Bulgarian Chemical Communications, Volume 49, Number 2, (pp. 483 – 486) 2017

An efficient ultrasound-promoted method for the synthesis of xanthene derivatives

S. Bagherpoor, M.A. Amrollahi*

Department of Chemistry, Yazd University, Yazd, Iran P.O. Box 89195-741

Received May 20, 2015; Accepted February 26, 2016

Zirconium (IV) chloride was used as an efficient, stable, inexpensive, environmentally friendly, and convenient catalyst for preparation of xanthene derivatives *via* one-pot three-component condensation of aldehydes with 2-naphthol and 5,5-dimethyl-1,3-cyclohexanedione under ultrasonic irradiation conditions. EtOH was found as an effective solvent for this transformation. This method offers several advantages such as high yields, simple procedure, low cost and short reaction times.

Keywords: Lewis acid, 2-Naphthol, One-pot, Ultrasonic, Xanthenes, Zirconium (IV) chloride

INTRODUCTION

Ultrasound irradiation is a very effective method and can be widely used in organic synthesis. Higher reaction rates, simple experimental procedure, and high yields are the notable features of the ultrasound approach as compared to established methods [1–3]. In recent times, xanthenes have attracted attention of medicinal chemists, as well as organic chemists due to their wide range of biological and pharmacological activities such as antiviral [4], antibacterial [5], and anti-inflammatory properties [6]. A variety of reagents and catalysts has been reported for the preparation of these compounds such as $Fe(HSO_4)_3$ [7], PVPP-BF_3 [8], $NaHSO_4.SiO_2$ [9], $Sr(OTf)_2$ [10], $Zr(HSO_4)_4$ [11], $RuCl_3 \cdot nH_2O$ [12], P_2O_5/Al_2O_3 [13], $BF_3.SiO_2$ [14], $C_2H_2O_4$ [15], P(4-VPH)HSO_4 [16], H_3NSO_3 [17], $BiCl_3$ [18], ZnO-NPs [19], SUSA [20], $Sc[N(SO_2C_8F_{17})_2]_3$ [21], Pd [22], $InCl_3$ [23], $BF_3.OEt_2$ [24], AcOH/H^+ [25], p-TSA [26]. The use of each of these materials has its own advantages, but it also suffers from one or more disadvantages such as prolonged reaction time, low yields, use of toxic and costly catalysts, harsh reaction conditions, and complex work-up procedures. Zirconium (IV) chloride ($ZrCl_4$) is generally considered to be a green, inexpensive, non-toxic (LD50: 1688 mg/kg) and commercially available zirconium salt [27]. Its application as a Lewis acid catalyst in various organic transformations has been reported [28–32]. In continuation of our studies towards the development of novel methodologies for the synthesis of biologically active heterocyclic compounds [33], herein we report a improved and convenient method for the synthesis of xanthene derivatives through the condensation of various aromatic aldehydes, 2-naphthol, and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) in the presence of $ZrCl_4$ as an efficient catalyst under silent and ultrasonic irradiation conditions.

EXPERIMENTAL

^1H- and ^{13}C-NMR spectra were recorded on Bruker Avance-400 MHz spectrometers. IR spectra were run on a Bruker Eqinox 55 spectrometer. Ultrasonic irradiation was run on Bandelin Sonopuls HD 3200 with an output power of 60 W. Purity determination of the substrates and reaction monitoring were accompanied by TLC using pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness.

General experimental procedure

Silent conditions. A mixture of aldehyde (1 mmol), 2-naphthol (1 mmol), dimedone (1.2 mmol) and $ZrCl_4$ (8 mol%) was stirred for appropriate time in EtOH at reflux temperature. The completion of the reaction was monitored by TLC ($CHCl_3$:MeOH 9:1). After cooling, the reaction mixture was poured onto crushed ice (20 g). The resulting precipitate was filtered under suction, and then recrystallized from EtOH to afford the pure product with yield of 70-82%. The results are summarized in Table 2.

Ultrasound irradiation. A mixture of aldehyde (1 mmol), 2-naphthol (1 mmol), dimedone (1.2 mmol) and $ZrCl_4$ (8 mol%) was irradiated with ultrasound at reflux temperature for appropriate time. After cooling, the reaction mixture was poured onto crushed ice (20 g). The resulting precipitate was filtered under suction, and then recrystallized from EtOH to afford the pure product with yield of 75-95%. The results are summarized in Table 2.

Selected spectra data

9,9-dimethyl-12-phenyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one Yield: 85%, White solid, m.p. 158-160 °C; IR (KBr): 2913, 1647, 1620, 1596, 1469, 1452, 1372. ^1H-NMR (400 MHz,

---

* To whom all correspondence should be sent:
E-mail: mamrollahi@yazd.ac.ir

CDCl3): δ 0.97 (s, 3H), 1.13 (s, 3H), 2.25 (d, 1H), 2.32 (d, 1H), 2.58 (s, 2H), 5.71 (s, 1H), 7.06 (t, 1H), 7.18 (t, 2H), 7.32-7.46 (m, 5H), 7.77 (d, 1H), 7.79 (d, 1H), 8.00 (d, 1H). ^{13}C-NMR (100 MHz, CDCl3): δ 27.5, 29.7, 32.6, 35.3, 41.8, 51.2, 114.71, 117.4, 118.1, 124.1, 125.3, 126.6, 127.4, 128.6, 128.8, 128.8, 129.2, 131.8, 131.9, 145.1, 148.2, 165.3, 197.2.

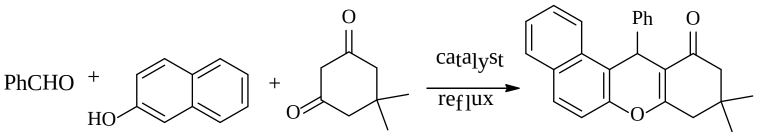
9,9-dimethyl-12-(p-tolyl)-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one Yeild: 85%, White solid, m.p. 172-174 °C; IR (KBr): 2957, 1646, 1620, 1597, 1511, 1466, 1369. ^{1}H-NMR (400 MHz, CDCl3): δ 1.00 (s, 3H), 1.14 (s, 3H), 2.23 (s, 3H), 2.35 (m, 2H), 2.6 (s, 2H), 5.7 (s, 1H), 6.99 (d, 2H), 7.24 (d, 2H), 7.32-7.43 (m, 2H), 7.46 (t, 1H), 7.78 (t, 2H), 8.03 (d, 1H). ^{13}C-NMR (100 MHz, CDCl3): δ 20.9, 27.3, 29.2, 32.3, 34.3, 41.4, 50.9, 114.4, 117.0, 117.9, 123.7, 124.8, 126.9, 128.2, 128.3, 128.7, 128.9, 131.4, 131.5, 135.6, 141.8, 147.7, 163.7, 196.9.

12-(2-fluorophenyl)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one Yeild: 87%, White solid, m.p. 175-177 °C; IR (KBr): 2948, 1649, 1620, 1595, 1515, 1485 (-CH_2 bend.), 1371. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.16 (s, 3H), 2.23-2.42 (m, 2H), 2.63 (s, 2H), 5.9 (s, 1H), 6.96-6.99 (m, 2H), 7.38-7.41 (m, 2H), 7.42-7.48 (m, 2H), 7.52 (t, 1H), 7.75-7.80 (m, 2H), 8.12 (d,1H).^{13}C-NMR (100 MHz, $CDCl_3$): 27.1, 27.2, 29.4, 32.2, 41.4, 50.8, 115.7, 116.5, 117.1, 118.8, 121.5, 123.2, 123.4, 124.0, 124.3, 124.9, 125.2, 127.1, 128.2, 128.4, 128.7, 128.9, 130.9, 165.2, 196.6.

RESULTS AND DISCUSSION

In our initial study, the reaction of benzaldehyde, 2-naphthol, and dimedone was considered as a model reaction to optimize the conditions. The reaction was first carried out in H_2O in the absence of $ZrCl_4$ and at reflux temperature. No reaction occurred under silent and ultrasound irradiation conditions (Table 1, entry 1). The reaction was then attempted in the presence of 8 mol % of $ZrCl_4$. The result in Table 1, entry 2 shows a trace amount of product prepared under both silent and ultrasound irradiation conditions. To find the best solvent, several solvents such as CH_2Cl_2, AcOEt, MeCN, EtOH and solvent-free conditions were employed as media. It was noticed that the highest yield was achieved with EtOH, when the reaction was performed under silent conditions (Table 1, entry 6), while the formation of the product was more facile and proceeded in shorter time and with high yield under ultrasonic irradiation conditions.

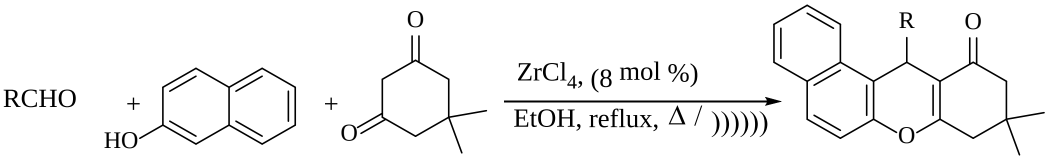
Table 1. Optimization of the reaction conditions for one-pot synthesis of 9,9-dimethyl-12-phenyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one under various conditions [a)]



Entry	Catalyst (mol%)	Solvent	Yield (%) [b)]
1	-	H_2O	-
2	$ZrCl_4$ (8)	H_2O	trace
3	$ZrCl_4$ (8)	CH_2Cl_2	-
4	$ZrCl_4$ (8)	AcOEt	-
5	$ZrCl_4$ (8)	MeCN	-
6	$ZrCl_4$ (8)	EtOH	75
7	$ZrCl_4$ (8)	solvent-free	trace
8[c)]	$ZrCl_4$ (8)	EtOH	65
9 [d)]	$ZrCl_4$ (8)	EtOH	40
10	$ZrCl_4$ (4)	EtOH	55
11	$ZrCl_4$ (6)	EtOH	60
12	$ZrCl_4$ (10)	EtOH	71
13	$ZrOCl_2.8H_2O$ (9)	EtOH	20
14	$ZnBr_2$ (8)	EtOH	70
15	$CoCl_2$ (8)	EtOH	40
16	$CuCl_2$ (8)	EtOH	35
17	$Ni(NO_3)_2$ (10)	EtOH	65

[(a)] Reaction conditions: benzaldehyde (1 mmol), 2-naphthol (1 mmol), dimedone (1.2 mmol), EtOH (5 mL), [b)] Isolated yields under normal conditions. [c)] 60 °C, [d)] room temp.

Table 2. Synthesis of benzo[a]xanthenone derivatives under silent and ultrasonic conditions [a)]



Entry	R	Time (min) Sonication/Silent	Yield (%) [b)] Sonication [c)]/Silent	Melting points (°C)		
				Found	Reported	Ref.
1	C_6H_5	20/120	85/75	158-160	151-153	[23]
2	$3\text{-}NO_2C_6H_4$	15/65	92/80	162-164	168-170	[23]
3	$4\text{-}NO_2C_6H_4$	15/60	95/82	181-182	178-180	[23]
4	$2\text{-}FC_6H_4$	17/70	87/80	175-177	-	
5	$4\text{-}ClC_6H_4$	18/70	85/78	185–187	180–182	[23]
6	$2\text{-}ClC_6H_4$	18/75	87/80	184-186	179-180	[23]
7	$4\text{-}OMeC_6H_4$	30/140	80/72	202-204	204-205	[23]
8	$2\text{-}OMeC_6H_4$	28/150	82/70	166-168	163-165	[23]
9	$4\text{-}MeC_6H_4$	25/130	84/75	172-174	176-178	[23]
10	$4\text{-}C_3H_7C_6H_4$	30/125	83/73	155-157	150-152	[20]
11	$3,4\text{-}(OMe)_2C_6H_3$	40/150	77/70	208-210	201–204	[12]
12	2-naphtyl	20/115	87/79	210-212	215-217	[20]
13	$3,4(Me)_2C_6H_3$	25/125	82/77	176–178	181–182	[10]
14	$4\text{-}OHC_6H_4$	40/145	75/70	155–156	151–153	[12]
15	$2,4\text{-}Cl_2C_6H_3$	17/65	90/80	182–184	178–181	[12]

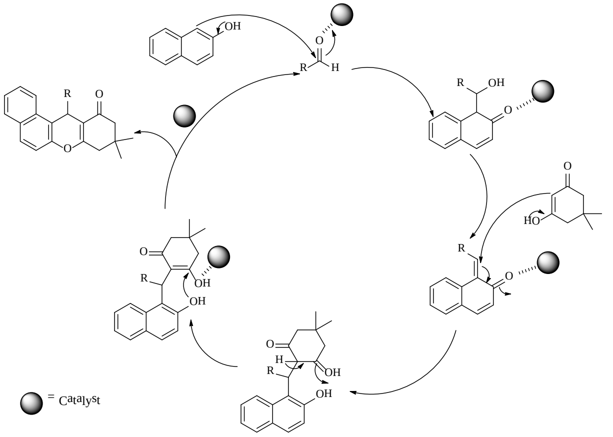
[a)] Reaction conditions: aldehyde (1 mmol), 2-naphthol (1 mmol), dimedone (1.2 mmol), EtOH (4 mL), [b)] Isolated yields. [c)] Constant frequency: 60 W.

Table 3. Comparison of the efficiency of $ZrCl_4$ with that of the reported catalysts for the synthesis of benzo[a]xanthenones.

Entry	Catalyst	Yield (%)	Ref.
1	$Sr(OTf)_2$ (10 mol%)	70-88%	[10]
2	$Zr(HSO_4)_4$ (2 mol%)	69-90%	[11]
3	$RuCl_3{\cdot}xH_2O$ (5 mol%)	75-92%	[12]
4	$ZrCl_4$ (8 mol%)	75-95%	This work

The effect of temperature on the reaction was also studied. We found that the best results were obtained in EtOH at reflux temperature under silent conditions (Table 1, entries 6, 8, 9). Similar reactions were then attempted in the presence of 4, 6, and 10, mol% of $ZrCl_4$. The results in Table 1, entries 6, 10-12 show that the use of 8 mol% of $ZrCl_4$ is sufficient to push the reaction forward. Higher loading of the catalyst had no significant influence on the reaction yield. Thus, 8 mol% of $ZrCl_4$ and a reaction temperature at reflux were the optimal conditions. When $ZrOCl_2.8H_2O$, $ZnBr_2$, $CoCl_2$, $CuCl_2$, and $Ni(NO_3)_2$ were used as catalysts, benzo[a]xanthenone was formed in lower yields (Table 1, entries 13-17).

Under the optimized conditions, xanthene derivatives were synthesized in high yields under silent and ultrasound irradiation conditions. Ultrasound irradiation accelerated such reactions. The results are summarized in Table 2. It can be observed that the process tolerates both electron-donating and electron–withdrawing substituents in the benzaldehydes.



Scheme 1. The proposed mechanism of synthesizing benzo[a]xanthenones catalyzed by $ZrCl_4$

In all cases, the reactions proceeded efficiently at reflux under mild conditions to afford the corresponding products in high yields. All the products were characterized by ^{1}H- and ^{13}C-NMR, and IR spectroscopy.

Finally, in order to assess the efficiency and generality of this methodology, we compared the method with some reported results in the literature (Table 3). It was found that $ZrCl_4$ is the most efficient catalyst with respect to reaction time, temperature, yield of the product, and catalyst nature.

Although the mechanism of the reaction has not yet been established experimentally, the formation of the product can be rationalized as outlined in Scheme 1.

In conclusion, we have developed an improved and convenient procedure for the synthesis of xanthene derivatives under ultrasonic irradiation in the presence of $ZrCl_4$ as a catalyst in EtOH at reflux temperature. The remarkable advantages of this method are: simple experimental procedure, short reaction times, high yields, and ease of product isolation.

Acknowledgements: *The authors thank the Research Council of Yazd University for the financial support.*

REFERENCES

1. T.J. Mason, J.P. Lorimer, Sonochemistry: Theory, Application and Uses of Ultrasound in Chemistry, John Wiley & Sons, New York, 1988.
2. K.S. Suslick, Ultrasound, its Chemical, Physical and Biological Effects, VCH, Weinheim, 1988.
3. T.S. Saleh, N.M.A. El-Rahman, A.A. Elkateb, N.O. Shaker, N.A. Mahmoud, S.A. Gabal, *Ultrason. Sonochem*, **19**, 491 (2012).
4. R.W. Lambert, J.A. Martin. J.H. Merrett, K.E.B. Parkes, G. Thomas, *Chem. Abstr.*, **126**, p212377y (1997).
5. T. Jpn. Hideo, *Chem. Abstr.*, **95**, 80922b (1981).
6. J.P. Poupelin, G. Saint-Ruf, O. Foussard-Blanpin, G. Narcisse, G. Uehida-Ernouf, R. Lacroix, *Eur. J. Med. Chem.*, 13, 67 (1978).
7. H.R. Shaterian, A. Hosseinian, M. Ghashang, *Turk. J. Chem.*, **33**, 233 (2009).
8. M. Mokhtary, S. Refahati, *Dyes Pigments*, **99**, 378 (2013).
9. B. Das, K. Laxminarayana, M. Krishnaiah, Y. Srinivas, *Synlett*, 3107 (2007).
10. J. Li, W. Tang, L. Lu, W. Su, *Tetrahedron Lett.*, **49**, 7117 (2008).
11. N. Foroughifar, A. Mobinikhaledi, H. Moghanian, *Int. J. Green Nanotechnology: Phys. Chem.*, **1**, 57 (2009).
12. K. Tabatabaeian, A. Khorshidi, M. Mamaghani, A. Dadashi, M.K. Jalali, *Can .J .Chem.*, **89**, 623 (2011).
13. A. Zarei, A.R. Hajipour, L. Khazdooz, *Dyes Pigments*, **85**, 133, (2010).
14. B.B.F. Mirjalili, A. Bamoniri, A. Akbari, *Tetrahedron Lett.*, **49**, 6454 (2008).
15. N.D. Kokare, J.N. Sangshetti, D.B. Shinde, *Chin. Chem. Lett.*, 19, 1186 (2008).
16. N. GhaffariKhaligh, *Ultrason. Sonochem.*, **19**, 736 (2012).
17. B. Rajitha, B.S. Kumar, Y.T. Reddy, *Tetrahedron Lett.*, **46**, 8691 (2005).
18. E. Soleimani, M.M. Khodaei, *Chin. Chem. Lett.*, **22**, 927 (2011).
19. G.B.D. Rao, M.P. Kaushik, A.K. Halve, *Tetrahedron Lett.*, **53**, 2741 (2012).
20. F. Shirini, N.G. Khaligh, *Dyes Pigments*, **95**, 789 (2012).
21. M. Hong, C. Cai, *J. Fluorine Chem.*, **130**, 989 (2009).
22. J.G. Wang, R. Harvey, *Tetrahedron*, **58**, 5927 (2002).
23. G.C. Nandi, S. Samai, R. Kumar, M.S. Singh, *Tetrahedron*, **65**, 7129 (2009).
24. W. Yuan, M. Shi, *Tetrahedron*, **66**, 7104 (2010).
25. A. Jha, J. Beal, *Tetrahedron Lett.*, **45**, 8999 (2004).
26. A. Bazgir, Z.N. Tisseh, P. Mirzaei, *Tetrahedron Lett.*, **49**, 5165 (2008).
27. X. Fan, X. Hu, X. Zhang, J. Wang, *Can. J. Chem.*, **83**, 16 (2005).
28. G. Song, B. Wang, H. Luo, L. Yang, *Catal. Commun*. **8**, 673 (2007).
29. B. Das, P. Thirupathi, I. Mahender, K.R. Reddy, B. Ravikanth, L. Nagarapu, *Catal. Commun.*, **8**, 535 (2007).
30. B. Das, P. Thirupathi, I. Mahender, V.S. Reddy, Y.K. Rao, *J. Mol. Catal. A: Chem.*, **247**, 233 (2006).
31. R. Kumar, G.C. Nandi, R.K. Verma, M.S. Singh, *Tetrahedron Lett*, **51**, 442 (2010).
32. M. Dabiri, S.C. Azimi, A. Bazgir, *Chem. Pap.*, **62**, 522 (2005).
33. H. Emtiazi, M.A. Amrollahi, *Helv. Chim. Acta*, **96**, 2196 (2013).

ЕФИКАСЕН УЛТРАЗВУКОВ МЕТОД ЗА СИНТЕЗ НА КСАНТЕНОВИ ПРОИЗВОДНИ

С. Багерпур, М.А. Амролахи*

Департамент по химия, Университет в Язд, Язд, Иран

Постъпила на 20 май,, 2015 г.; приета на 26 февруари, 2016 г.

(Резюме)

Използван е циркониев (IV) хлорид като ефикасен, стабилен, евтин, екологично съвместим и удобен катализатор за приготвянето на ксантенови производни чрез едно-стадийна три-компонентна кондензация на алдехиди с 2-нафтол и 5,5-диметил-1,3-циклохександион при ултразвуково облъчване. Етанолът е най-подходящия разтворител за случая. Този метод предлага няколко предимства, като висок добив, проста процедура, ниска цена и кратки реакционни времена.