Bioorganic & Medicinal Chemistry Letters 19 (2009) 5590–5593

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and in vitro study of 14-aryl-14*H*-dibenzo[*a.j*]xanthenes as cytotoxic agents

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ARTICLE INFO

Article history:
Received 6 July 2009
Revised 7 August 2009
Accepted 10 August 2009
Available online 13 August 2009

Keywords:
Xanthenes
One-pot reaction
Condensation
Aldehyde
β-Naphthol
Tantalum(V) chloride
Solvent-free
Cytotoxicity

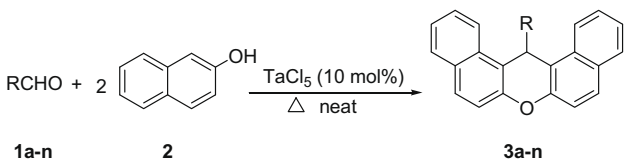
ABSTRACT

A simple and expedient method for the synthesis of a series of 14-aryl-14*H*-dibenzo[*a.j*]xanthenes is described through a one-pot condensation of β-naphthol with aryl aldehydes catalysed by $TaCl_5$ under solvent-free conventional heating. The major advantages of the present method are: high yields, less reaction time, solvent-free condition and easy purification of the products. The synthesized 14-aryl-14*H*-dibenzo[*a.j*]xanthenes were evaluated against a panel of six human cancer lines of different tissues. Synthesized compound **3o** showed IC_{50} of 37.9 and 41.3 μM against Colo-205 and 502713, respectively, whereas **3g** showed IC_{50} of 41.9 μM against Colo-205.

In recent times xanthenes and, specifically benzoxanthenes have attracted attention of medicinal chemists as well as organic chemists due to their wide range of biological and pharmacological activities such as antiviral,[1] antibacterial,[2] and anti-inflammatory properties,[3] as well as in photodynamic therapy[4] and for antagonism of the paralyzing action of zoxazolamine.[5] Further, these compounds have found wide usage such as dyes,[6] in laser technologies,[7] and as pH-sensitive fluorescent materials for visualization of biomolecules.[8] Several methods have been reported for the synthesis of xanthenes and benzoxanthenes, which include trapping of benzynes by phenols,[9a,b] cyclodehydrations,[9c] cyclocondensation between 2-hydroxyaromatic aldehydes and 2-tetralone[9d] and intramolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenones.[9e] Also, 14-aryl-14*H*-dibenzo[*a.j*]xanthenes and related products have been prepared by the reaction of β-naphthol with formamide,[9f] 2-naphthol-1-methanol[9g] and carbon monoxide.[9h] The reaction of β-naphthol with aldehydes or acetals under acidic conditions have also been reported.[10] However, many of these existing methodologies suffer from one or more disadvantages such as prolonged reaction times,[10b–e] low yields, use of harmful organic solvents,[10d] requirement of excess of catalyst/reagents, and harsh reaction conditions. Keeping in view the disadvantages associated with earlier reported protocols as well as increasing importance of benzoxanthenes in pharmaceutical and industrial chemistry, there still remains a need for the development of an efficient, low cost and ecofriendly protocol for the synthesis of benzoxanthenes. Also, the dibenzoxanthene moieties has not been explored for their cytotoxic activities, therefore, we opined that investigation related to their cytotoxicity shall be of importance.

Our continued endeavour in the development of ecofriendly and solvent-free protocols[11] prompted us to develop an efficient, convenient and facile method for the synthesis of benzoxanthenes by the condensation of aldehydes with β-naphthol catalyzed by tantalum(V) chloride (Scheme 1). In recent years, tantalum(V) chloride has been found to be an efficient Lewis acid[12] in various organic transformations due to it's readily availability at a low cost, high oxophilicity and relatively low toxicity.

In an initial study, 0.5 mmol of benzaldehyde (**1a**) was reacted with 1 mmol of β-naphthol (**2**) in 1,2-dichloroethane (2 mL) for



1a-n **2** **3a-n**

Scheme 1.

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doi:10.1016/j.bmcl.2009.08.033

Table 1
Solvent effect on the reaction of benzaldehyde and β-naphthol catalysed by $TaCl_5$[a]

Entry	Solvent	Reaction time (h)	Yield[b] (%)
1	$ClCH_2CH_2Cl$	2	20
2	MeCN	2	10
3	MeOH	2	5
4	DMF	2	20
5	$CHCl_3$	2	40

[a] 10 mol %.
[b] Isolated yield.

2 h in reflux conditions in the presence of $TaCl_5$ (10 mol %). However, 14-phenyl-14*H*-dibenzo[*a.j*]xanthene was obtained in only 20% yield. The studies on effect of common organic solvents on the course of the reaction as delineated in Table 1 clearly revealed that the use of solvent is not beneficial to improve the yield of the desired product.

Hence, we turned our attention to the reaction under solvent-free conditions. We carried out the reaction of benzaldehyde (**1a**) with β-naphthol (**2**) and $TaCl_5$ in neat condition and the reaction mixture

Table 2
$TaCl_5$ catalyzed synthesis of 14-aryl-14*H*-dibenzo[*a.j*]xanthenes[a]

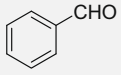
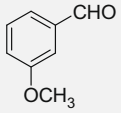
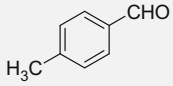
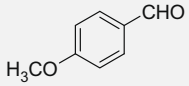
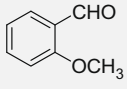
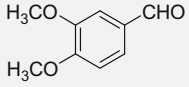
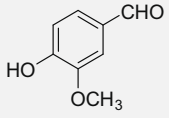
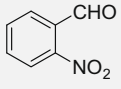
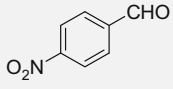
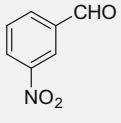
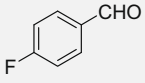
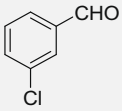
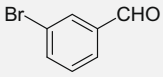
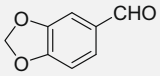
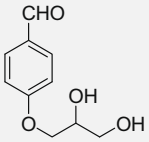
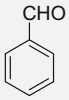
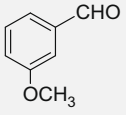
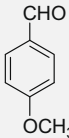
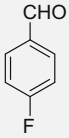
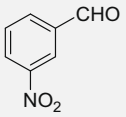
Entry	R–CHO	Product	Time (h)	Yield[b] (%)	Mp (°C)
1		**3a**	1	95	186–187
2		**3b**	1	94	179–180
3		**3c**	1	94	238–239
4		**3d**	1	93	205–206
5		**3e**	1	80	210–211
6		**3f**	1	96	194–195
7		**3g**	1	85	205–206
8		**3h**	1	72	292–294
9		**3i**	1	90	309–310
10		**3j**	1	93	213–214

Table 2 (*continued*)

Entry	R–CHO	Product	Time (h)	Yield[b] (%)	Mp (°C)
11		**3k**	1	95	241–243
12		**3l**	1	70	184–185
13		**3m**	2	88	192–193
14		**3n**	1	96	239–240
15		**3o**	1	59	204–205

[a] All the products were characterized by spectral data and also by comparison with reported data.
[b] Yield refers to pure recrystallized product.

Table 3
Comparison of $TaCl_5$ with other catalysts for the synthesis of 14- aryl-14*H*-dibenzo[*a.j*]xanthenes

Substrate	Catalyst	Catalyst (mol %)	Reaction time	Yield[a] (%)
	Iodine	10	2.5 h	90[10c]
	LiBr	15	65 min	82[10g]
	*p*TSA	2	4 h	89[10d]
	Selectfluor®	10	8 h	93[10b]
	Sulfamic acid	10	8 h	93[10e]
	$TaCl_5$	10	1 h	95
	Iodine	10	4 h	89[10c]
	LiBr	15	70 min	80[10g]
	*p*TSA	2	6 h	80[10d]
	Selectfluor®	10	10 h	92[10b]
	Sulfamic acid	10	10 h	92[10e]
	$TaCl_5$	10	1 h	93
	Iodine	10	3 h	88[10c]
	LiBr	15	65 min	82[10g]
	*p*TSA	2	3 h	92[10d]
	Selectfluor®	10	11 h	92[10b]
	Sulfamic acid	10	11 h	92[10e]
	$TaCl_5$	10	1 h	94
	Iodine	10	2.5 h	93[10c]
	*p*TSA	2	3 h	90[10d]
	Selectfluor®	10	6 h	93[10b]
	Sulfamic acid	10	6 h	93[10e]
	$TaCl_5$	10	1 h	95
	Iodine	10	3 h	92[10c]
	LiBr	15	70 min	81[10g]
	*p*TSA	2	2.5 h	90[10d]
	Selectfluor®	10	12 h	91[10b]
	Sulfamic acid	10	12 h	91[10e]
	$TaCl_5$	10	1 h	93

[a] References for earlier methods.

Table 4
IC_{50} values of synthesized compounds against human cancer cell lines of different tissues

S. no.	Compound code	IC_{50} (μM)					
		Colon		CNS		Lung	Prostate
		SW-620	502713	Colo-205	SK-N-SH	A-549	PC-3
1	**3g**	54.4	45.4	41.9	44.3	74.3	61.1
2	**3h**	63.2	50	—	55	—	82
3	**3o**	49.1	41.3	37.9	44	127.9	63.9

was heated at 100 °C, and the corresponding benzoxanthene **3a** was obtained in 95% yield (Table 2, entry 1). This success then encouraged us to generalize the scope of this method.[13] Several structurally diverse aldehydes (Table 2) were subjected to condensation with β-naphthol under the catalytic influence of $TaCl_5$ (10 mol %) and solvent-free conventional heating, and 14-aryl-14*H*-dibenzo[*a.j*]-xanthenes were obtained in high yields. Also, tolerance of the present method towards various functionalities present in the substrates viz. ethers, methylenedioxy, halides, hydroxy and nitro groups generalizes the scope of the present method. Further, the versatility and the utility of the present method could easily be gauged by comparison with the earlier reported protocols (Table 3). We have chosen some model substrates and the comparison has been made with respect to the catalytic amount used, reaction time and yields. It is noteworthy to mention here that 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 4-fluorobenzaldehyde and 3-nitrobenzaldehyde provided the desired product within 1 h with higher yield than the earlier reported methods.

All the compounds were assayed for in vitro cytotoxicity[14] against a panel of six human cancer cell lines including SW-620, 502713 and Colo-205 (Colon), SKNSH (CNS), A-549 (Lung) and PC-3 (Prostate) using sulforhodamine B. The synthesized 14-aryl-14*H*-dibenzo[*a.j*]xanthenes were evaluated against six cancer lines for their cytotoxic profiles and the results are summarized in Table 4. Compound **3g** having 4-hydr-oxy-3-methoxy aryl showed significant cytotoxic activity against Colo-205 with an IC_{50} value of 41.9 μM whereas other similarly substituted compounds in this series (**3b**, **3d**, **3e** and **3f**) were devoid of any cytotoxic activity. *O*-Nitro substituted aryl (**3h**) showed some degree of cytotoxic activity against different colon, CNS and prostrate cell lines whereas *p*- or *m*-nitro substituted aryls (**3i** and **3j**, respectively) did not show cytotoxic activity against any human cancer cell lines. The more polar compound having two aliphatic hydroxyl groups (**3o**) showed more potent cytotoxic activity against Colo-205 and Colon-502713 with an IC_{50} value of 37.9 and 41.3 μM, respectively.

In conclusion, a novel and highly efficient procedure has been developed for the synthesis of 14-aryl-14*H*-dibenzo[*a.j*]xanthenes by condensation reaction of diverse aldehydes with β-naphthol in one-pot using $TaCl_5$ as the catalyst under solvent-free condition. The main advantages of the present method are: solvent-free reaction conditions, good to excellent yields, simple work-up and purification of the products. Also, some of the synthesized compounds (**3g**, **3h** and **3o**) have shown cytotoxic activities in micro molar range thereby suggesting that these moieties could be further developed as possible anticancer agents by the structural modifications.

Acknowledgments

A.K.B. is grateful to Dr. S. Sivaram, Director, NCL, Pune and Dr. Ganesh Pandey, Head, Division of Organic Chemistry for their constant encouragement and support. K.C.R. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for a Senior Research Fellowship.

Supplementary data

Selected NMR spectra (^1H NMR, ^{13}C NMR and DEPT spectra of compounds **3b**, **3f**, **3l** and **3n**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.08.033.

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13. *General Synthetic procedure*: to a mixture of aldehyde (1 mmol), and β-naphthol (2 mmol), $TaCl_5$ (10 mol %) was added and heated at 100 °C for the appropriate time (Table 1) till the completion (TLC) of reaction. The reaction mass was cooled to room temperature, DCM (25 mL) was added to it and washed with water. The DCM extract was dried (anhydrous Na_2SO_4), filtered and evaporated to furnish a solid residue. The pure 14-aryl-14*H*-dibenzo[*a.j*]xanthene was obtained by recrystallization of the solid from EtOH. All the products were characterized by spectral data.[15]
14. *In vitro cytotoxicity of synthesized compounds against human cancer cell lines*: the human cancer cell lines were procured from National Cancer Institute, Frederick, USA. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4, supplemented with 10% fetal calf serum, 100 μg/ml streptomycin and 100 units/ml penicillin) in a carbon dioxide incubator (37 °C, 5% CO2, 90% RH). The cells at subconfluent stage were harvested from the flask by treatment with trypsin [0.05% in PBS (pH 7.4) containing 0.02% EDTA]. Cells with viability of more than 98% as determined by trypan blue exclusion were used for determination of

cytotoxicity. The cell suspension of 1 × 105 cells/ml was prepared in complete growth medium.

Stock solutions (2×10^{-2} M) of compounds were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μg/ml of gentamycin to obtain working test solutions of required concentrations.

In vitro cytotoxicity against six human cancer cell lines was determined[16,17] using 96-well tissue culture plates. The 100 μl of cell suspension was added to each well of the 96-well tissue culture plate. The cells were allowed to grow in carbon dioxide incubator (37 °C, 5% CO2, 90% RH) for 24 h. Test materials (100 μl) were added after 24 h of incubation to the wells containing cell suspension. The plates were further incubated for 48 h in a carbon dioxide incubator. The cell growth was stopped by gently layering trichloroacetic acid (50%, 50 μl) on top of the medium in all the wells. The plates were incubated at 4 °C for 1 h to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove trichloroacetic acid, growth medium, low molecular weight metabolites, serum proteins etc and air-dried. The plates were stained with sulforhodamine B dye (0.4% in 1% acetic acid, 100 μl) for 30 min. The plates were washed five times with 1% acetic acid and then air-dried. The adsorbed dye was dissolved in Tris–HCl Buffer (100 μl, 0.01 M, pH 10.4) and plates were gently stirred for 10 min on a mechanical stirrer. The optical density was recorded on ELISA reader at 540 nm.

The cell growth was determined by subtracting mean OD value of respective blank from the mean OD value of experimental set. Percent growth in presence of test material was calculated considering the growth in absence of any test material as 100% and in turn percent growth inhibition in presence of test material was calculated. Adriamycin, 5-FU and paclitaxel were used as positive control.

15. *Selected physical data*: *14-(3-methoxyphenyl)-14H-dibenzo[a,j]xanthene* (**3b**): IR ($CHCl_3$): ν_{max} 3018, 2958, 2933, 1593, 1487, 1458, 1431, 1400, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.61 (s, 3H), 6.41 (s, 1H), 6.48–6.53 (m, 1H), 7.01–7.13 (m, 3H), 7.34–7.60 (m, 6H), 7.74–7.82 (m, 4H), 8.35–8.40 (d, J = 8.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.0, 55.0, 111.0, 115.0, 117.2, 118.1, 120.8, 122.8, 124.8, 126.8, 128.8, 128.9, 129.3, 131.1, 131.5, 146.6, 148.8, 159.6. Anal. Calcd for $C_{28}H_{20}O_2$ (388.46): C, 86.57; H, 5.19. Found: C, 86.45; H, 5.06.

14-(3,4-Dimethoxyphenyl)-14H-dibenzo[a,j]xanthene (**3f**): IR ($CHCl_3$): ν_{max} 3018, 2927, 1593, 1514, 1458, 1259, 1215, 1141 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.68 (s, 3H), 3.69 (s, 3H), 6.45 (s, 1H), 6.63–6.67 (m, 1H), 6.91–6.92 (m, 1H), 7.10–7.11 (m, 1H), 7.38–7.58 (m, 6H), 7.77–7.85 (m, 4H), 8.40 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.5, 55.7, 55.8, 110.8, 111.7, 117.5, 118.0, 120.4, 122.8, 124.3, 126.8, 128.9, 131.2, 131.5, 137.7, 147.6, 148.8, 149.1. Anal. Calcd for $C_{29}H_{22}O_3$ (418.48): C, 83.23; H, 5.30. Found: C, 83.03; H, 5.12.

14-(3-Chlorophenyl)-14H-dibenzo[a,j]xanthene (**3l**): IR ($CHCl_3$): ν_{max} 2918, 2852, 2362, 2335, 1596, 1458, 1377, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.46 (s, H), 6.94–7.12 (m, 2H), 7.39–7.64 (m, 8H), 7.79–7.86 (m, 4H), 8.32 (d, J = 8.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.8, 116.6, 118.1, 122.5, 124.5, 126.5, 126.8, 127.0, 128.4, 129.0, 129.2, 129.7, 131.1, 131.3, 134.5, 147.7, 148.8. Anal. Calcd for $C_{27}H_{17}ClO$ (392.88): C, 82.54; H, 4.36. Found: C, 82.26; H, 4.18.

14-(Benzo[d][1,3]dioxol-5-yl)-14H-dibenzo[a,j]xanthene (**3n**): IR ($CHCl_3$): ν_{max} 3018, 2925, 2358, 2329, 2252, 1593, 1515, 1485, 1400, 1249, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.71 (s, 2H), 6.39 (s, 1H), 6.59 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 1.8 Hz, 1H), 7.06–7.10 (m, 1H), 7.36–7.57 (m, 6 H), 7.74–7.83 (m, 4 H), 8.34 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.6, 100.8, 107.8, 108.9, 117.3, 118.1, 121.3, 122.7, 124.3, 126.8, 128.9, 131.1, 131.4, 139.1, 146.0, 147.9, 148.7. Anal. Calcd for $C_{28}H_{18}O_3$ (402.44): C, 83.57; H, 4.51. Found: C, 83.39; H, 4.42.

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