



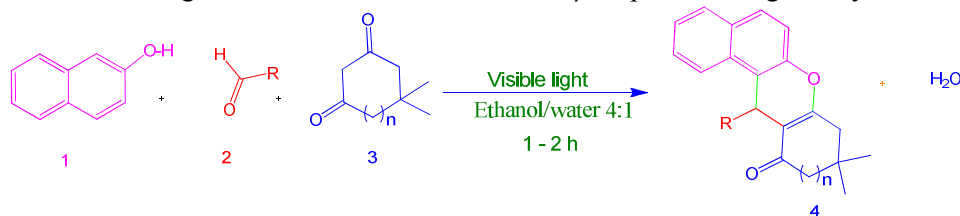
VISIBLE LIGHT AS A PROMOTER FOR THE EFFICIENT AND GREEN SYNTHESIS OF TETRAHYDROBENZOXANTHENE DERIVATIVES

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Abstract : A visible light promoted clean and efficient, multicomponent approach for the synthesis of tetrahydrobenzoxanthen-11-one is reported. The given process eliminates the use of toxic catalysts, bases and solvents, which harmfully affect the environment and human beings. Other advantages of the given methodology consist of easy-going reaction conditions, operational simplicity, broad substrate scope, short reaction times, easy workup, high yields. And the use of green solvent make the protocol very attractive.

keywords : Visible light, xanthenes, benzoxanthenes, β -naphthol and green synthesis.



Scheme 1

Introduction:

Xanthenes and benzoxanthenes display different type of activities such as anti-inflammatoryⁱ, antibacterialⁱⁱ and antiviral agentsⁱⁱⁱ. They are used as antagonists for the paralyzing action of zoxazolamine^{iv} and are also used in photodynamic therapy^v. They can also be used in laser technologies^{vi} and in synthesis of dyes^{vii}. Rhodamine B and Rhodamine 6G are the very well known dyes having xanthene framework. Due to the aforementioned properties, synthesis of xanthenes has gained prominence in medicinal as well as in synthetic organic chemistry.

Traditionally, various method have been explored for the synthesis of tetrahydrobenzo(a)xanthenes-11-ones. Usually they were synthesized by the condensation of cyclic 1,3-diketone with an aldehyde and β -naphthol, which by the use of perchloric acid adsorbed on silica gel^{viii}, PTSA in Ionic liquid^{ix}, tetrabutyl ammonium fluoride^x, indium chloride and phosphorus pentoxide^{xi}, dodecatungstophosphoric acid^{xii}, NaHSO₄.SiO₂^{xiii}, strontium triflate^{xiv}, silica sulfuric acid^{xv}, cyanuric chloride^{xvi}, proline triflate^{xvii} in wateriodine^{xviii} and Zr(HSO₄)^{xix}.

Although, various methods have been reported, but many of them suffer from one or more drawbacks such as use of toxic and expensive catalysts and organic solvents, very high temperature, unsatisfactory yields and long reaction time. Hence, it is necessary to develop an efficient and convenient method to construct these important biologically active heterocyclic compounds.

In recent years organic chemists have long aspired to synthesize heterocyclic molecule using visible light due to the fact that visible light can serve as an attractive, ecofriendly sustainable, unending and universally available energy source that allows easy handling and promotes an elevation of green standard for chemical transformations^{xx}. Consequently, Chemists have successfully performed an increasing number of visible light driven synthesis as an safe approach and provide green, economically and energetically beneficial route for assembly of organic molecules.^{xxi}

Within the context of green chemistry principles another thrust area is the development of catalyst free^{xxii} synthesis.

Multicomponent reactions (MCRs) offer a unique way to efficiently generate libraries of complex molecules with high degree of diversity in a single operation with improved atom and time economy, the development of novel MCRs have attracted increased awareness from research groups working in the areas of drug discovery and organic synthesis as they involves simple purification, atom economy and operational 'simplicity'^{xxiii-xxix}. We had the opportunity to explore for the first time visible light as a promoter towards the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo(a)xanthenes-11-one derivatives.

Results and Discussion

Initially, the reaction between benzaldehyde (1a), 5,5-dimethyl-1,3-cyclohexanedione / 5,5-dimethylcyclopentane-1,3-dione and β -naphthol was investigated without use of any solvent, only a trace amount of products were detected (entries 1–2). Then we perform the reaction in different solvents. Only a trace amount of products were detected in toluene, DMF, DMSO, n-butyl acetate, EtOAc and THF (entries 3–8). The reaction proceeded in glycerol sluggishly (entry 11) and in ethanol a huge improvement was observed (entry 11). Encouraged by the observed determinant effect of polar protic solvents on the reaction, we decided to investigate the efficiency of ethanol as a solvent for this reaction. As we expected, the reaction proceeded very well. After that we tried mixed solvent system of ethanol/water to carry out the above transformation (entries 12-15). Interestingly, all starting materials were soluble in ethanol/water solvent system. We used different ratio of ethanol/water solvent system and found that 4:1 ratio led to a noticeable increase in yield and drastic reduction in reaction time (entry 15). As shown in **Table 1**, the best results were obtained at room temperature.

Table 1. Initial optimization of the solvent system^a

Entry	Solvent	Additive	Temperature	Time (h)	Yield (%) ^b
1	None	None	RT	12	Trace
2	None	None	RT	24	Trace
3	Toluene	None	RT	12 h	Trace
4	DMF	None	RT	12 h	Trace
5	DMSO	None	RT	12 h	Trace
6	n-Butyl acetate	None	RT	12 h	Trace
7	EtOAc	None	RT	12	Trace

8	THF	None	RT	12	Trace
9	Methanol	None	RT	8	40
10	Ethanol	None	RT	6	64
11	Glycerol	None	RT	10	56
12	Ethanol/water 1:1	None	RT	2.5	68
13	Ethanol/water 2:1	None	RT	1.5	76
14	Ethanol/water 3:1	None	RT	1.5	80
15	Ethanol/water 4:1	None	RT	1	95

a; All reactions were carried out with **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol) and different solvents (5 ml) under visible light irradiation using a CFL at rt under air. b; Isolated yields

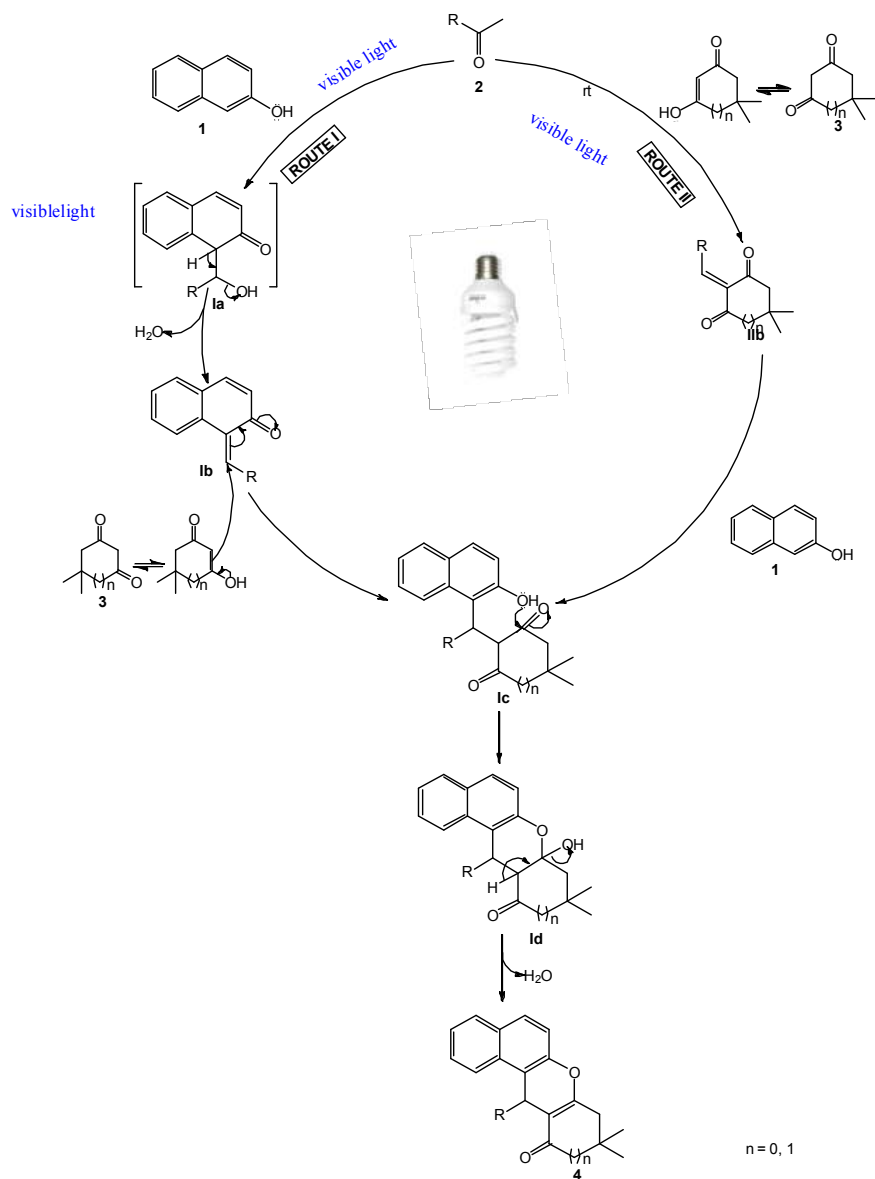
After the optimization of the best solvent system we now carried out a series of experiments using light of different intensities (8W, 15W, 20W, 22W, 24W and 32W), and found that CFL, 24W gave the best yield in short reaction time. We observed that the yields and reaction time were the same when 20W and 22W CFLs were used but when CFLs of lower intensities were used, a little decrease in yield and increase in reaction time was observed. On the other hand, use of a CFL of higher intensity did not have any appreciable effect on yield or reaction time.

To extend the scope of the reaction and to generalize this method, a variety of structurally diverse non-aromatic/ aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione / 5,5-dimethylcyclopentane-1,3-dione, and β -naphthol were examined, and the results are summarized in **Table 2**. Various non aromatic and aromatic aldehydes containing electron-withdrawing and electron-donating substituent at ortho, meta or para-positions were smoothly converted to their corresponding tetrahydroxanthene-11-ones in high to excellent yields. To further expand the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione with 5,5-dimethylcyclopentane-1,3-dione was examined. To our delight, under the same optimized conditions, the reactions proceeded steadily to afford a series of xanthene based compounds in good yields. We have also tried to make benzoxanthene-11-ones using α -naphthol or other phenols instead of β -naphthol. It was found that under the same conditions, when β -naphthol was replaced by other phenols/ α -naphthol, either no product was obtained or product formation took place with very poor yield. Identity of the synthesised products was confirmed by comparing the physical and spectral data (IR & ^1H NMR) with those of the reported compounds^{xiv-xxiv}.

Table 2: Visible light catalyzed condensation of aldehydes, 1,3-dicarbonyl compounds and β -naphthol.

Entry	R	product	Time (min)	Yield (%)	MP (°C)	Colour of product
1	C ₆ H ₅ -	4a	25	92	147-149	White solid
2	<i>o</i> -MeO.C ₆ H ₄ -	4b	30	87	164-166	White solid
3	<i>p</i> -Cl.C ₆ H ₄ -	4c	25	92	179-181	White solid
4	<i>o,p</i> -Cl ₂ .C ₆ H ₃ -	4d	20	90	176-179	White solid
5	<i>m</i> -HO.C ₆ H ₄	4e	35	76	237-239	White solid
6	<i>o</i> -NO ₂ .C ₆ H ₄ -	4f	30	84	221-223	Pale yellow solid
7	<i>p</i> -NO ₂ .C ₆ H ₄ -	4g	20	92	175-177	White solid
8	2-HO-3-EtO.C ₆ H ₃ -	4h	40	85	188-190	White solid
9	-CH=CH-C ₆ H ₅	4i	40	87	146-148	White solid

From the mechanistic point of view it is found that the formation of desired product proceeds via two routes (**scheme 2**). **Route I** initiated by the nucleophilic addition between β -naphthol and aldehydes which result in formation of intermediate **Ib**, the formation of this intermediate is promoted by visible light. Intermediate **Ib** now react with 1,3-diketone by Michael addition which gives **Ic**. Now **Ic** proceeds by intramolecular cyclisation followed by dehydration affords the desired product **4**. Now in the second possible **route II**, first step proceeds by Knoevenagel condensation between 1,3-diketone and aldehyde which gives intermediate **Iib**, this step is promoted by visible light. Now this intermediate **Iib** proceeds with Michael addition of β -naphthol giving **Ic** which cyclises intramolecularly followed by dehydration, affords the corresponding product **4**.



Scheme 2: Proposed mechanism for the synthesis of benzoxanthen-11-ones.

Experimental procedure:

A mixture of β -naphthol **1** (1 mmol), aromatic/ non-aromatic aldehyde **2** (1 mmol) and cyclic 1,3 dicarbonyl **3** (1 mmol) in mixed solvent of ethanol/water (4:1 ratio) were taken in the presence of visible light. This reaction mixture was allowed to stir vigorously at room temperature. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane; 2:8 v/v). After completion of the reaction, the solid obtained was collected by filtration and washed with warm water followed by washing with cool aqueous ethanol. The crude product was recrystallized from ethanol to afford analytically pure desired product **4**.

Spectral data:

Compound 4a: *9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 151–152 °C. IR(KBr, cm^{-1}): 3067, 2965, 2876, 1643, 1366, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.85 (d, $J = 8.2$ Hz, 1H), 7.76–7.71 (m, 2H), 7.42–7.01 (m, 8H), 5.62 (s, 1H), 2.56 (s, 2H), 2.24 (d, $J = 16.2$ Hz, 1H), 2.18 (d, $J = 16.1$ Hz, 1H), 1.12 (s, 3H), 0.99 (s, 3H).

Compound 4b: *12-(2-Methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 163–163 °C. IR (KBr, cm^{-1}): 3060, 2938, 1637, 1371, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.21 (d, $J = 8.1$ Hz, 1H), 7.62–7.55 (m, 2H), 7.33–7.13 (m, 4H), 7.02 (t, $J = 7.1$ Hz, 1H), 6.69–6.62 (m, 2H), 5.83 (s, 1H), 3.82 (s, 3H), 2.46 (s, 2H), 2.20 (d, $J = 16.1$ Hz, 1H), 2.10 (d, $J = 16.2$ Hz, 1H), 1.20 (s, 3H), 1.12 (s, 3H).

Compound 4c: *12-(4-Chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 178–182°C. IR (KBr, cm^{-1}): 3074, 2921, 1643, 1371, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.80 (d, $J = 8.2$ Hz, 1H), 7.70–7.71 (m, 2H), 7.36–7.03 (m, 7H), 5.58 (s, 1H), 2.48 (s, 2H), 2.24 (d, $J = 16.0$ Hz, 1H), 2.17(d, $J = 16.1$ Hz, 1H), 1.12 (s, 3H), 0.99 (s, 3H).

Compound 4d: *12-(2,4-Dichlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 182–185°C. IR (KBr, cm^{-1}): 3050, 2944, 2861, 1644. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.05 (d, $J = 8.1$ Hz, 1H), 7.70–7.70 (m, 2H), 7.40–7.28 (m, 2H), 7.20–7.11 (m, 3H), 7.16 (d, $J = 6.6$ Hz, 1H), 5.85 (s, 1H), 2.52 (s, 2H), 2.47 (d, $J = 16.1$ Hz, 1H), 2.25 (d, $J = 16.1$ Hz, 1H), 1.14 (s, 3H), 1.02 (s, 3H).

Compound 4e: *12-(3-Hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 243–246 °C. IR(KBr, cm^{-1}): 3406, 3056, 2939, 1624, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.84 (d, $J = 8.2$ Hz, 1H), 7.74–7.73 (m, 2H), 7.42–7.27 (m, 3H), 7.01 (t, $J = 7.1$ Hz, 1H), 6.81 (s, 1H), 6.62 (d, $J = 7.1$ Hz, 1H), 6.51 (d, $J = 6.1$ Hz, 1H), 5.61 (s, 1H), 5.20 (s, 1H), 2.44 (s, 2H), 2.33 (d, $J = 16.1$ Hz, 1H), 2.42 (d, $J = 16.1$ Hz, 1H), 1.22 (s, 3H), 0.99(s, 3H).

Compound 4f: *9,9-Dimethyl-12-(3-nitrophenyl)-8,9,10,12-tetrahydrobenzo- [a]-xanthen-11-one* White solid; mp 166–173°C. IR (KBr, cm^{-1}): 3058, 2941, 1635, 1514. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.10 (s, 1H), 7.87–7.88 (m, 5H), 7.41–7.31 (m, 4H), 5.72 (s, 1H), 2.53 (s, 2H), 2.35 (d, $J = 16.1$ Hz, 1H), 2.23 (d, $J = 16.1$ Hz, 1H), 1.12 (s, 3H), 0.99 (s, 3H).

Compound 4g: *12-(2-Hydroxy-3-methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 211–216°C. IR(KBr, cm^{-1}): 3281, 3073, 2952, 1624, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.34 (s, 1H), 7.82–7.72 (m, 3H), 7.32–7.37 (m, 3H), 6.50–6.48 (m, 2H), 6.44 (d, $J = 4.3$ Hz, 1H), 5.74 (s, 1H), 3.77 (s, 3H), 2.45 (s, 2H), 2.34 (d, $J = 16.1$ Hz, 1H), 2.25 (d, $J = 15.2$ Hz, 1H), 1.25 (s, 3H), 0.91 (s, 3H).

Compound 4h: *12-(5-Nitro-2-hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one* White solid; mp 263–266 °C. IR(KBr, cm^{-1}): 3310, 2933, 1643, 1450, $^1\text{HNMR}$ (300 MHz, CDCl_3): δ 10.23 (s, 1H), 7.83–7.63 (m, 3H), 7.41–7.41(m, 5H), 7.12 (d, $J = 9.1$ Hz, 1H), 5.71 (s, 1H), 2.72 (d, $J = 17.1$ Hz, 1H), 2.64 (d, $J = 17.6$ Hz, 1H), 2.53 (d, $J = 17.3$ Hz, 1H), 2.43 (d, $J = 17.2$ Hz, 1H), 1.14 (s, 3H), 1.03 (s, 3H)

Compound 4i 12-Isopropyl-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-one

White solid; mp 117–122°C. IR (KBr, cm^{-1}): 3052, 2940, 1641, 1377. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.06 (d, $J = 8.3$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.64 (d, $J = 8.6$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.31 (t, $J = 7.4$ Hz, 1H), 7.21 (d, $J = 9.2$ Hz, 1H), 4.71 (d, $J = 3.1$ Hz, 1H), 2.51 (d, $J = 18.2$ Hz, 1H), 2.40 (d, $J = 18.2$ Hz, 1H), 2.31 (d, $J = 16.0$ Hz, 1H), 2.35 (d, $J = 16.1$ Hz, 1H), 2.19 (m, 1H), 1.24 (s, 3H), 1.16 (s, 3H), 0.91 (d, $J = 6.3$ Hz, 3H), 0.62 (d, $J = 6.1$ Hz, 3H).

Conclusion

In summary, we have developed an efficient one pot synthesis of 14-aryl-14H-dibenzo[a]xanthene and 12-aryl-8, 9, 10, 12-tetrahydrobenzo[a]-xanthen-11-one derivatives by condensation of various substituted benzaldehydes, β -naphthol and dimedone in mixed solvent system of ethanol/water and visible light as a catalyst. This methodology is endowed with several advantages such as non-toxic and inexpensive catalysts, easy work-up procedure, use of non-hazardous solvent, low temperature and short reaction time. Therefore we are able to say that this synthesis follows several philosophy of green chemistry.

References:

- i. Poupelin, J. P.; Saint-Ruf, G.; Foussard-Blanpin, O.; Marcisse, G.; Uchida-Ernouf, G.; Lacroix, R. *Eur J Med Chem.* 13, 67 (1978)
- ii. Hideo, T.; Teruomi, J.; inventors. 56005480. *Jpn. Patent.* (1981).
- iii. Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. *PCT Int. Appl.* (1997), *WO 97006178*.
- iv. Saint-Ruf, G.; Hieu, H. T.; Poupelin, J. P. *Naturewissenschaften.* 62, 584-585 (1975).
- v. (a) Ion, R. M.; Frackowiak, D.; Planner, A.; Wiktorowicz, K. *Acta Biochim Pol.* 45, 833 (1998). (b) Ion, R. M. *Prog Catal.* 2, 55 (1997).
- vi. (a) Sirkencioglu, O.; Talinli, N.; Akar, A. *J. Chem. Res.* 502 (1995). (b) Ahmad, M.; King, T. A.; Ko, D. K.; Cha, B. H.; Lee, J. J. *Phys. D: Appl. Phys* 35, 1473 (2002).
- vii. Knight, C. G.; Stephens, T. *Biochem. J.* 258, 683 (1989).
- viii. Mo, L. P.; Chen, H. L. *J. Chin. Chem. Soc.* 57, 157 (2010).
- ix. Khurana, J. M.; Magoo, D. *Tetrahedron Lett.* 50, 4777 (2009).
- x. Gao, S.; Tsai, C. H.; Yao, C. F. *Synlett.* 949 (2009).
- xi. Nandi, G. C.; Samai, S.; Ram, K.; Singh, M. S. *Tetrahedron.* 65, 7129 (2009).
- xii. Wang, H. J.; Ren, X.-Q.; Zhang, Y.-Y.; Zhang, Z.-H. *J. Braz. Chem. Soc.* 20, 1939 (2009).
- xiii. Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. *Synlett.* 3107 (2007).
- xiv. Li, J.; Tang, W.; Lu, L.; Su, W. *Tetrahedron Letters.* 49, 7117 (2008).
- xv. Nazeruddin, G. M.; Pandharpatte, M. S.; Mulani, K. B.; *Indian J Chem.* 50 B, 1532 (2011).
- xvi. Zhang, Z.-H.; Zhang, P.; Yang, S.-H.; Wang, H.-J.; Deng, J. *Chem. Sci.* 122, 427 (2010).
- xvii. Li, J.; Lu, L.; Su, W. *Tetrahedron Lett.* 51, 2434 (2010)
- xviii. Wang, R.-Z.; Zhang, L.-F.; Cui, Z.-S. *Synth Commun.* 39, 2101 (2009).
- xix. Foroughifar, N.; Mobinikhaledi, A.; Moghanian, H.; *International J. Green Nanotechnology: Physics and Chemistry. 1,* 57 (2009).
- xx. (a) A. Gualandi, M. Marchini, L. Mengozzi, M. Natali, M. Lucarini, P. Ceroni, P. G. Cozzi, *ACSCatal.*, 5, 5927-5931 (2015); (b) J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 131, 8756 (2009); (c) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 77, 322 (2008); (d) T. P. Yoon, M. A. Ischay, J. Du, *Nat.*

- Chem., 2, 527-532 (2010); (e) G. Ciamician, *Science*, 36, 385 (1912); (f) A. Albin and M. Fagnoni, *Green Chem.*, 6,1.3 (2004); (g) K. Zeitler, *Angew. Chem. Int. Ed.*, 48, 9785 (2009); (h) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2, 527 (2010); (i) A. G. Condie, J. C. Gonzalez-Goalez and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 132,1464 (2010); (j) J. M. R. Narayanam and C. R. Stephenson, *J. Chem. Soc.Rev.*, 40, 102 (2011); (k) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 130, 12886 (2008); (l) D. A. Nicewicz and D. W. C. Macmillan, *Science*, 322, 77 (2008).
- xxi.** (a) S. Ghosh, F. Saikh, J. Das, A. K. Pramanik, *Tetrahedron Lett.*, 54, 58-62 (2013). (b) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 322, 77 (2008); (c) J. M. R. Narayanam, J.W.Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 131, 8756 (2009); (d) M-Y. Cao, X. Ren, Z. Lu, *TetrahedronLett.*, 56, 3732-3742 (2015); (e) I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science*, 346, 725-728 (2014); (f) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 130,12886 (2008).
- xxii.** (a) N. A. A. Ahmad, S. M. Rokade, A. M. Garande and P. M. Bhate, *Tetrahedron Letters*, 55, 5458 (2014); (b) F. Nemati, M. M. Hosseini and H. Kiani, *J. Saudi Chem. Soc.*, (2013) DOI: 10.1016/j.jscs.2013.02.004 (c) P. T. Anastas and T. C. Williamson, *Green Chemistry: Designing Chemistry for the Environment*, ACS Symposium Series, Washington DC, (1996) ; (d) G. Choudhary and R. K. Peddinti, *Green Chem.*, 13, 276–282 (2011); (e) H. R. Safaei, M. Shekouhy, S. Rahmanpur and A. Shirinfeshan, *Green Chem.*, 14, 1696–1704 (2012).
- xxiii.** Dömling, A., *Chem. Rev.*, 106, (2006) 17–89, doi:10.1021/cr0505728,
- xxiv.** Zhu, J., *Eur. J. Org. Chem.*, 1133–1144 (2003) doi:10.1002/ejoc.200390167
- xxv.** Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, 39, 79-87 (2006).
- xxvi.** Dabiri, M.; Salehi, P.; Bahramnejad, M.; Sherafat, F. *J. Comb. Chem.* 12, 638-642 (2010). <http://dx.doi.org/10.1021/cc100043z>
- xxvii.** Dabiri M.; Salehi P.; Koohshari M.; Hajizadeh Z.; and Ian D.; *Geec M. ARKIVOC*, 204-214 (2014).
- xxviii.** Kappe, C. O. *Eur. J. Med. Chem.*, 35, 1043-1052 (2000). [http://dx.doi.org/10.1016/S0223-5234\(00\)01189-2](http://dx.doi.org/10.1016/S0223-5234(00)01189-2)
- xxix.** Anastas P. and Williamson T., *Green Chemistry Frontiers in Benign Chemical Synthesis and Procedures*, Oxford Science Publications. New York, 1998.

Received on June 5, 2017.