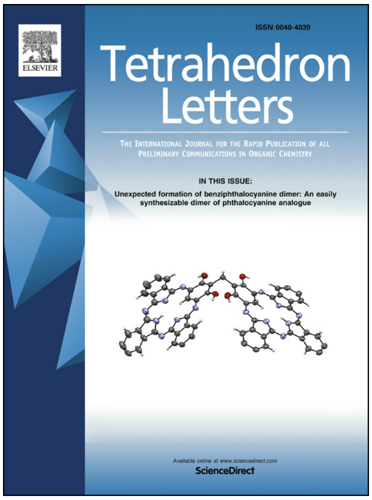

Metal free Lewis acid promoted one-pot synthesis of 14-aryl -14H dibenzo [a,j] xanthenes and their simple biological evolution

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Metal free Lewis acid promoted one-pot synthesis of 14-aryl -14H dibenzo [a,j] xanthenes and their simple biological evolution

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ABSTRACT

A green, competent one-pot synthesis of 14-aryl 14H-dibenzo [a, j] xanthene and its bio-computational studies are reported. Target compounds are prepared by the condensation of 2-naphthol with benzaldehyde and its substituents using metal free benzyltrimethylammonium tribromide (BTMA-Br_3) catalyst under solvent free thermal and microwave conditions. . This technique has more advantages such as high yield, a clean procedure, low reaction time, simple workup and mild Lewis organo acid catalyst.

1. Introduction

The chemical sciences play an imperative role in the process of drug discovery and synthetic routes to develop in order to deliver more clinically effective remedies.[1] The benzo-fused xanthene functionality is a key structural element of many biologically active compound. Particularly 14-aryl-14H-dibenzo [a,j] xanthene has attracted considerable attention by chemists because of their biological and pharmaceutical properties such as anti-inflammatory[2] antiviral[3] and antibacterial activities and antagonists for the paralyzing acting of zoxazolamine.[4] Besides, these compounds can also be used as dyes,[5] pH-sensitive fluorescent materials for visualization of bio-molecules[6] and utilized in laser technologies[7]. In view of these striking applications, the synthesis of xanthenes derivatives has received up surging interest. The chemical synthesis of 14-aryl-14H-di benzo [a. j] xanthenes and related compounds have been prepared by the reaction of 2-naphthol with Formamide, 2-naphthol-1-methanol and carbon monoxide.[8] On the other hand, a number of methods have been documented by condensation of 2-naphthol and aldehydes in the presence of strontium sulfamic acid,[9] Amberlyst-15,[10] $K_5CoW_{12}O_{40}.3H_2O$,[11] $FeCl_3$,[12] WO_3/ZrO_2,[13] PS/$AlCl_3$,[14] Alum,[15] $In(OTF)_3$,[16] PVPP-BF_3,[17] $Mg(HSO_4)_2$,[18] ionic liquid [H-NMP][HSO_4],[19] Poly(4-vinylpyridinium)hydrogen sulfate[20], mesoporous SBA-15,[21] sulfonated starch nanoparticles,[22] and various methods.[23] However, all these methods have some drawbacks such as poor yields, prolonged reaction times, toxic organic solvents, excess reagents; Metal based catalysts and harsh reaction conditions. Therefore, in recent years, a significant attention has been focused on designing environmentally benign synthetic strategies processes have received much more attention.

A few years ago, Chaudhuri *et al.,* reported,[24] the environmentally benign synthesis of various organic ammonium tribromide and their application in bromination reactions since, Heterogenization of homogeneous catalysts has been an interesting area of research from an industrial point of view; this combines the advantages of homogeneous catalysts such as high activity, selectivity, *etc.* In this significance that Benzyltrimethylammonium tribromide (BTMA-Br_3) is a non-toxic, stable, mild and solid and economically cheap and efficient metal free organic Lewis acid. This catalyst contains a benzyl ring with quaternary ammonium tribromide salt. It has been used for bromination and oxidation of aromatic compounds such as phenols, aromatic amines, acetanilide, alcohols, ethers, and thiols, N-bromination of amides, Hofmann degradation of amides[25] *etc.* In this part of the work, we have taken an opportunity to further explore the catalytic activity of BTMA-Br_3 towards the formation of C-C and C–X bond (X=N, O & S) by condensation reaction with 2-naphthol and benzaldehydes under solvent free and micro wave irradiation by employing BTMA-Br_3 as a novel organic Lewis acid catalyst (Scheme-1). The reaction afforded 14-aryl-14H-di benzo [a, j] xanthenes in excellent yields.

Initially we conducted a model reaction using 2-naphthol (2 mmol) and 4-NO_2 benzaldehyde (1 mmol) in ethanol (EtOH) as the solvent in the absence of catalyst at room temperature for 180 min. The reaction did not proceed even after 180 minutes (Table 1, entries 1 and 2) under reflux. Then the reaction is conducted using 4.8 mol% of BTMA-Br_3 catalyst in the presence of various solvents at reflux conditions. The reaction was sluggish even under these conditions and afforded very low product yields (Table 1, entries 7 - 11). But very good results (Table 1, entry 5) were obtained with the composite BTMA-Br_3 (4.8 mol%), at 110°C in the absence of solvent. Encouraged by

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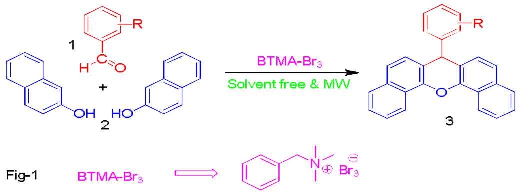
the results with BTMA-Br_3, and based on literature reports[27] we have used BTMA-Br_3 as calyst under solvent free conditions for rest of the one-pot reactions.

To establish the optimal amount of catalyst, the title reaction was run with different initial amounts of the BTMA-Br_3 (1.7, 3.3 and 6.4 mol%) and the product yields were 40, 70 and 92% respectively (Table 1, entries 3, 4 and 6). The results suggest that for chosen reaction conditions 4.8 mol% of BTMA-Br_3 catalyst was adequate to carry out the reaction efficiently. The reactions afforded good results at 110°C (Scheme 1).

We next investigated the scope of microwave (MW) irradiation by using optimal condition, affording the desired product in good yields, with undiminishing efficiency. To ascertain the effect of microwave on these reactions, the same reactions were carried out without microwave under otherwise similar conditions;[28] which afforded lower yields and took longer reaction times (Table 2).



Scheme 1. The synthesis of 14-aryl-14H-di benzo [a. j] xanthenes

Table 1. Catalyst Optimization in various reaction conditions

Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield (%)
1	EtOH	0	0	180	0
2	None	0	0	180	0
3	None	1.7	110	30	40
4	None	3.3	110	30	70
5	None	4.8	110	25	94
6	None	6.4	110	35	92
7	EtOH	4.8	Reflux	180	50
8	DCE	4.8	Reflux	180	30
9	ACN	4.8	Reflux	180	25
10	MeOH	4.8	Reflux	180	50
11	$CHCl_3$	4.8	Reflux	180	30

Table 2. The synthesis of 14-aryl-14H-di benzo [a. j] xanthene derivative by BTMA-Br_3

Entry	R	Product	Time (min) SF/MW	Yield(%) SF	Yield(%) MW
1	H	3a	20/5	87	90
2	4-F-	3b	20/4	89	92
3	3-Br-	3c	24/6	90	91
4	4-OH-	3d	23/5	91	92
5	4-Cl-	3e	22/4	92	93
6	2-Cl-	3f	24/6	91	92
7	4-Me-	3g	22/5	89	93
8	4-$(CH_3)_2$N-	3h	21/5	90	90
9	4-OH, 3-MeO-	3i	25/6	90	93
10	4-MeO-	3j	20/5	90	93
11	3-MeO-	3k	22/6	92	94
12	3-NO_2-	3l	21/5	92	96
13	2-NO_2-	3m	23/6	93	92
14	3, 4-Meo	3n	25/6	91	92
15	3, 4, 5-Meo-	3o	25/5	91	93
16	4-NO_2-	3p	25/6	94	96

Note: All Solvent free (SF) reactions are carried out at 110°C

Also the reaction with respect to variety of aromatic aldehydes bearing substitutions at ortho-, meta-, and para-positions participated well in this reaction (Table-2). Mechanistically, we assume that the reaction proceeds via the formation of orthoquninonemethide from 2-naphthol and aldehyde. Subsequent Michael addition of 2-napthol followed by cyclodehydration would give the desired 14-aryl-14H-di benzo [a, j] xanthenes in the presence of BTMA-Br_3 catalyst by the highlighting role of this catalyst as a promoter for the condensation reaction by elimination of water or ammonia molecules (Mechanism-1).

Antimicrobial activity

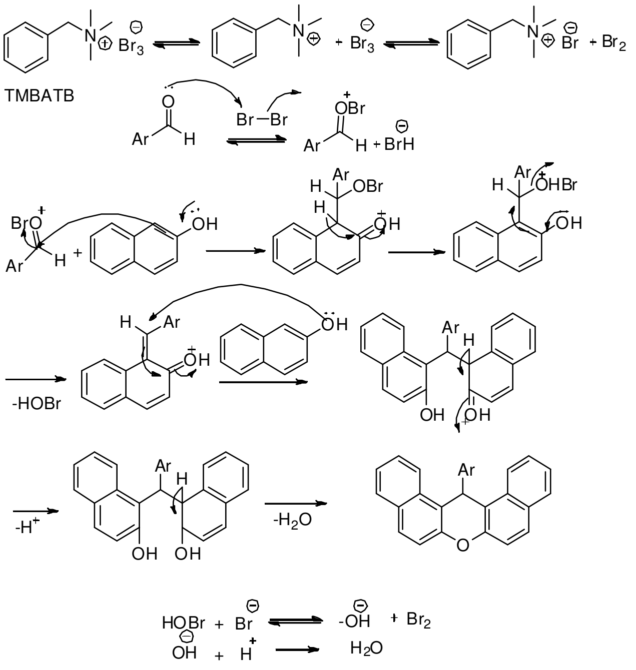
The 14-aryl-14H-dibenzo [a, j] Xanthenes derivatives are very good cytotoxic agents[26] which have shown fairly good antimicrobial activity compared to Amplicine and Miconazole as standard compounds (Table-3 entries R1 & R2). The functional groups containing nitrogen, oxygen, and alkyl substituent compounds (3-d, h, i, l, m & p) indicated moderately to good anti bacterial activity against Gram-Ve bacteria such as Escherichia Coli & Pseudomonas Aeruginosa. But halogen and oxygen containing (3-b, c & e) xanthenes directly bound to phenyl ring derivatives have shown slightly too moderate antifungal activity against fungal microorganisms such as Aspergills Niger and Fusarium Moniliforme.

Table 3. Antimicrobial inhibition zones (mm) of 14-aryl-14H-di benzo [a, j] xanthenes

		Bacterial inhibition zone (mm)		Fungal inhibition zone (mm)	
Entry	Product	Escherichia Coli	Pseudomonas Aeruginosa	Aspergillus Niger	Fusarium Moniliforme
1	3a	+	+	++	++
2	3b	+	+	++	++
3	3c	+	+	++	++
4	3d	++	++	+	+
5	3e	+	+	++	+
6	3f	+	+	++	++
7	3g	+	++	+	+
8	3h	+++	++	++	+
9	3i	++	+++	++	+
10	3j	+	++	++	+
11	3k	++	++	+	+
12	3l	++	++	-	+
13	3m	+++	+++	+	++
14	3n	+++	+++	++	+
15	3o	+++	+++	++	+
16	3p	+++	+++	++	++
R1	Ampicillin	++++	+++++	-	-
R2	Miconazole	-	-	++++	++++

Inhibition Zones (mm): Inactive (-); slightly active (+); moderately active (++); good active (+++); very good active (++++).

In summary, we have developed one pot synthesis of pharmacologically potent 14-aryl-14H-di benzo [a, j] xanthenes using a catalytic amount of metal-free BTMA-Br_3 under solvent-free conditions. The reactions were also conducted under microwave irradiation. Both the methods have multiple advantages such as short reaction times, simple work up, good yields, high selectivity and the use of desk top catalyst. Further studies to extend such easy-to-handle protocols are still in progress in our laboratory.



Mechanisum 1. Plausible Mechanism for the Reaction

Acknowledgments

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28. **Synthesis of 14-(4-Nitro Phenyl)-14H-dibenzo [a, j] xanthene:** The reaction mixture of 2-napthol (2 mmol), 4-nitro benzaldehyde (1mmol) and BTMA-Br_3 (60 mg) was heated at 110 °C for about 25 minutes. After completion reaction the mixture was cooled to room temperature and extracted in to ethyl acetate and washed with 15% Na_2CO_3; the resultant mixture was purified by column chromatography using silica gel (60-120 mesh size) and recrystallized in aqueous EtOH (15%) to obtain pure product (3a-3p). And also in Microwave irradiated technique, the above same reaction mixture was placed in a laboratory microwave oven (BPL, 800T model) on a silica gel solid support and heated at 300 W for the appropriate time 6 min. Further the product isolation and purification methods are same as above mentioned.

Supplementary Material

Supplementary data associated with this article can be found, in the online version.

Highlights of the manuscript

Metal free Lewis acid promoted one-pot synthesis of 14-aryl -14H dibenzo [a,j] xanthenes and their simple biological evolution

- A green one-pot synthesis of 14-aryl 14H-dibenzo [a, j] xanthenes is developed under solvent free conditions
- Metal free benzyltrimethylammonium tribromide worked as an efficient catalyst
- Microwave assisted reactions reduced reaction times and incresed product yields
- Prepared xanthenes are very good cytotoxic agents with fairly good antimicrobial activity

Graphical Abstract

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Metal free Lewis acid promoted one-pot synthesis of 14-aryl -14H dibenzo [a,j] xanthenes and their simple biological evolution

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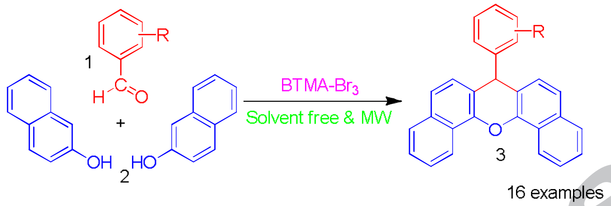
Uppalaiah Kusampally[a], Ramakanth Pagadala[b], Kamatala Chinna Rajanna[a*]



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