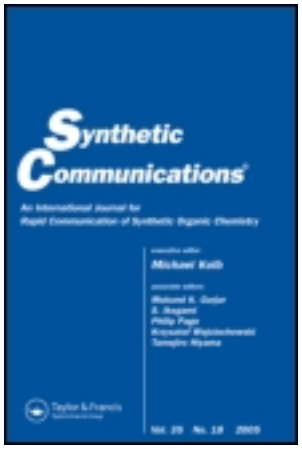

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CARO'S ACID–SILICA GEL–CATALYZED ONE-POT SYNTHESIS OF 12-ARYL-8,9,10,12-TETRAHYDROBENZO[a] XANTHEN-11-ONES

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The synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-ones from aldehyde, β-naphthol, AND dimedone in the presence of a catalytic amount of Caro's acid–silica gel in good yields under solvent-free conditions is reported.

Keywords: Aldehydes; dimedone; multicomponent reaction; β-naphthol; solvent-free; xanthen

INTRODUCTION

Multicomponent reactions (MCRs) have attracted considerable interest because of their exceptional synthetic and practical efficiency.[1] MCRs involve three or more starting materials reacting in a single flask to form a new product. One example of an MCR is a three-component, one-pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-ones.

The preparation of xanthenes, especially benzoxanthenes, has received significant attention in previous years because of the broad spectrum of their biological and pharmaceutical properties, such as antiviral,[2] antibacterial,[3] and anti-inflammatory[4] activities as well as efficacy in photodynamic therapy[5] technologies. A number of xanthene-based compounds are also available from plant sources.[6] Various methods have been reported for the synthesis of xanthenes and benzoxanthenes, including cyclocondensation of 2-hydroxyaromatic aldehydes with 2-tetralone,[7] trapping of benzynes by phenols,[8] and the reaction of 2-naphthol with aldehydes and formamide.[9]

However, these methodologies suffer from one or more disadvantages such as poor yield, lack of easy availability or preparation of the starting materials, prolonged reaction time, use of toxic organic solvents, and requirements for excess of reagents/catalysts, special apparatus, and harsh reaction conditions.

There is an increasing interest in the use of environmentally feasible reagents, particularly in solvent-free conditions. Avoiding organic solvents during reactions

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in organic synthesis leads to a clean, efficient, and economical technology, not only with the increased safety, simplicity of workup, and reduction of cost, but also increased amount of reactants can be achieved in the same equipment without huge modifications. Reactivity and sometimes selectivity may be enhanced without dilution.[10]

The syntheses of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-one derivatives involves the use of a number of catalysts such as *p*-toluenesulfonic acid (PTSA),[11] $Sr(OTf)_2$,[12] and I_2.[13]

Recently, the use of Caro's acid–silica gel (CA-SiO_2) as catalyst or promoter in organic synthesis has attracted great interest from many chemists. CA-SiO_2 can enhance the reactivity and selectivity of many types of reaction, such as oxidative coupling of thiols to disulfides,[14] conversion of thioamides into amides,[15] and carbonyl compounds from oximes.[16]

RESULTS AND DISCUSSION

In connection with our ongoing work on the synthesis of heterocyclic compounds with CA-SiO_2,[17] we report a facile procedure for preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-one derivatives with CA-SiO_2 as a nontoxic, inexpensive, and easily available reagent (Scheme 1).

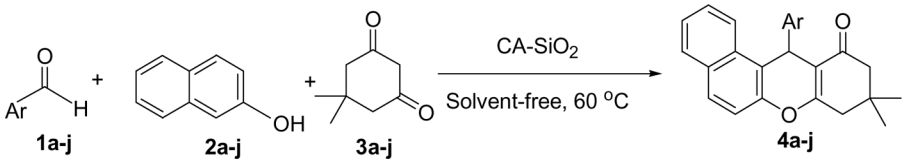
To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from room temperature to 70 °C. We found that the yield of product **4** was improved and the reaction time was shortened as the temperature was increased to 60 °C. The yield plateaued when temperature was further increased to 70 °C (Table 1, entry 5). Therefore, the most suitable reaction temperature is 60 °C.

To find the optimum quantity of Caro's acid–silica gel, the reaction of aromatic aldehyde, β-naphthol, and dimedone was carried out under thermal solvent-free conditions, using different quantities of Caro's acid–silica gel (Table 2).

Under the optimized reaction condition, a series of derivatives were synthesized (Table 3).

We found that with several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *meta* and *para* positions, the reaction proceeded very efficiently in all cases, but for electron-withdrawing substituents, shorter reaction times are needed to drive the reaction to completion.

All reaction products were known and characterized by ^1H NMR, infrared (IR), gas chromatography (GC)–mass, and melting points by comparing them with those obtained from authentic samples.



Scheme 1. Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-one.

Table 1. Optimization of temperature for the reaction of benzaldehyde, β-naphthol, and dimedone

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	30	70	55
2	40	65	66
3	50	50	72
4	60	45	80
5	70	55	75

[a]Yields refer to the pure isolated products.

Table 2. Optimization amount of CA-SiO_2 for the reaction of benzaldehyde, β-naphthol, and dimedone

Entry	Catalyst (g)	Time (min)	Yield (%)[a]
1	0.06	55	65
2	0.08	50	73
3	0.1	45	80

[a]Yields refer to the pure isolated products.

Table 3. Synthesis of compound **4a–j** by Caro's acid

Entry[a]	Ar	Product	Time (min)	Yield (%)[b] of **4**	Mp (°C)
1	C_6H_5	**4a**	45	80	149–152[18]
2	4-HO-C_6H_4	**4b**	40	75	223–226[18]
3	4-Me-C_6H_4	**4c**	50	80	175–177[18]
4	4-OMe-C_6H_4	**4d**	55	80	203–205[18]
5	4-NO_2-C_6H_4	**4e**	35	90	175–176[18]
6	3-NO_2-C_6H_4	**4f**	40	85	166–168[18]
7	2-NO_2-C_6H_4	**4 g**	45	80	224–226[18]
8	4-Cl-C_6H_4	**4 h**	30	90	188–189[18]
9	2-Cl-C_6H_4	**4i**	35	87	179–182[18]
10	4-Br-C_6H_4	**4j**	35	89	185–187[13]

[a]All the products were characterized by comparison of spectroscopic data and melting points with those reported in the literature.
[b]Yield refers to the pure isolated products.

CONCLUSION

In conclusion, we have described a simple, one-pot, three-component reaction involving aldehydes, β-naphthol, and dimedone for the synthesis of a series of 12-aryl-8,9,10,12-tetrahydrobenzo[a] xanthen-11-one derivatives under solvent-free conditions. Particularly valuable features of this method include the greater yields of the products, short times, an easy workup procedure, and the use of cheap, nontoxic, and easily available CA-SiO_2, which make it a useful and attractive process for the synthesis of these important compounds.

EXPERIMENTAL

Chemicals and Apparatus

All the chemicals were purchased from Merck Company. Melting points were measured using a Barnstead Electrothermal instrument. GC/mass analysis was performed using Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal. IR spectra were recorded as KBr discs on the Fourier transform (FT)-IR Brucker Tensor 27 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AQS-Avance spectrometer at 300 MHz, using TMS as an internal standard.

Representative Procedure for the Synthesis of 12-Aryl-8,9,10,12-tetrahydrobenzo[a] Xanthen-11-ones Using CA-SiO_2

A mixture of aromatic aldehyde (1 mmol), β-naphthol (1 mmol), dimedone (1.2 mmol), and CA-SiO_2 (0.1 gr) was magnetically stirred at 60 °C for the appropriate time as indicated in Table 3. The reaction was followed by thin-layer chromatography (TLC). After completion, the reaction mixture was washed with $CHCl_3$. For further purification, it was crystallized with ethanol to afford the pure product.

General Procedure for the Preparation of Catalyst

In small portions of potassium persulfate (4.5 g) were added to ice-cooled 98% sulfuric acid (4.7 g) with stirring; to this, crushed ice (13 g) and water (4 g) were added. The temperature was kept below 15 °C. Silica gel (5 g, TLC grade, Kieselgel 60 G, particle size 15 μm) was added in portions to the mixture, and the mixture was stirred for 4 h in an ice-water bath. The mixture was then filtered under suction and dried in a desiccator to give a white free-flowing power.[14]

Selected Spectroscopic Data

9,9-Dimethyl-12-phenyl-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4a). White solid; mp 149–152 °C; IR (KBr): 3060, 2890, 1654, 1380, 1240, 1185, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 1.11 (s, 3H), 2.26 (d, $J = 16.2$ Hz, 1H), 2.33 (d, $J = 16.2$ Hz, 1H), 2.57 (s, 2H), 5.70 (s, 1H), 7.42–7.04 (m, 8H), 7.78–7.74 (m, 2H), 7.99 (d, $J = 8.1$ Hz, 1H).[18]

12-(4-Hydroxyphenyl)-9,9-dimethyl-12-phenyl-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4b). White solid; mp 223–226 °C; IR (KBr): 3309, 2963, 1645, 1578, 1384, 1230, 1183, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (s, 3H), 1.12 (s, 3H), 2.27 (d, $J = 16.2$ Hz, 1H), 2.34 (d, $J = 16.2$ Hz, 1H), 2.56 (s, 2H), 5.49 (s, 1H), 5.63 (m, 1H), 6.61 (d, $J = 8.4$ Hz, 2H), 7.45–7.15 (m, 5H), 7.78–7.73 (m, 2H), 7.98 (d, $J = 8.1$ Hz, 1H).[18]

9,9-Dimethyl-12*p*-tolyl-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4c). White solid; mp 175–177 °C; IR (KBr): 3070, 2951, 2863, 1645, 1597, 1373, 1228, 1070, 818 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.89 (s, 3H), 1.06 (s, 3H), 2.14 (s, 3H), 2.30 (d, $J = 16.2$ Hz, 1H), 2.41 (d, $J = 16.2$ Hz, 1H), 2.60 (d, $J = 17.4$ Hz,

1H), 2.72 (d, $J = 17.4$ Hz, 1H), 5.52 (s, 1H), 6.98 (d, $J = 7.2$ Hz, 2H), 7.17–7.15 (m, 2H), 7.46–7.42 (m, 3H), 8.04–7.88 (m, 3H).[18]

12-(4-Methoxyphenyl)-9,9-dimethyl-12-phenyl-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4d). White solid; mp 203–205 °C; IR (KBr): 3062, 2955, 1648, 1232, 1175, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.97 (s, 3H), 1.11 (s, 3H), 2.26 (d, $J = 16.2$ Hz, 1H), 2.33 (d, $J = 16.2$ Hz, 1H), 2.55 (s, 2H), 3.68 (s, 3H), 5.65 (s, 1H), 6.70 (d, $J = 8.4$ Hz, 2H), 7.44–7.22 (m, 5H), 7.77–7.72 (m, 2H), 7.99 (d, $J = 8.1$ Hz, 1H).[18]

9,9-Dimethyl-12-(4-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4e). White solid; mp 175–176 °C; IR (KBr): 3069, 2958, 1593, 1516, 1374, 1225, 1167, 1064, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.94 (s, 3H), 1.13 (s, 3H), 2.26 (d, $J = 16.2$ Hz, 1H), 2.36 (d, $J = 16.2$ Hz, 1H), 2.59 (s, 2H), 5.81 (s, 1H), 7.52–7.33 (m, 5H), 7.82–7.79 (m, 3H), 8.04 (d, $J = 8.4$ Hz, 2H).[18]

9,9-Dimethyl-12-(3-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4f). White solid; mp 166–168 °C; IR (KBr): 3071, 2955, 1528, 1374, 1225, 1169, 1025, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.95 (s, 3H), 1.13 (s, 3H), 2.26 (d, $J = 16.2$ Hz, 1H), 2.36 (d, $J = 16.2$ Hz, 1H), 2.61 (s, 2H), 5.81 (s, 1H), 7.47–7.35 (m, 4H), 7.95–7.80 (m, 5H), 8.10 (s, 1H).[18]

9,9-Dimethyl-12-(2-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4g). White solid; mp 224–226 °C, IR (KBr): 3069, 2957, 1526, 1369, 1225, 1172, 1026, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.86 (s, 3H), 1.11 (s, 3H), 2.19 (d, $J = 16.2$ Hz, 1H), 2.29 (d, $J = 16.2$ Hz, 1H), 2.52 (d, $J = 17.4$ Hz, 1H), 2.60 (d, $J = 17.4$ Hz, 1H), 6.58 (s, 1H), 7.46–7.03 (m, 6H), 7.86–7.77 (m, 3H), 8.56 (d, $J = 8.1$ Hz, 1H)[18].

12-(4-Chlorophenyl)-9,9-dimethyl-12-(2-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4h). White solid; mp 188–189 °C; IR (KBr): 3070, 2925, 1645, 1374, 1225, 1172, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96 (s, 3H), 1.12 (s, 3H), 2.26 (d, $J = 16.2$ Hz, 1H), 2.34 (d, $J = 16.2$ Hz, 1H), 2.56 (s, 2H), 5.67 (s, 1H), 7.45–7.11 (m, 7H), 7.79–7.75 (m, 2H), 7.90 (d, $J = 8.1$ Hz, 1H).[18]

12-(2-Chlorophenyl)-9,9-dimethyl-12-(2-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4i). White solid; mp 179–182 °C; IR (KBr): 3075, 2930, 1645, 1373, 1227, 1175, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.13 (s, 3H), 2.24 (d, $J = 16.2$ Hz, 1H), 2.34 (d, $J = 16.2$ Hz, 1H), 5.98 (s, 1H), 7.07–6.96 (m, 2H), 7.49–7.26 (m, 5H), 7.76–7.72 (m, 2H), 8.23 (d, $J = 8.4$ Hz, 1H).[18]

12-(4-Bromophenyl)-9,9-dimethyl-12-(2-nitrophenyl)-8,9,10,12-tetrahydro-benzo[a] xanthen-11-one (4j). White solid; mp 185–187 °C; IR (KBr): 2962, 2868, 1643, 1593, 1483, 1375, 1145, 1006, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.97 (s, 3H), 1.12 (s, 3H), 2.25 (d, $J = 16.2$ Hz, 1H), 2.30 (d, $J = 16.2$ Hz, 1H), 2.57 (s, 2H), 5.67 (s, 1H), 7.20–7.46 (m, 7H), 7.78 (t, $J = 7.6$ Hz, 2H), 7.89 (d, $J = 8.4$ Hz, 1H).

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