kee, T. C.; Cardellina, J. H., II; Gulakowski, R. J.; Mc Mahon, J. B.; Boyd, M. R. *J. Med. Chem.* **1996**, *39*, 507; (f) Chakraborty, D. P.; Das Gupta, A.; Bose, P. K. *Ann. Biochem. Exp. Med.* **1957**, *17*, 59; (g) Srinivasan, S.; Sarada, D. V. L. *J. Biomed. Biotechnol.* **2012**. http://dx.doi.org/10.1155/2012/310850.
2. Mali, R. S.; Pandhare, N. A.; Sindkhedkar, M. D. *Tetrahedron Lett.* **1995**, *36*, 7109.
3. (a) Mc Kee, T. C.; Covington, C. D.; Fuller, R. W.; Bokesch, H. R.; Young, S.; Cardellina, J. H. I.; Kadushin, M. R.; Soejarto, D. D.; Stevens, P. F.; Cragg, G. M.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 252; (b) Melliou, E.; Magatis, P.; Mitaku, S.;

Skaltsounis, A.-l.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 8; (c) Kostova, I. *Curr. Med. Chem.* **2005**, *5*, 29; (d) Basile, A.; Sorbo, S.; Spadaro, V.; Bruno, M.; Maggio, A.; Faraorne, N.; Rosselli, S. *Molecules* **2009**, *14*, 939; (e) Ju, Y.; Still, C. C.; Sacalis, J. N.; Li, J.; Ho, C. T. *Phytother. Res.* **2001**, *15*, 441; (f) Kapoor, S. K.; Kohli, J. M.; Sharma, Y. N.; Zaman, A. *Phytochemistry* **1972**, *11*, 477; (g) Omura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1995**, *48*, 745; (h) Kuno, F.; Otoguro, K.; Shiomi, K.; Iwai, Y.; Omura, S. *J. Antibiot.* **1996**, *49*, 742; (i) Kuno, F.; Shiomi, K.; Otoguro, K.; Sunazuka, T.; Omura, S. *J. Antibiot.* **1996**, *49*, 748; (j) Otoguro, K.; Kuno, F.; Omura, S. *Pharmacol. Ther.* **1997**, *76*, 45; (k) Otoguro, K.; Shiomi, K.; Yamaguchi, Y.; Arai, N.; Sunazuka, T.; Masuma, R.; Iwai, Y.; Omura, S. *J. Antibiot.* **2000**, *53*, 50.

4. (a) He, Z.; Lin, X.; Zhu, Y.; Wang, Y. *Heterocycles* **2010**, *81*, 965; (b) Lin, X.; Dai, X.; Mao, Z.; Wang, Y. *Tetrahedron* **2009**, *65*, 9233; (c) Berger, S.; Haak, E. *Tetrahedron Lett.* **2010**, *51*, 6630; (d) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1865**, *1990*, 73; (e) Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. *J. Org. Chem.* **2009**, *74*, 8963; (f) Appendino, G.; Cravotto, G.; Giovenzana, G. B.; Palmisano, G. *J. Nat. Prod.* **1999**, *62*, 627; (g) Jacquot, Y.; Refouvelet, B.; Bermont, L.; Adessi, G. L.; Leclercq, G.; Xicluna, A. *Pharmazie* **2002**, *57*, 233; (h) Liu, Y.; Zhu, J.; Qian, J.; Jiang, B.; Xu, Z. *J. Org. Chem.* **2011**, *76*, 9096.
5. (a) Sarma, R.; Sarmah, M. M.; Lekhok, K. C.; Prajapati, D. *Synlett* **2010**, 2847; (b) Ahadi, S.; Zolghadr, M.; Khavasi, H. R.; Bazgir, A. *Org. Biomol. Chem.* **2013**, *11*, 279.
6. (a) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267; (b) Anastas, I. P.; Williamson, T. Green Chemistry. In *Frontiers in Benign Chemical Synthesis and Processes*; University Press: London, 1998; (c) Loupy, A. *Top. Curr. Chem.* **1999**, *206*, 153; (d) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025; (e) Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8701; (f) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159.
7. (a) Santra, S.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2012**, *53*, 1974; (b) Rahman, M.; Bagdi, A. K.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2011**, *52*, 4437; (c) Kundu, D.; Debnath, R. K.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2009**, *50*, 6998; (d) Kundu, D.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2009**, *50*, 2668; (e) Kundu, D.; Bagdi, A. K.; Majee, A.; Hajra, A. *Synlett* **2011**, 1165.