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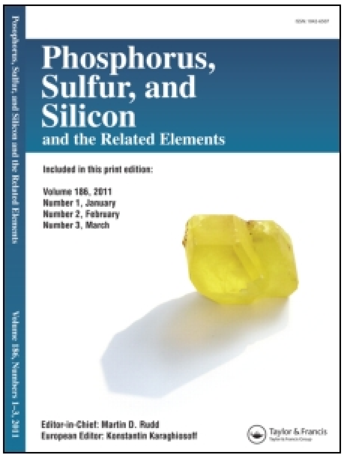

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Synthesis of 14-Substituted-14*H*-Dibenzo[*a,j*] Xanthenes and 1,8-Dioxo-Octahydroxanthenes Using Silica Chloride (SiO_2-Cl) Under Solvent-Free Conditions

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SYNTHESIS OF 14-SUBSTITUTED-14*H*-DIBENZO[*a,j*] XANTHENES AND 1,8-DIOXO-OCTAHYDROXANTHENES USING SILICA CHLORIDE (SiO_2-Cl) UNDER SOLVENT-FREE CONDITIONS

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A simple and efficient synthesis of 14-substituted-14H-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroxanthenes has been accomplished by the one-pot condensation of β-naphthol or dimedone and aldehydes under solvent-free conditions in the presence of SiO_2-Cl as a heterogeneous catalyst.

Keywords Dimedone; 1,8-dioxo-octahydroxanthenes; β-naphthol; silica chloride; solvent-free; 14-substituted-14*H*-dibenzo[*a,j*]xanthenes

INTRODUCTION

The synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes has been considered of great interest to organic chemists owing to their wide range of biological and therapeutic properties such as antiviral,[1] antibacterial,[2] and anti-inflammatory activities,[3] as well as in photodynamic therapy[4] and for antagonism of the paralyzing action of zoxazolamine.[5] Furthermore, due to their useful spectroscopic properties, they are used as dyes,[6] in laser technologies,[7] and in fluorescent materials for visualization of biomolecules.[8] The most common methods for the synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes are the reaction of β-naphthol with aldehydes or acetals in the presence of a catalyst, such as *p*-TSA,[9] sulfamic acid,[10] AcOH-H_2SO_4,[11] cyanuric chloride,[12] I_2,[13] $HClO_4$-SiO_2,[14] $Yb(OTf)_3$,[15] BF_3-SiO_2,[16] LiBr,[17] $Al(HSO_4)_3$,[18] Dowex-50W,[19] $NaHSO_4$-SiO_2,[20] ceric sulfate,[21] ionic liquid,[22] $K_5CoW_{12}O_{40}$ $3H_2O$,[23] $NH_4H_2PO_4/SiO_2$,[24] or cellulose sulfuric acid.[25]

However, most of these procedures have significant drawbacks such as long reaction times,[10,20] low yields,[17,19] harsh reaction conditions,[10,18,20] difficult workup,[24] and use of environmentally toxic or expensive reagents or media.[11,15,19,21–23] Thus, there is still a need for a simple and general procedure for the one-pot synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes.

Homogeneous acidic catalysts such as H_2SO_4, HCl, and BF_3 are commonly used for organic synthesis. However, the above-mentioned catalysts have several disadvantages

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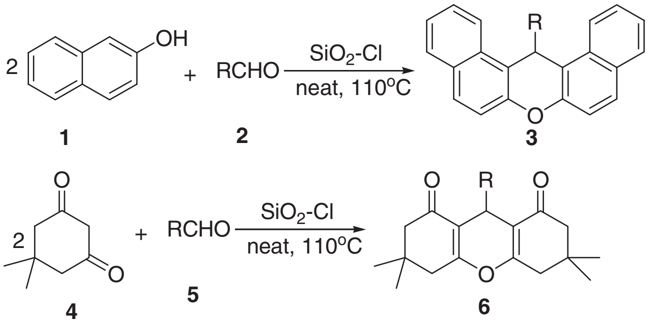
because they are corrosive, toxic, or volatile, and generate large amounts of waste. Silica chloride (SiO_2-Cl), which was easily prepared from silica gel and thionyl chloride, is a good solid acid in terms of convenience, cheapness, easy production, and insolubility in all organic solvents. Due to its insolubility in organic solvents, excellent in situ proton generation, and acceptance of different nucleophiles, SiO_2-Cl can be used for different purposes in organic chemistry, such as SiO_2-Cl–catalyzed protection of carbonyl compounds,[26] acetylation of alcohols,[27] synthesis of 2-aminothiazoles,[28] and as a starting material for the preparation of other silica bonded reagents.[29] In this article, we report a simple, efficient, and environmentally benign synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes. During our study, we also observed the formation of 1,8-dioxo-octahydroxanthenes in excellent yields by a one-pot condensation of dimedone and aldehydes under solvent-free conditions in the presence of SiO_2-Cl (see Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

We started to study this reaction by examining the amount of catalyst for the reaction involving β-naphthol (2 mmol) with benzaldehyde (1 mmol) to afford the product 14-phenyl-14*H*-dibenzo[*a,j*]xanthene under solvent-free conditions at 110°C. The best result was obtained with 250 mg/mmol SiO_2-Cl. Higher amounts of catalyst did not improve the result to any great extent (see Table I).

To optimize the temperature of the reaction and compare the efficiency of the solvent-free vs. solution conditions, a model reaction was examined in several solvents, including

Table I The amount of catalyst of optimization of reaction conditions of 14-phenyl-14*H*-dibenzo[*a,j*]xanthenes

Entry	SiO_2-Cl (mg/mmol)	Yield (%)
1	100	58
2	150	72
3	200	84
4	250	93
5	300	91
6	350	93
7	400	91

Table II Solvent and temperature of optimization of reaction conditions of 14-phenyl-14*H*-dibenzo[*a,j*]xanthenes

Entry	Solvent	Temp. (°C)	Yield (%)
1	CH_2Cl_2	Reflux	47
2	CH_3CN	Reflux	86
3	THF	Reflux	36
4	DMF	110	56
5	DMSO	110	52
6	Benzene	Reflux	22
7	Solvent-free	90	72
8	Solvent-free	100	88
9	Solvent-free	110	93
10	Solvent-free	120	91
11	Solvent-free	130	92
12	Solvent-free	140	91

CH_2Cl_2, MeCN, THF, benzene, DMF, DMSO, and solvent-free conditions. Thus, a mixture of β-naphthol (2 mmol), benzaldehyde (1 mmol), and SiO_2-Cl (0.25 g) in the appropriate solvent (10mL) or solvent-free was stirred for 3 h. As is shown in Table II, acetonitrile as a solvent under reflux and thermal solvent-free at 110°C showed the best results, but solvent-free conditions eliminate the use of solvents, especially toxic acetonitrile.

A range of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes was synthesized by the reaction of β-naphthol (**1**, 2 mmol) with aldehyde (**2**, 1 mmol). The reaction proceeded at 110°C within 4 h in excellent yields after the addition of the acid catalyst SiO_2-Cl (see Table III). In these experiments, the catalyst was isolated by filtration and could be run up to three recycles with no significant loss of activity (Table III, entry 1). In addition, we noticed also

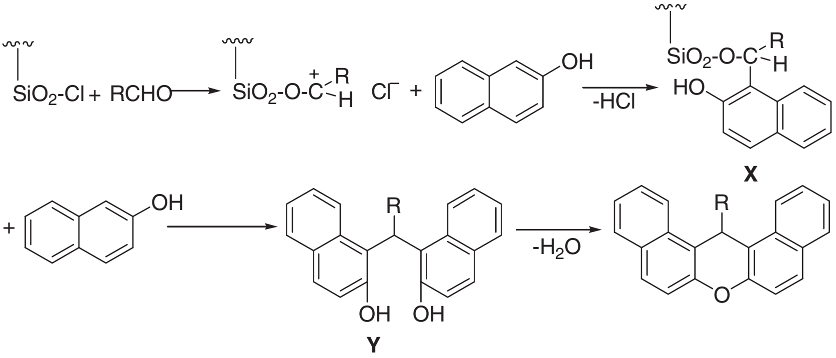
Table III Preparation of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes catalyzed by SiO_2-Cl[a]

Entry	R	Products	Time (h)	Yield (%)	Mp (°C) Found	Reported[ref.]
1	Ph	**3a**	3	93 (78, 67)	181–182	183–185 [21]
2	$4\text{-}(CH_3)C_6H_4$	**3b**	3.5	88	225–226	224–227 [21]
3	$4\text{-}(MeO)C_6H_4$	**3c**	3.5	89	204–205	202–204 [21]]
4	$2\text{-}(MeO)C_6H_4$	**3d**	3.5	86	256–257	258–259 [12]
5	$4\text{-}(Cl)C_6H_4$	**3e**	3	96	285–286	286–289 [21]
6	$2\text{-}(Cl)C_6H_4$	**3f**	3	92	213–214	212–214 [21]
7	$4\text{-}(Br)C_6H_4$	**3g**	3	94	295–296	297–298 [22a]
8	$4\text{-}(NO_2)C_6H_4$	**3h**	3	93	303–304	306–308 [21]
9	$3\text{-}(NO_2)C_6H_4$	**3i**	3	94	208–209	210–211 [21]
10	$2\text{-}(NO_2)C_6H_4$	**3j**	3	89	288–289	290–291 [21]
11	$2, 4\text{-}(Cl)_2C_6H_4$	**3k**	4	87	250–251	252–254 [21]
12	$3, 5\text{-}(MeO)_2C_6H_4$	**3l**	4	85	186–187	188–189 [22a]
13	$4\text{-}(I)C_6H_4$	**3m**	4	90	>300	
14	Naphth-1-yl	**3n**	4	83	200–201	202–204 [21]
15	Pyrid-4-yl	**3o**	4	85	227–228	229–230 [22a]
16	Et	**3p**	4	82	146–147	148–151 [21]
17	*i*-Pr	**3q**	4	80	156–157	155–157 [12]

[a] All of the isolated products are known compounds, and their spectral and physical data have been reported in the literature.[12,21,22a]

that the reaction was able to tolerate various aldehydes, including aromatic and aliphatic derivatives.

This new synthetic strategy resulted in a remarkable improvement in synthetic efficiency, and more importantly, it enhanced the utilization efficiency of the modified silica chloride, and decreased the production of chemical waste without using a highly toxic reagent for the synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes. The Si-Cl bond is labile and can give rise to Lewis acid centers on silica (Scheme 2). The Cl is easily displaced selectively by the acetyl oxygen of aldehyde by a nucleophilic substitution reaction, generating a cationic center on the carbonyl carbon, which is easily attacked by the nucleophile β-naphthol to form intermediate X. Interception of this intermediate by β-naphthol produces Y, which subsequently cyclizes to the corresponding 14-substituted-14*H*-dibenzo[*a,j*]xanthenes.



Scheme 2

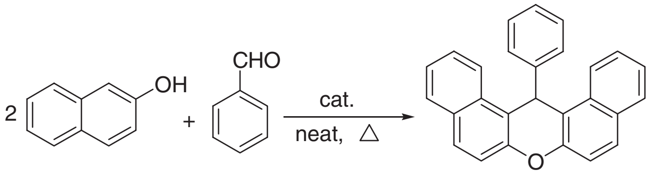
In order to assess the capability of the present method with respect to the reported methods for the preparation of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes from β-naphthol and aldehydes, the synthesis of compound **3a** was compared with the reported methods. It is clear from Table IV that the present method has high yields, moderate reaction times, simple procedure, and uses inexpensive and environmentally benign catalysts.

Encouraged by these results, we were delighted to observe that the present protocol could safely be extended to the condensation reaction involving dimedone **4** and aldehyde **5**. 1,8-Dioxo-octahydroxanthenes were obtained in excellent yields (see Table V).

CONCLUSION

In conclusion, we have developed a simple and highly efficient practical method for synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxo-octahydroxanthenes using SiO_2-Cl under solvent-free conditions. The notable features of this method are simple experimental procedure and excellent yields (80–96%), which make it a useful and attractive process for the synthesis of 14-substituted-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxo-octahydroxanthenes. We believe that this methodology will be a valuable addition to the existing methods.

Table IV Comparison of the effect of catalysts in synthesis of **3a**



Entry	Catalysis	Temp (°C)	Time (h)	Yield (%)	Reference
1	Sulfamic acid (10 mol%)	125	8	89	10
2	BF_3-SiO_2 (80 mg/mmol)	60	0.25	90	16
3	I_2 (20 mol%)	90	2.5	87	13
4	LiBr (15 mol%)	130	1	76	17
5	$Al(HSO_4)_3$ (50 mg/mmol)	125	0.5	86	18
6	Dowex-50W (400 mg/mmol)	100	1.5	78	19
7	$HClO_4$-SiO_2 (200 mg/mmol)	100	3.5	89	14
8	$NaHSO_4$-SiO_2 (10 mol%)	125	8	85	20
9	Cyanuric chloride (20 mol%)	110	0.6	94	12
10	Ceric sulfate (20 mol%)	100	2	88	21
11	SiO_2-Cl (250 mg/mmol)	110	3	93	The research

EXPERIMENTAL

NMR spectra were determined on a Bruker AV-300 spectrometer at room temperature using TMS as internal standard; coupling constants (*J*) were measured in Hz. Elemental analyses were performed by a Vario-III elemental analyzer. Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used throughout without further purification unless otherwise stated.

Preparation of SiO_2-Cl

To an oven-dried (120°C, vacuum) sample of silica gel (10 g) in a round-bottomed flask (250 mL) equipped with a condenser and a drying tube, thionyl chloride (40 mL) was added, and the mixture was refluxed for 48 h. The unreacted thionyl chloride was distilled off. The resulting white-grayish powder was flame-dried and stored in a tightly capped bottle.

Table V Preparation of 1,8-dioxo-octahydroxanthenes catalyzed by SiO_2-Cl[a]

Entry	R	Products	Time(h)	Yield(%)	Mp(°C) Found	Reported[ref.]
1	Ph	**6a**	3	89	201–203	204–205 [30]
2	4-$(CH_3)C_6H_4$	**6b**	3.5	87	220–221	217–218 [30]
3	4-$(MeO)C_6H_4$	**6c**	3.5	86	242–243	245–247 [30]
4	2-$(Cl)C_6H_4$	**6d**	4	87	243–245	224–226 [30]
5	4-$(Cl)C_6H_4$	**6e**	3	91	225–226	228–230 [30]
6	4-$(I)C_6H_4$	**6f**	4	89	242–244	

Typical Procedure: Preparation of 14-Substituted-14*H*-dibenzo[*a,j*] xanthenes and 1,8-Dioxo-octahydroxanthenes

To a mixture of β-naphthol or dimedone (2 mmol) and aldehyde (1 mmol), SiO_2-Cl (250 mg) was added. The mixture was stirred at 110°C for an appropriate time (Table III). After completion of the reaction (TLC), ethyl acetate (20 mL) was added, and the solid catalyst was removed by filtration. The solvent was evaporated, and the crude product was recrystallized from EtOH to afford the pure product **3** or **6**. All products were characterized by comparison of their physical data and ^{1}H NMR/^{13}C NMR data with those of authentic samples. The spectral data of some new 14-substituted-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxo-octahydroxanthenes are given below.

14-(4-Iodophenyl)-14*H*-dibenzo[*a,j*]xanthene (3m). White solid, mp >300°C. IR (KBr, cm^{-1}): 3432, 3022, 2918, 1635, 1590, 1243, 833, 802. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.60$ (s, 1H, ArCH), 7.32–7.80 (s, 14H, ArH), 8.22 (d, $J = 8.2$ Hz, 2H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): $\delta = 39.8$, 116.5, 118.9, 123.2, 125.1, 126.7, 129.6, 129.8, 130.8, 131.6, 131.9, 133.4, 144.0, 150.1. Anal. calcd for $C_{27}H_{17}IO$: C 66.96, H 3.54; found C 67.12, H 3.34.

9-(4-Iodophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthene-1,8(5*H*,9*H*)-dione (6f). White solid, mp 242–244°C. IR (KBr, cm^{-1}): 3446, 3022, 2923, 1650, 1592, 1355, 1262, 1211, 1150, 705. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.02$ (s, 6H, CH), 1.16 (s, 6H, CMe_2), 2.22–2.36 (q, $J = 16.2$ Hz, 4H, CH_2), 2.53 (s, 4H, CH_2), 4.76 (s, 1H, CH), 7.18 (d, $J = 8.2$ Hz, 2H, ArH), 7.36 (d, $J = 8.2$ Hz, 2H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): $\delta = 28.4$, 29.6, 31.8, 33.2, 41.6, 51.7, 116.8, 120.4, 130.8, 131.4, 143.9, 164.3, 192.8. Anal. calcd for $C_{23}H_{25}IO_3$: C 57.99, H 5.29; found C 58.14, H 5.20.

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