Tetrahedron Letters 52 (2011) 5610–5612

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

A novel one pot route to flavones under dual catalysis, an organo- and a Lewis acid catalyst

Gourhari Maiti *, Rajiv Karmakar, Rudraksha N. Bhattacharya, Utpal Kayal

Department of Chemistry, Jadavpur University, Kolkata 700 032, India

ARTICLE INFO

Article history:
Received 16 June 2011
Revised 12 August 2011
Accepted 13 August 2011
Available online 24 August 2011

Keywords:
Flavones
One pot
Dual catalysis
Ferric chloride
Aerial oxidation

ABSTRACT

Substituted phenylacetylenes react with various *o*-hydroxy aromatic aldehydes under dual catalysis of piperidine and $FeCl_3$ in refluxing toluene to yield flavones in good to excellent yield. Atmospheric oxygen acts as stoichiometric oxidant in the process. Some of these compounds had been recently reported to show fair insecticidal activity against *Spodoptera frugiperda*.

Flavones, also known as 2-phenyl-4-chromones represent one of the largest groups of natural products and are highly diverse. A large number of derivatives have been identified and the number is still growing rapidly. The chromone framework is widely identified as a privileged structure for drug development or pharmacophore. Both natural and synthetic flavones exhibit a wide spectrum of biological activity including anti-oxidant, anti-cancer, anti-HIV, anti-hypertensive, and anti-inflammatory properties.[1–5] Because of their antioxidant ability, many of the flavonoids are responsible for health-promoting functions in organism, which are important for the prevention of diseases that are associated with an oxidative damage of membranes, proteins and DNA.[6] This has led to a wide interest among the community of organic chemists to synthesize flavones, both by the development of annulation methodology[7] and by target oriented convergent synthesis.[8]

Traditionally, chromones have been prepared by the Baker–Venkatraman rearrangement[9] or by annulation involving oxidative cyclization of various 2-hydroxychalcones and cyclodehydration of substituted 1-(2-hydroxyaryl)-3-arylpropan-1,3-dione. Later, classical Baker–Venkatraman reaction have been modified to one pot synthesis using 2-hydroxyacetophenone derivatives and acyl chloride in the presence of DBU-pyridine.[10] Very recently, Buckle and co-workers [11] observed that 2-hydroxy acetophenone when heated with an excess of benzoyl chloride in an open K_2CO_3 wet acetone system, flavone was obtained but only in modest yield.

The palladium catalyzed carbonylation of *o*-iodophenols with terminal alkynes have become an attractive alternative to synthesize chromones, but the scope is limited due to the formation of five-membered aurones as the side product.[12] Yang and Alper have developed ligand free Pd-catalyzed cyclocarbonylation of *o*-iodophenols with terminal alkynes in ionic liquids.[7e] Considering therapeutic importance of flavones, one pot diversity oriented approach is highly desired. We were interested in investigating an alternative one pot atom-economy route to flavones as delineated below (Fig. 1).

Herein, we report a new synthetic route to flavones **3** from 2-hydroxyaryl aldehyde **1** and aryl acetylene **2** in the presence of piperidine (20 mol %) and $FeCl_3$ (10 mol %) under reflux in toluene in open air (Scheme 1).

It is noteworthy that iron(III) salts/complexes have a rich heritage to catalyze aerial oxidation including photooxidation[13] and have also been used as stoichiometric oxidant in many cases.[14]

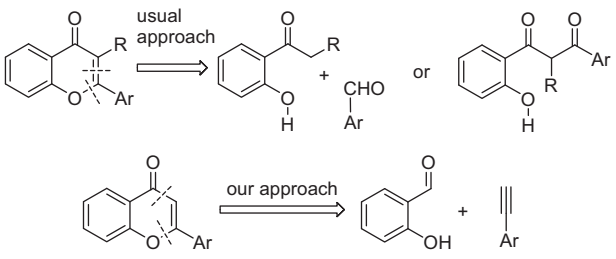
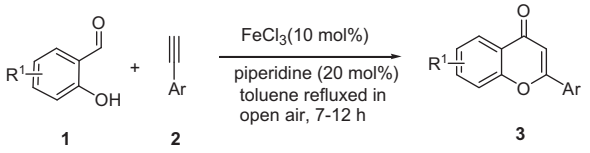


Figure 1. Retrosynthetic analysis.

* Corresponding author.
E-mail address: ghmaiti123@yahoo.co.in (G. Maiti).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.08.078



Scheme 1. Synthesis of flavones.

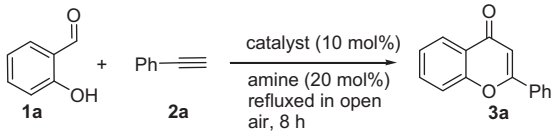
The present investigation involves oxidation by two units of iron salt. The concept of dual catalysis[15] and organocatalysis[16] is of increasing importance in recent times.

In a preliminary experiment, a solution of salicylaldehyde **1a** (1.0 mmol) and phenyl acetylene **2a** (1.5 mmol) in toluene (3 mL) was refluxed in the presence of $FeCl_3$ (10 mol %) and piperidine (20 mol %) for 8 h in open air to afford the desired chromone **3a** in 80% yield. Then, to optimize the reaction conditions the same reaction was studied by using various Lewis acids and organocatalysts, a dual catalyst system and also the catalyst-solvent combination under identical reaction conditions. The results are summarized in Table 1.

It is quite apparent from Table 1 that among various Lewis acid catalysts-organocatalysts combination screened, only $FeCl_3$-piperidine catalyst combination afforded the best results with respect to the reaction time and yield are concerned. It was also found that the use of 10 mol % of $FeCl_3$ gave the best result. Use of less than 10% of $FeCl_3$ decreases the yield and more than 10 mol % does not improve the rate as well as the yield of the product. The presence of aerial oxygen is essential for this transformation without which the reaction does not occur at all. The role of aerial oxygen in some oxidation reaction is known in the literature.[17] It is also very clear from Table 1 that piperidine is the best choice of the base as a catalyst. It should be noted here that the primary or tertiary amines could not catalyze the reaction. This indicates that an imminium ion is formed with the secondary amine in the reaction pathway.

A series of 2-hydroxy arylaldehydes and arylacetylenes were subjected to the optimized reaction conditions[21] and the results are summarized in Table 2.

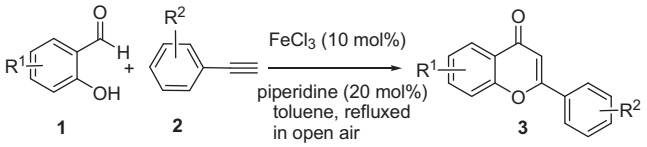
Table 1
Optimization of the reaction conditions

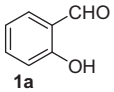
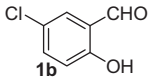
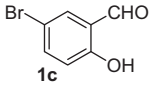
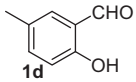
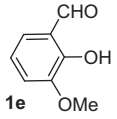
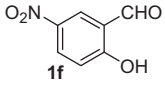


Entry	Catalyst	Base	Solvent	Yield[a,b] (%)
1	$FeCl_3$	Piperidine	Toluene	80
2	$FeCl_3$	Piperidine	Xylene	72
3	$FeCl_3$	Piperidine	CH_3CN	32
4	$FeCl_3$	Piperidine	DCM	[c]
5	$FeCl_3$	Piperidine	CH_3NO_2	C
6	$FeCl_3$	Piperidine	Toluene	[c]
7	$FeCl_3$	Morphine	Toluene	37
8	$FeCl_3$	*N*-Methylaniline	Toluene	08
9	$FeCl_3$	Pyrrolidine	Toluene	63
10	$FeCl_3$	K_2CO_3	Toluene	[c]
11	$FeCl_3$	Aniline	Toluene	[c]
12	$FeCl_3$	L-Proline	Toluene	26
13	$FeCl_3$	Nil	Toluene	20
14	Nil	Piperidine	Toluene	[c]
15	*p*-TsOH	Piperidine	Toluene	[c]
16	$InCl_3$	Piperidine	Toluene	[c]
17	$InCl_3$	Piperidine	CH_3NO_2	[c]
18	$SnCl_3$	Piperidine	Toluene	06
19	$Yb(OTf)_3$	Piperidine	Toluene	[c]
20	$Zncl_2$	Piperidine	Toluene	[c]

[a] Reaction condition: salicyaldehyde (1.0 mmol), phenylacetylene (1.0 mmol) in 3 mL of solvent, catalyst (0.1 mmol), amine (0.2 mmol), refluxed in open air for 8 h.
[b] Pure, isolated yield after column chromatography.
[c] Desired product not formed.

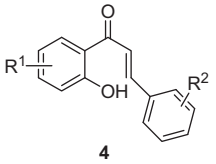
Table 2
One pot synthesis of flavones under dual catalysis



Entry	Aldehyde	R^2	Product[a,b]	Time (h)	Yield[c] (%)
1	 1a	H	**3a**	8	80
2	 1b	H	**3b**	7	86
3	**1b**	4-F	**3c**	8	87
4	**1b**	4-Cl	**3d**	10	83
5	**1b**	4-Br	**3e**	10	84
6	 1c	H	**3f**	7	82
7	**1c**	4-Cl	**3g**	10	85
8	 1d	H	**3h**	12	85
9	**1d**	4-Br	**3i**	12	84
10	 1e	H	**3j**	10	86
11	**1e**	4-Cl	**3k**	8	82
12	**1e**	4-Br	**3l**	8	86
13	 1f	H	**3m**	10	74

[a] Reaction condition: 2-hydroxy arylaldehyde (1.0 mmol), arylacetylene (1.0 mmol) in 3 mL toluene, $FeCl_3$ (0.1 mmol), piperidine (0.2 mmol), refluxed in open air.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR and HRMS.
[c] Pure, isolated yield after column chromatography.

Along with the desired flavones, about 3–5% of *o*-hydroxy chalcone **4** was formed in every cases under the reaction conditions which could easily be separated by column



chromatography and characterized by spectral analysis. It is to be mentioned here that the formation of flavones certainly did not proceed through chalcone intermediate as *o*-hydroxy chalcone when refluxed in toluene in open air with $FeCl_3$ (10 mol %) and piperidine (20 mol %) could not furnish flavone. Keeping with all these facts, the probable mechanism for the formation of flavones is shown in Figure 2.

Various 2-hydroxy arylaldehydes having both positive and negative inductive and mesomeric groups responded well to the reaction. In the reaction, atmospheric oxygen was used as the ultimate stoichiometric oxidant leaving only water as the by-product. 2-hydroxy-1-naphthaldehyde did not furnish the desired product, instead a very complex mixture was formed. 1-Ethynyl-3-nitrobenzene when used as the terminal alkyne also did not respond to the

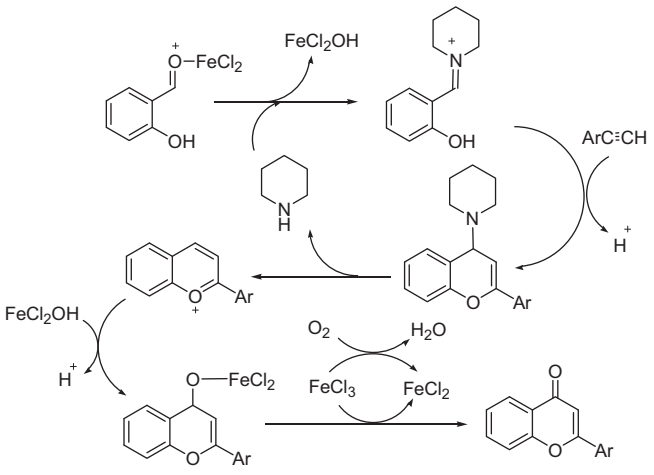


Figure 2. Probable mechanism.

reaction condition. This may be explained by the low nucleophilicity of the alkyne due to the conjugation with the aromatic ring containing a strong electron withdrawing functional group.

It is very interesting to note that how the variation of catalyst solvent system can lead to different products, the major reactants remaining similar. Skouta et al.[18] showed that the reaction between salicylaldehyde and phenyl acetylene in the presence of a tributylphosphine and AuCN as the catalyst in toluene at 150 °C afforded isoflavone. On the other hand, phenyl acetylene, salicylaldehyde, and piperidine in the presence of copper(I) halides as catalyst in DMF, potassium carbonate, and nBu$_4$NBr yielded benzofurans in modest yield. In the absence of potassium carbonate and nBu$_4$NBr under similar reaction condition afforded the propoargyl amine derivatives.[19]

The compounds **3b** and **3f** have recently been reported to show good activity against *Spodoptera frugiperda*, the fall armyworm which is regarded as a pest and can wreak havoc with crops if left to multiply. The 50% lethal times (LT_{50}) of **3b** and **3f** were shown to be 53 and 44 h, respectively.[20]

In conclusion, we have developed a new methodology toward one pot synthesis of flavones under dual catalysis of piperidine, an organocatalyst and ferric chloride, a Lewis acid. The notable advantages of this method are operational simplicity, use of inexpensive and eco-friendly $FeCl_3$ as catalyst, employment of atmospheric oxygen as the stoichiometric oxidant and ease of isolation of products. Further studies in this area to explore the synthetic applications of the reaction are progress.

Acknowledgments

We thank the Department of Chemistry, Jadavpur University for the financial and infrastructural support from UGC-CAS and PURSE-DST Programme. R.K. and U.K. thank CSIR, New Delhi for awarding the fellowships. We are also thankful to Mr. S. Dutta, IICB, Kolkata for providing instrumental facilities.

Supplementary data

Supplementary data (^{1}H, ^{13}C NMR spectral data of compound **3b**–**m**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.078.

References and notesx

1. (a) Atmani, D.; Chaher, N.; Berboucha, M.; Debbache, N.; Boudaoud, H. *Curr. Nutr. Food Sci.* **2009**, *5*, 225–237; (b) Dixon, R. A.; Steele, C. *Plant Sci.* **1999**, *4*, 394–400.
2. Liu, H. L.; Jiang, W. B.; Xie, M. X. *Recent Pat. Anti-Cancer Drug Discovery* **2010**, *5*, 152–164.
3. Carneiro, C. D.; Amorim, J. C.; Cadena, S. M. S. C.; Noleto, et al *Food Chem. Toxicol.* **2010**, *48*, 2380–2387.
4. Theoharides, T. C. In *Chemistry and Molecular Aspects of Drug Design*; Rekka, E. A., Kourounakis, P. N., Eds.; CRC Press: Boca Raton, FL, 2008; pp 215–226.
5. Meragelman, K. M.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 546–548.
6. Ferguson, L. R. *Mutat. Res.* **2001**, *475*, 89–111.
7. (a) Alvim, J., Jr.; Severino, R. P.; Marques, E. F.; Martinelli, A. M.; Vieira, P. C.; Fernandes, J. B.; da Silva, M. F.; Das, G. F.; Corrêa, A. G. *J. Comb. Chem.* **2010**, *12*, 687–695; (b) Yao, N.; Song, A.; Wang, X.; Dixon, S.; Lam, K. S. *J. Comb. Chem.* **2007**, *9*, 668–676; (c) Sarda, S. R.; Jadhav, W. N.; Pawar, R. P. *Int. J. ChemTech Res.* **2009**, *1*, 539–543; (d) Zhao, J.; Zhao, Y.; Fu, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3769–3773; (e) Yang, Q.; Alper, H. *J. Org. Chem.* **2010**, *75*, 948–950.
8. (a) Minassi, A.; Giana, A.; Ech-Chahad, A.; Appendino, G. *Org. Lett.* **2008**, *10*, 2267–2270; (b) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300–9305; (c) Furuta, T.; Nakayama, M.; Suzuki, H.; Tajimi, H.; Inai, M.; Nukaya, H.; Wakimoto, T.; Kan, T. *Org. Lett.* **2009**, *11*, 2233–2236.
9. (a) Baker, W. *J. Chem. Soc.* **1933**, 1381–1389; (b) Mahal, H. S.; Venkataraman, K. *Curr. Sci.* **1933**, *2*, 214.
10. (a) Riva, C.; DeToma, C.; Donadd, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997**, 195; (b) Ganguly, A. K.; Kaur, S.; Mahata, P. K.; Biswas, D.; Pramanik, B. N.; Chan, T. *Tetrahedron Lett.* **2005**, *46*, 4119; (c) Ganguly, A. K.; Mahata, P. K.; Biswas, D. *Tetrahedron Lett.* **2006**, *47*, 1347; (d) Bois, F.; Beney, C.; Mairotte, A. M.; Boumendjel, A. *Synlett* **1999**, 1480.
11. Chee, C. F.; Buckle, M. J.; Rahman, N. A. *Tetrahedron Lett.* **2011**, *52*, 3120–3123.
12. Ciattini, P. G.; Morera, E.; Ortar, G.; Rossi, S. S. *Tetrahedron* **1991**, *47*, 6449.
13. (a) Shulpin, G. B.; Kats, M. M. *React. Kinet. Catal. Lett.* **1990**, *41*, 239–243; (b) Walters, M. A.; Chaparro, J.; Siddiqui, T.; Williams, F.; Ulku, C.; Rheingold, A. L. *Inorg. Chem. Acta* **2006**, *359*, 3996–4000.
14. Haas, R. H.; Shirley, D. A. *J. Org. Chem.* **1965**, *30*, 4111–4113.
15. For selected examples, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (e) Ma, J.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583; (f) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246–5251; (g) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959–4962.
16. (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308; (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; (c) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.
17. (a) Marko, I.-E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044–2046; (b) Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194–197; (c) Velusamy, S.; Punniyamurthy, T. *Org. Lett.* **2004**, *6*, 217–219.
18. Skouta, R.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1117–1119.
19. Li, H.; Liu, J.; Yan, B.; Li, Y. *Tetrahedron Lett.* **2009**, *50*, 2353–2357.
20. Romanelli, G. P.; Virla, E. G.; Duchowicz, P. R.; Gaddi, A. L.; Ruiz, D. M.; Bennardi, D. O.; Ortiz, E. D. V.; Autino, J. C. *J. Agric. Food Chem.* **2010**, *58*, 6290–6295.
21. *Representative experimental procedure for the synthesis 2-phenyl-4H-chromen-4-one* (**3a**): A mixture of 2-hydroxybenzaldehyde (122 mg, 1.0 mmol), phenyl acetylene (153 mg, 1.5 mmol), anhydrous ferric chloride (16 mg, 0.10 mmol) and piperidine (17 mg, 0.20 mmol) were added to dry toluene (3 mL) taken in a 25 mL round bottom flask fitted with a reflux condenser and a calcium chloride guard tube and was refluxed for 6–12 h. Completion of the reaction was monitored by TLC. The reaction mixture was decomposed with water and extracted with diethyl ether (3 × 15 mL), washed with water followed by brine solution and dried over anhydrous Na_2SO_4. Filtered and volatiles were removed in vacuo and the crude residue was purified by column chromatography over silica gel (100–200 mesh), eluting with 8–15% ethyl acetate in petroleum ether to afford **3a** (178 mg, 80%) as a white solid and 1-(2-hydroxyphenyl)-3-phenylpropenone **4a** (9 mg, 4%). Spectral and analytical data of **3a**: mp 97–98 °C. IR (KBr): 1128, 1225, 1375, 1448, 1465, 1495, 1568, 1645, 2355, 2923, 3088 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (s, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.50–7.61 (m, 4H), 7.71 (t, J = 7.5 Hz, 1H), 7.90–7.96 (m, 2H), 8.24 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 107.6, 118.1, 124.0, 125.3, 125.8, 126.4, 129.1, 131.6, 131.8, 133.8, 156.3, 163.5, 178.1. HRMS for $[C_{15}H_{11}O_2]^+$ calcd 223.0754; found 223.0748. Spectral and analytical data of **4a**: mp 79–80 °C. IR (KBr): 975, 1020, 1029, 1152, 1235, 1340, 1438, 1448, 1574, 1639 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.95 (t, J = 8.0 Hz, 1H), 7.63–7.67 (m, 3H), 7.89–7.94 (m, 2H), 12.85 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 118.6, 118.8, 120.0, 120.1, 128.6, 129.0, 129.6, 130.9, 134.6, 136.4, 145.4, 163.6, 193.7.