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RESEARCH ARTICLE

$SiO_2/ZnCl_2$-Catalyzed Heterocyclic Synthesis: Green, Rapid and Efficient One-Pot Synthesis of 14-*H*-dibenzo [*a, j*]Xanthenes, 1,8-Dioxo-octahydroxanthenes and 1,8-Dioxo-Decahydroacridines Under Solvent-Free Conditions

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Abstract: A green and highly efficient protocol for the one-pot synthesis of a variety of 14-aryl-14-*H*-dibenzo [*a,j*]xanthenes and 9-aryl-1,8-dioxo-octahydroxanthenes has been developed via cyclocondensation of aryl aldehydes with 2-naphthol or dimedone using SiO_2-$ZnCl_2$ (silzic) as a reusable heterogeneous catalyst under solvent-free reaction conditions. In addition, a one-pot, three-component condensation of aryl aldehydes, dimedone and ammonium acetate or aryl amines has been developed to furnish 9-aryl-1,8-dioxo-decahydroacridines in good to excellent yields under the same reaction conditions.

Keywords: Xanthenes, Acridine, Silzic, One-pot synthesis, Solvent-free, Heterogeneous catalyst, Multi-component reaction

Introduction

Xanthene derivatives are important *O*-heterocycles in medicinal chemistry field as well as in industry. In particular, 14*H*- dibenzo[*a,j*]xanthenes and 1,8-dioxo-octahydroxanthenes have gained remarkable interest due to their various synthetic and industrial applications. For example, they possess a large array of pharmacological activities such as anti-inflammatory[1], anti-bacterial[2] and antiviral properties[3]. Besides, some of them are served as leuco-dyes[4], intracellular pH indicators and as fluorescent materials[5]. Moreover, application of such compounds in photodynamic therapy as well as in laser technologies has also been reported[6,7]. 14*H*-Dibenzo[*a,j*]xanthene derivatives are generally synthesized either by dehydration of bis(2-hydroxy-1-naphthyl)methane derivatives[8] or by condensation of 2-naphthol with aromatic aldehydes in the presence of H_2SO_4 using acetic acid as solvent[9]. Using of environmentally hazardous and toxic acidic catalysts under harsh conditions, long reaction time, and tedious experimental procedures are serious disadvantages of these

traditional methods. Therefore, efforts for improving this synthesis via milder catalyzed-protocols have been reported. Synthesis of aryl-14*H*- dibenzo[*a,j*]xanthenes via condensation of aldehydes and 2-naphthol has been developed in the presence of various catalysts such as *p*-TSA (in boiling 1,2-dichloroethane for 20 h)[10], cyanuric chloride[11], LiBr[12]. Greener approaches for synthesis of aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxo-octahydroxanthenes through condensation of aldehydes and 2-naphthol or 5,5-dimethyl-1,3-cyclohexanedione (dimedone) using ionic liquids as well as inorganic solid support catalysts under solvent-free conditions have also been developed[13-19]. Nevertheless, some of these protocols are disadvantageous in terms of readily unavailability of catalyst ($Yb(OTf)_3$/$[BPy]BF_4$), or long reaction times under thermal conditions at elevated temperature[20]. Also 1,8-dioxo-decahydroacridines are polyfunctionalized 1,4-dihydropyridine derivatives (DHPs), a class of nitrogen heterocycles of broad spectrum of important biological properties and pharmaceutical applications[21-25] .

So, the development of novel synthetic strategies for heterocycles which have advantages with respect to using, less expensive and readily available catalysts or reagents, cleaner reactions, and simple isolation of the product are of interest[26]. The protocol involves the employment of SiO_2-$ZnCl_2$ as an efficient catalyst in achieving cyclocondensation of aryl aldehydes with 2-naphthol or dimedome resulting in formation of aryl-14*H*- dibenzo[*a,j*] xanthene derivatives or aryl-1,8-dioxo-octahydroxanthenes respectively, in good to excellent yields under solvent-free conditions. Under the same conditions, a variety of aryl-1,8-dioxo-decahydroacridines has also been efficiently synthesized through a one-pot, three-component condensation of aromatic aldehydes, dimedone and ammonium acetate or aryl amines.

Experimental

Melting points were determined using a Griffin melting point apparatus. The IR spectra were recorded with Mattson FTIR spectrometer 5000. Absorption maxima were measured in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were recorded with Bruker 200, 300 MHz spectrometer instruments in CDCl3. The chemical shifts (δ) were measured in ppm and with the solvents as references (For CDCl3, 1H: δ = 7.26 ppm, 13C: δ = 77.0 ppm). MS spectra were recorded on GC-MS QP-1000 EX Shimadzu mass spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm).

General procedure for the synthesis of aryl-14H- dibenzo[a,j]xanthenes (3) and 9-aryl-1,8-dioxooctahydroxanthens (**5**)

To a mixture of aldehyde **2** (1 mmol) and 2-naphthol or dimedone (2 mmol) was added Silzic (which prepared as reported[33]) (0.2 g mol%) and the mixture was allowed to stir at 100 ^oC for the total recorded time. After completion (the reaction was monitored by TLC), was added EtOAc (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, and the residue was subjected to short column chromatography using pet.ether-EtOAc (9:1) to give pure **3** or **5**. The products are known compounds and all spectroscopic data were in agreement with literature.

Selected spectral data for some products

14-(3,4-Dimethoxyphenyl)-14H-dibenzo[a,j]xanthenes

(3 g, Table 1): Mp=198 IR (KBr, cm^{-1}): ν 3064, 2932, 2832, 1622, 1592, 1514, 1457, 1433,1401, 1239, 1140, 1072, 1020, 961, 859,819, 748 cm-1; ^1H NMR (300 MHz, CDCl3) δ = 8.21 (d, J=6.0 Hz, 2H), 7.22-7.70 (m, 12H), 6.93 (d, J=8.0 Hz, 1H), 6.72 (s, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.26 (s, 1H),3.49 (s, 6H) ppm.

3,3,6,6-Tetramethyl-9(3,5-dimethoxy-phenyl)-1,8-dioxo-octahydroxanthene

(5 h, Table 2) Mp. = 200 °C; IR (KBr, cm^{-1}): ν 3061, 2981, 2890, 1666, 1628, 1510, 1358, 1261, 841, 573, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.51-7.3 (m, 3H, Ar-H), 4.72 (s, 1H, CH), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.47 (s, 4H, 2xCH_2), 2.23 (s, 4H, 2xCH_2), 1.12 (s, 6H, 2xCH_3), 1.03 (s, 6H, 2xCH_3). EI-MS: 410 (M+); Anal. Calcd. For $C_{25}H_{30}O_5$: C, 73.17; H, 7.32; Found: C, 73.26; H, 7.45.

Typical procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives

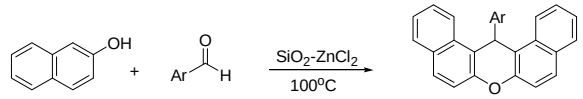
To a stirred mixture of aldehyde (5 mmol), dimedone (10 mmol) and aryl amine (6 mmol), was added Silzic (0.2 g mol%) and the mixture was allowed to stir at 100 °C for the total recorded time. After completion (the reaction was monitored by TLC), was added EtOAc (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, and the residue was subjected to short column chromatography using pet.ether-EtOAc (9:1) to give pure 6. The decahydroacridinediones **6** except for **6f**, are known compounds and all spectroscopic data were in agreement with literature.

*Data for **6f***

Mp = 226 °C; IR (KBr, cm^{-1}): ν 3043, 2955, 2936, 1641, 1574, 1508, 1361, 1218, 1096, 921, 734; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 9 Hz, 2H, Ar-H), 7.05 (d, J = 9 Hz, 2H, Ar-H), 6.69 (s, 2H, Ar-H), 5.26 (s, 1H, CH), 3.81 (s, 6H, 2xOCH_3), 3.77 (s, 3H, OCH_3), 2.48 (s, 3H, CH_3), 2.07-2.20 (m, 6H), 1.84 (d, J = 18 Hz, 2H), 0.96 (s, 6H, 2xCH_3), 0.86 (s, 6H, 2xCH_3); EI-MS: 552 (M+Na)+; Anal. Calcd. For $C_{33}H_{39}NO_5$ (529.28): C, 74.83; H, 7.42; N, 2.64. Found: C, 74.97; H, 7.31, N, 2.49.

Results and Discussion

A convenient one-pot synthesis of aryl-14*H*- dibenzo[*a,j*]xanthenes through the reaction of 2-naphthol with aromatic aldehydes in the presence of SiO_2-$ZnCl_2$ (silzic) under solvent-free conditions has been achieved. Stirring a mixture of 2-naphthol (2 equiv) and aromatic aldehyde (1 equiv.) in the presence of SiO_2-$ZnCl_2$(0.2 g mol%) at 100 °C led to the formation of aryl-14*H*- dibenzo[*a,j*]xanthenes **3a-i** in excellent yield (Scheme 1, Table 1).



1 **2** **3a-i**

***3a**; Ar =Ph, **3b**; Ar =4- OMeC$_6$H$_4$, **3c**; Ar=4-ClC$_6$H$_4$, **3d**; Ar =4-MeC$_6$H$_4$, **3e**; Ar=4-NO$_2$C$_6$H$_4$, **3f**; Ar=4-BrC$_6$H$_4$C$_6$H$_4$, **3g**; Ar=2,4-diOMeC$_6$H$_3$, **3h**; Ar=3,5-diOMeC$_6$H$_3$, **3i**; Ar=3,4,5-triOMeC$_6$H$_2$*

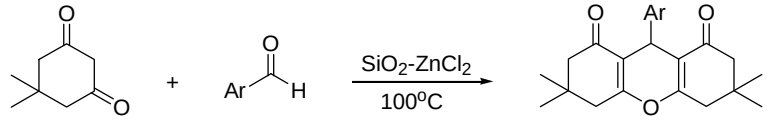
Scheme 1

Table 1. SiO_2/$ZnCl_2$-Catalyzed one-pot synthesis of aryl-14-*H*-dibenzo [*a, j*]xanthenes

Entry	Substrate 2	Time, min	Product	Yield, %[a]	mp, °C	Lit. mp, °C
1	4-H	40	3a	81	181	182[16]
2	4-OMe	45	3b	83	185	
3	4-Cl	40	3c	83	289	290[16]
4	4-Me	45	3d	79	224-6	226[16]
5	4-NO_2	40	3e	84	308	309[16]
6	4-Br	40	3f	82	293	295[16]
7	3,4-diOMe	40	3g	75	198-9	198[11]
8	3,5-diOMe	40	3h	77	185-7	
9	3,4,5-triOMe	40	3i	80	195-7	

[a]*Isolated yield*

Also one-pot synthesis of 1,8-dioxo-octahydroxanthenes through the reaction of dimedone with aromatic aldehydes in the presence of SiO_2-$ZnCl_2$ (silzic) under solvent-free conditions has been achieved. Stirring a mixture of dimedone (2 equiv.) and aromatic aldehyde (1 equiv.) in the presence of SiO_2-$ZnCl_2$(0.2 g mol%) at 100 ^oC led to the formation of 1,8- dioxooctahydroxanthenes 5a-k in excellent yield (Scheme 2, Table 2).



4 **2** **5a-k**

***5a**; Ar =Ph, **5b**; Ar =4- $OMeC_6H_4$, **5c**; Ar=4-ClC_6H_4, **5d**; Ar =4-MeC, **5e**; Ar=4-$NO_2C_6H_4$, **5f**; Ar=4-BrC_6H_4, **5g**; Ar=2,4-di$OMeC_6H_3$, **5h**; Ar=3,5-di$OMeC_6H_3$, **5i**; Ar=3,4,5-tri$OMeC_6H_2$, **5j**; Ar=3-OMe,4-OH-C_6H_3, 5k; Ar=4-CNC_6H_4*

Scheme 2

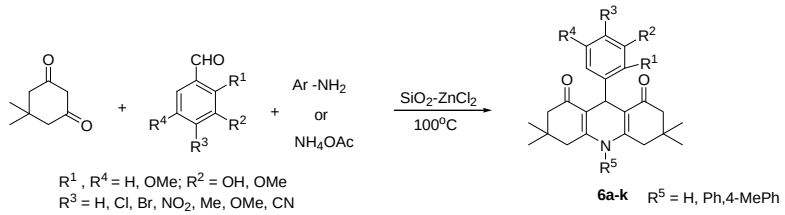
Table 2. SiO_2/$ZnCl_2$-Catalyzed one-pot synthesis of 1,8-dioxooctahydroxanthenes

Entry	Aldehyde/Ar	Time, min	Product	Yield, %[a]	mp, ^oC	Lit. mp, ^oC
1	4-H	25	**5a**	87	202-204	204-206[15]
2	4-OMe	23	**5b**	89	238-240	242-243[14]
3	4-Cl	25	**5c**	87	230-232	229-230[15]
4	4-Me	22	**5d**	90	215-217	215-216[14]
5	4-NO_2	27	**5e**	85	225-226	222-224[14]
6	4-Br	25	**5f**	86	232-234	233-235[19]
7	2,4-diOMe	28	**5g**	82	207-208	209-211[34]
8	3,5-diOMe	27	**5h**	80	198-200	---
9	3,4,5-triOMe	25	**5i**	90	204-205	205[26]
10	Vanillin	30	**5j**	80	222-224	224[19]
11	4-CN	28	**5k**	85	214-216	217-218[14]

[a]*Isolated yield*

The results summarized in Table 1 and Table 2 showed that the formation of aryl-14*H*-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroexanthene proved to be general and quite efficient for aryl aldehydes and tolerated a variety of functional groups on the phenyl ring regardless of whether electron-donating or electron-withdrawing in character. Thus, chloro, bromo, nitro, methyl and methoxy containing aromatic aldehydes were reacted smoothly to give the respective aryl-14*H*- dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroexanthene in excellent yields. Identification of 3- aryl-14*H*- dibenzo[a,j] xanthenes and 1,8-dioxo-octahydroexanthene was carried out by spectroscopic analyses as well as by comparing their properties to those reported. For example, the ^1H NMR spectra of the benzoxanthenes 3 obtained by the present method showed, no absorption bands for the hydroxyl group protons was observed, In the IR spectra, no any absorption for hydroxyl group (OH) was observed but, rather, all products displayed a characteristic ether-linkage (C-O) stretching band at ν_{max} 1213-1227 cm^{-1}, indicating the cyclization step clearly.

The multi-component reaction of dimedone (2 mole), benzaldehyde (1 mole) and aromatic amine (or ammonium acetate) (1.2 mole) in the presence of Silzic (0.2 g mol%) at 100 ^oC to produce 1,8-dioxo-decahydroacridines under solvent-free conditions, was studied. (Scheme 3, Table 3).



Scheme 3

Table 3. $SiO_2/ZnCl_2$-Catalyzed one-pot synthesis of 1,8-dioxodecahydroacridines

Entry	Aldehyde/Ar	Amine/ NH_4OAc	Time, min	Product	Yield, %[a]	mp, °C	Lit. mp, °C
1	Ph	$PhNH_2$	25	6a	87	220-222	220-222[35]
2	4-ClC_6H_4-	$PhNH_2$	23	6b	89	240-242	243[35]
3	4-BrC_6H_4-	$PhNH_2$	25	6c	87	215-8	
4	4-MeC_6H_4-	$PhNH_2$	22	6d	90	173-5	
5	4-$MeOC_6H_4$	$PhNH_2$	27	6e	85	228-230	220-222[35]
6	3,4,5-$(OMe)_3C_6H_2$	4-$MeC_6H_4NH_2$	25	6f	86	224-226	-----
7	2,4-$(OMe)_2C_6H_3$	NH_4OAc	28	6g	82	193-5	
8	3,5-$(OMe)_2C_6H_3$	NH_4OAc	27	6h	80	176-8	
9	4-$NO_2C_6H_4$	NH_4OAc	25	6i	75	289-90	286-288[29]
10	Ph	NH_4OAc	30	6j	70	190-192	190-192[31]
11	4-$MeOC_6H_4$	NH_4OAc	30	6k	75	268-270	270-272[32]

[a]*Isolated yield*

In all cases, aromatic aldehydeds with substituents caring either electron- donating or electron- withdrawing groups reacted successfully and gave the expected products in good yields and short reaction times.

The structure elucidation of acridine derivatives **6** was assigned on the basis of both elemental and spectral analyses. Also by comparison of their physical and spectroscopic data with those of authentic samples[27-32].

Conclusion

In summary, we have developed a simple, mild and efficient protocol for the one-pot syntheses of various 14*H*-dibenzo[a,j]xanthenes, 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines, employing the cheap SiO_2-$ZnCl_2$ mixture. Under solvent free, by condensation of aryl aldehyde with 2-naphthol ,dimedone and with dimedone in presence of amine. High yields, short reaction times and easy work up are some advantages of this reaction. Exploring this protocol for the condensation of mixed nucleophiles with aldehydes for synthesizing an array of novel heterocycles for biological evaluation is on-going project in our laboratory.

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