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# A rapid and efficient method for the synthesis of 14*H*-dibenzo[*α.j*] xanthenes, aryl-5*H*-dibenzo [*b.i*]xanthene-5,7,12,14-(13*H*)-tetraone and 1,8-dioxo-octahydroxanthenes by acidic ionic liquid

Abbas Rahmati

*Department of Chemistry, University of Isfahan, P.O. Box 81746-7344, Isfahan, Iran*

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## Abstract

Various xanthenes have been synthesized by the condensation of *β*-naphthol, 2-hydroxynaphthalene-1,4-dione or dimedone with various aldehydes in the presence of trifluoroacetic acid as catalyst in 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate (TMGT) ionic liquid within 1 h at 75 °C.

*Keywords:* Ionic liquid; 14H-Dibenzo[*α.j*]xanthenes; β-Naphthol; 2-Hydroxynaphthalene-1,4-dione; Dimedone

The development of simple method to synthesize worthful organic compounds from readily available compounds is one of the major tasks in organic synthesis [1]. Xanthene's heterocycles and derivatives are interest because they are an important class of natural compounds such as Bikaverin and Guayin [2] which exhibiting a wide spectrum of pharmaceutical and biological properties such as antiviral [3], antibacterial [4], antiinflamatory [5], u-opiat agonist [6], antitomor [7], neuropharmacological [8], CNS stimulating [9] and applied in photodynamic therapy [10]. As a result, numerous procedures for their synthesis have been reported [2,11–13].

The classical synthesis of aryl-14*H*-dibenzoxanthenes, involves the condensation of *β*-naphthol with aldehydes in the presence of an acid catalyst. For this reason in menthion reaction different acidic catalysts such as sulfamic acid, *p*-toluene sulfonic acid, amberelyst-15, wet cyanuric chloride; $H_2SO_4$, $H_3PO_4$ or $HClO_4$, $NaHSO_4$, $Fe(HSO_4)_3$; LiBr, alum, hetropolyacides, Silica sulfuric acid, $BF_3.SiO_2$, Dowex-50W, $SiO_2/HClO_4$, iodine and Selectfluor$^{TM}$ have been used [14–30]. In addition, expediting the synthesis using microwave irradiation in the presence of sulfamic acid and LiBr, requires special instrumentation. Also aryl-5*H*-dibenzo[*b.i*]xanthene-5,7,12,14-(13*H*)-tetraone and 1,8-dioxo-octahydroxanthenes were prepared by reaction of 2-hydroxynaphthalene-1,4-dione and dimedone or 1,3-cyclohexanedione with various aldehydes in acidic media, respectively [31,32]. However, most of these reactions require long reaction times, high temperature, and use of toxic solvents. Also by-products are produced in this reaction.

During recent years, ionic liquids have attracted interests as environmentally friendly reagents due to their favorable characteristics such as solvophobic properties and catalytic activities [33,34]. This property of ionic liquids is very efficient for multi-component reactions (MCRs).

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*E-mail address:* a.rahmati@sci.ui.ac.ir.

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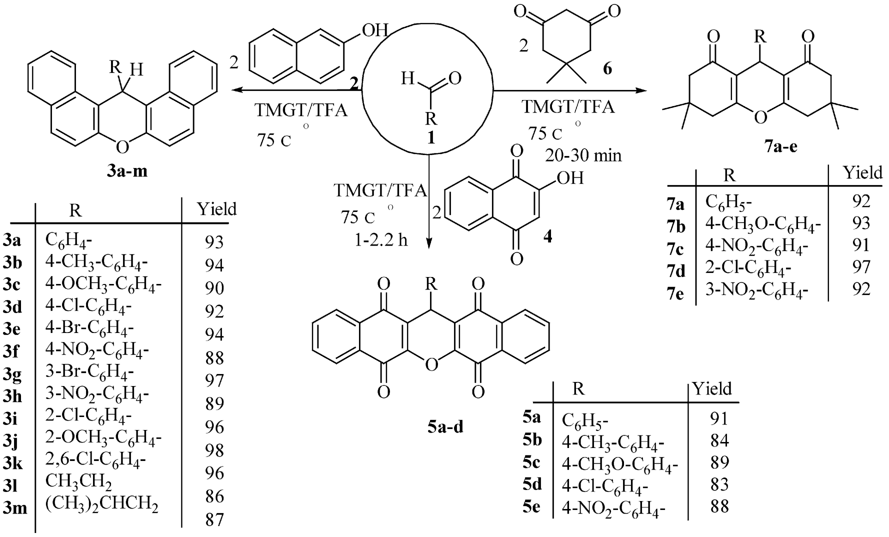

3a-m

| | R | Yield |
|---|---|---|
| **3a** | $C_6H_4$- | 93 |
| **3b** | 4-$CH_3$-$C_6H_4$- | 94 |
| **3c** | 4-$OCH_3$-$C_6H_4$- | 90 |
| **3d** | 4-Cl-$C_6H_4$- | 92 |
| **3e** | 4-Br-$C_6H_4$- | 94 |
| **3f** | 4-$NO_2$-$C_6H_4$- | 88 |
| **3g** | 3-Br-$C_6H_4$- | 97 |
| **3h** | 3-$NO_2$-$C_6H_4$- | 89 |
| **3i** | 2-Cl-$C_6H_4$- | 96 |
| **3j** | 2-$OCH_3$-$C_6H_4$- | 98 |
| **3k** | 2,6-Cl-$C_6H_4$- | 96 |
| **3l** | $CH_3CH_2$ | 86 |
| **3m** | $(CH_3)_2CHCH_2$ | 87 |

7a-e

| | R | Yield |
|---|---|---|
| **7a** | $C_6H_5$- | 92 |
| **7b** | 4-$CH_3O$-$C_6H_4$- | 93 |
| **7c** | 4-$NO_2$-$C_6H_4$- | 91 |
| **7d** | 2-Cl-$C_6H_4$- | 97 |
| **7e** | 3-$NO_2$-$C_6H_4$- | 92 |

5a-d

| | R | Yield |
|---|---|---|
| **5a** | $C_6H_5$- | 91 |
| **5b** | 4-$CH_3$-$C_6H_4$- | 84 |
| **5c** | 4-$CH_3O$-$C_6H_4$- | 89 |
| **5d** | 4-Cl-$C_6H_4$- | 83 |
| **5e** | 4-$NO_2$-$C_6H_4$- | 88 |

Scheme 1. Synthesis of xanthenes.

During the course of our studies on the development of new routs for the synthesis of organic compounds using ionic liquids and our interest to trifluoroacetic acid (TFA) based ionic liquids [35,36], we wish to introduce a rapid and easy procedure for the synthesis of 14*H*-dibenzo[*α.j*]xanthenes, aryl-5*H*-dibenzo[*b.i*]xanthene-5,7,12,14-(13*H*)-tetraone and 1,8-dioxo-octahydroxanthenes by the condensation of *β*-naphthol **2**, 2-hydroxynaphthalene-1,4-dione **4** and dimedone **6** with various aldehydes **1** in the presence of the acidic ionic liquid under classical heating conditions at 75 °C (Scheme 1).

Initially, in order to examine the best ionic liquid, different ionic liquids such as tetramethylguanidinium triflouroacetate (TMGT), tetramethylguanidinium acetate (TMGA), tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC), methylimidazolium triflouroacetate (MIT), 1-butyl-3-methylimidazolium bromide ([bmim]Br) and 1-butyl-3-methylimidazolium hexaflouroposphate ([bmim]$PF_6$) in this condensation reaction were applied. Although good yields were previously reported using TBAB [37], it was found that no satisfactory results were obtained with the studied ionic liquids alone. On the contrary, the use of 0.1 mmol TFA with ionic liquids TMGT and MIT gave acceptable results [38]. The use of only 0.1 mmol TFA with out ionic liquids yield of reaction was 80%.

As indicated in Table 1, it was also found that the efficiency of the reaction is mainly affected by the amount of catalyst and temperature. The best results were obtained in the presence of 0.2 mmol TFA and 0.3 g of ionic liquid at 75 °C. It is interesting to note, however, the yield of the reaction was not significantly affected by increasing the amount of TFA. Also, in the absence of catalyst, the reaction yield was 0% even at 130 °C after 24 h, while increased to 80% in the absence of ionic liquid when just TFA was used through the reaction. Although satisfactory result was obtained with TFA alone, because of the difficulties and dangers associated with the evaporation of TFA at the studied temperature, the presence of a typical ionic liquid as a retentive solvent, that keeps the TFA in vessel and prevents its evaporation [39], seems to be mandatory.

After optimization of reaction, to further explore the scope and limitations of this reaction, we extended the reaction of *β*-naphthol with various alkyl and aryl aldehydes carrying either electron-releasing or electron-withdrawing substituents. Also, we replaced the 2-hydroxynaphthalene-1,4-dione **4** and 5,5-dimethyl-1,3-cyclohexanedione **6** instead of 2-naphthol **2** in various conditions. The results showed that the reaction proceeds very efficiently in all cases. The reaction temperature for **3f** and **3h** was 100 °C.

Acidic strength of ionic liquid in pure form before and after heating in the absence of reactants was also investigated. It was found out that the acidic strength was not significantly affected by temperature up to 110 °C, while decreased gradually from 110 to 130 °C where 70% reduction occurred after 20 h.

Comparison of the time, temperature, and yield of our method for the synthesis of 14-(4-methylphenyl)-14*H*-dibenzo[*α.j*]xanthenes with the literature are indicated in Table 2. This compound was obtained with high yield from 80 to 92%. However, reaction times and temperature in this work have been reduced considerably relative to the $I_2$, Selectfluor$^{TM}$, *p*-toluene sulfonic acid, sulfamic acid and $Yb(OTf)_3$-ionic liquid.

Table 1
Optimization of one-pot synthesis of 14-(4-methylphenyl)-14*H*-dibenzo [*α.j*]xanthene under classical heating conditions in the presence of TMGT (0.3 g).[a].

| Experimental number | TFA catalyst (mmol) | Time (h) | Temperature (°C) | Yield (%) |
|---|---|---|---|---|
| 1 | 0.1 | 1 | 125 | 86 |
| 2 | 0.2 | 1 | 125 | 96 |
| 3 | 0.5 | 1 | 125 | 96 |
| 4 | 1 | 1 | 125 | 96 |
| 5 | 2 | 1 | 125 | 96 |
| 6 | 0.2 | 1 | 25 | 30 |
| 7 | 0.2 | 1 | 50 | 65 |
| 8 | 0.2 | 1 | 75 | 94 |
| 9 | 0.2 | 1 | 100 | 95 |
| 10 | 0.2 | 1 | 125 | 96 |
| 11 | 0.2[b] | 1 | 75 | 80 |
| 12 | 0.5[b] | 1 | 75 | 86 |
| 13 | 0.2 | 0.3 | 75 | 66 |
| 14 | 0.2 | 0.6 | 75 | 84 |
| 15 | 0.2 | 1 | 75 | 94 |
| 16 | 0.2 | 1.3 | 75 | 94 |
| 17 | 0 | 24 | 75 | 0 |

[a] *p*-Methylbenzaldehyde(1mmol) and *β*-naphthol (2 mmol).
[b] In the absence of ionic liquid.

Table 2
Comparison of TMGT/TFA-catalyzed method with different synthesis methods of 14-(4-methylphenyl)-14*H*-dibenzo[*α.j*]xanthenes.

| Experimental number | Catalyst | Solvent | Time (h)[a] | Temperature (°C) | Yield (%) [Ref.] |
|---|---|---|---|---|---|
| 1 | LiBr | – | 1.08 | 130 | 82 [22] |
| 2 | $I_2$ | – | 3 | 90 | 88 [29] |
| 3 | Selectofor | – | 11 | 125 | 92 [30] |
| 4 | *P*-TSA | – | 3 (18)[b] | 125 | 92 [15] |
| 5 | $NH_2SO_3H$ | – | 11 | 125 | 92 [14] |
| 6 | $Yb(OTf)_3$ | $[BPy]BF_4$ | 6 | 120 | 93 [40] |
| 7 | $CF_3CO_2H$ | TMGT/TFA | 1 | 75 | 94 |

[a] Solvent-free conditions.
[b] Reflux conditions.

In conclusion, we have introduced an efficient, easy and clean approach for the synthesis of biologically active aryl-14*H*-dibenzo[*α.j*]xanthenes, aryl-5*H*-dibenzo[*b.i*]xanthene-5,7,12,14-(13*H*)-tetraone and 1,8-dioxooctahydro-xanthenes using TFA as a catalyst in ionic liquid media. Less waste and ease of product separation are all among desirable factors in chemical industries which we have considered in our chemistry approach.

## 1. Experimental

To the 50 mL solution of 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidin (5.70 g, 50 mmol) in n-hexane, trifluoroacetic acid (6.90 g, 60 mmol) was added in portions within 30 min. The obtained mixture was then stirred for 5 h at ambient temperature. After completion of the reaction, the mixture was cooled at 0 °C for 8 h. A biphasic mixture was formed. The product was obtained by decantation of the solvent followed by washing the remained residue with n-hexane to remove organic impurities, and finally heating the product at 80 °C until complete evaporation of n-hexane residues. 12.58 g of acidic ionic liquid was obtained.

### *1.1. General procedure*

A mixture of aldehyde (1 mmol), *β*-naphthol **2**, 2-hydroxynaphthalene-1,4-dione **4** or 5,5-dimethyl-1,3-cyclohexanedione **6** (2 mmol), and TMGT/TFA (0.32 g) was heated at 75 °C for reported time. The solid material residues were then washed with water and filtered. For further purification, it was crystallized from ethanol to afford pure product. All the products (except **3k**) are known compounds, which were characterized by IR and $^1$H NMR spectral data and their mp's compared with literature reports.

*14-(2,6-dichlorophenyl)-14H-dibenzo[α.j]xanthene (3K).* White solid, mp: 286–287 °C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3426, 1597, 1250 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 7.05 (s, CH), 6.98–8.06 (m, 15H-arom); $^{13}$C NMR (CDCl$_3$): $\delta$ 36.34 (CH), 112.34, 117.74, 123.86, 123.89, 126.55, 128.43, 128.79, 129.83, 130.90, 131.80, 132.35, 137.94, 149.88; MS, *m/z* (%): 428 (M + 2, 5), 426 (M$^+$, 100), 279 (35), 251 (20), 216 (75), 189 (30), 151 (15), 121 (25), 39 (50).

The ionic liquid was separated from the products by washing, and then water was removed by vacuum evaporation. However, for recovery of remained organic material in ionic liquid, these compounds were extracted by addition of *n*-hexane (10 mL) to ionic liquid. The mixture was stirred for 2 h. Then it was cooled at 0 °C for 4 h. By decanted of the mixture ionic liquid was obtained.

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## References

[1] P. Laszlo, Organic Reactions: Simplicity and Logic, Wiley, New York, 1995.
[2] A. Bekaert, J. Andrieux, M. Plat, Tetrahedron Lett. 33 (1992) 2805.
[3] R.W. Lambert, J.A. Martin, J.H. Merrett, et al. PCT Int. Appl. (1997), WO9706178.
[4] T. Hideo, Chem. Abstr. 95 (1981) 80922b; Jpn. Tokkyo Koho J.P. 56005480, 1981.
[5] J.P. Poupelin, G.S. Ruf, O.F. Blanpin, et al. Eur. J. Med. Chem. 13 (1978) 67.
[6] R.H.B. Galt, M.J. Horbury, R.J. Pearce, et al. J. Med. Chem. 32 (1989) 2357.
[7] G.W. Rewcastle, G.J. Atwell, L. Zhuang, et al. J. Med. Chem. 34 (1991) 217.
[8] C. Kaiser, A.M. Pavloff, E. Garvey, et al. J. Med. Chem. 15 (1972) 665.
[9] J.W. Lewis, M.J. Readhead, J. Med. Chem. 13 (1970) 525.
[10] R.M. Ion, A. Planner, K. Wiktorowicz, et al. Acta Biochim. Pol. 45 (1998) 833.
[11] A. Jha, J. Beal, Tetrahedron Lett. 45 (2004) 8999.
[12] D.W. Knight, P.B. Little, J. Chem. Soc. Perkin Trans. 1 (2001) 1771.
[13] D.W. Knight, P.B. Little, Synlett (1998) 1141.
[14] B. Rajitha, B.S. Kumar, Y.T. Reddy, et al. Tetrahedron Lett. 46 (2005) 8691.
[15] A.R. Khosropour, M.M. Khodaei, H. Moghannian, Synlett (2005) 955.
[16] S. Ko, C.F. Yao, Tetrahedron Lett. 47 (2006) 8827.
[17] M.A. Bigdeli, M.M. Heravi, G.H. Mahdavinia, Catal. Commun. 8 (2007) 1595.
[18] R.J. Sarma, J.B. Baruah, Dyes Pigm 64 (2005) 91.
[19] A. Khoramabadi-Zad, Z. Kazemi, H. Amiri-Rudbari, J. Korean Chem. Soc. 46 (2002) 541.
[20] Z. Karimi-Jaberi, M.M. Hashemi, Monatsh. Chem. 139 (2008) 605.
[21] H.R. Shaterian, M. Ghashang, J. Braz. Chem. Soc. 19 (2008) 1053.
[22] A. Saini, S. Kumar, J.S. Sandhu, Synlett (2006) 1928.
[23] M. Dabiri, M. Baghbanzadeh, M. Shakouri, et al. Bioorg. Med. Chem. Lett. 18 (2008) 436.
[24] M.M. Amini, M. Seyyedhamzeh, A. Bazgir, Appl. Catal. A 323 (2007) 242.
[25] M. Seyyedhamzeh, P. Mirzaei, A. Bazgir, Dye Pigment 76 (2008) 836.
[26] B.B.F. Mirjalili, A. Bamoniri, A. Akbari, Tetrahedron Lett. 49 (2008) 6454.
[27] G. Imani-Shakibaei, P. Mirzaei, A. Bazgir, Appl. Catal. A 325 (2007) 188.
[28] M.A. Bigdeli, M.M. Heravi, G.H. Mahdavinia, J. Mol. Catal. A 275 (2007) 25.
[29] P.S. Kumar, B.S. Kumar, B. Rajitha, et al. Arkivoc xii (2006) 46.
[30] B. Das, B. Ravikanth, R. Ramu, et al. J. Mol. Catal. A 255 (2006) 74.
[31] A. Bazgir, Z. Noroozi Tisseh, P. Mirzaei, Tetrahedron Lett. 49 (2008) 5165.
[32] E.C. Horning, M.G. Horning, J. Org. Chem. 11 (1946) 95.
[33] N. Jain, A. Kumar, S. Chauhan, et al. Tetrahedron 61 (2005) 1015.
[34] T. Welton, Chem. Rev. 248 (2004) 2459.
[35] A. Shaabani, A. Rahmati, Catal. Lett. 100 (2005) 177.
[36] A. Shaabani, A. Rahmati, S. Naderi, Bioorg. Med. Chem. Lett. 15 (2005) 5553.
[37] S. Kantevari, M. Venu Chary, A.P. Rudra Das, et al. Catal. Commun. 9 (2008) 1575.
[38] G. Zhao, T. Jiang, H. Gao, et al. Green Chem. 6 (2004) 75.
[39] P. Wasserscheid, T. Welton, Ionic Liquids in Synthesis, Wiley-VCH, 2003.
[40] W. Su, D. Yang, C. Jin, et al. Tetrahedron Lett. 49 (2008) 3391.