Methanesulfonic Acid-Catalyzed One-Pot Synthesis of 12-Aryl or 12-Alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one Derivatives

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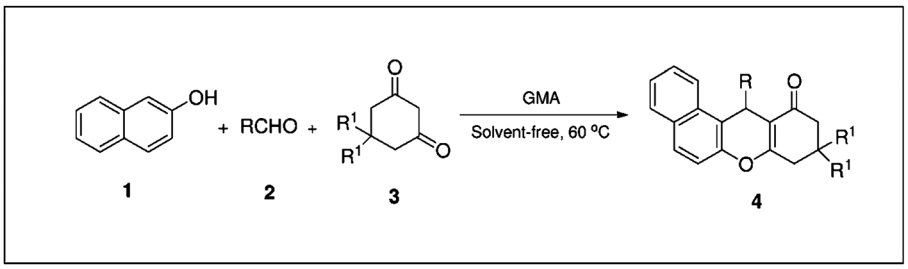

An efficient synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives has been developed under solvent-free conditions by one-pot condensation of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds in the presence of a catalytic amount of methanesulfonic acid. The protocol has advantages of mild condition, short reaction time, high yield, and operational simplicity.

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INTRODUCTION

Xanthene derivatives are important heterocyclic compounds that possess diverse biological and therapeutic properties such as antibacterial, antiviral, antifungal, antiproliferative, anticancer, and anti-inflammatory activities [1–5]. Among this class of molecules, xanthone is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activities [6,7]. Several elegant strategies for the synthesis of tetrahydrobenzo[*a*]xanthen-11-ones involving different types of catalysts have been reported [8–19]. The above methods show varying degrees of successes as well as limitations such as prolonged reaction times, low yields, use of toxic organic solvents, special apparatus, harsh reaction conditions, and complex work-up procedures. Keeping in view the disadvantages associated with reported protocols as well as increasing importance of tetrahydrobenzo[*a*] xanthen-11-ones in pharmaceutical and industrial chemistry, there still remains a high demand for the development of an efficient, low-cost, and eco-friendly protocol to construct this type of heterocyclic compounds.

Multicomponent reactions (MCRs) have attracted considerable interest in combinatorial and medicinal chemistry because they offer rapid and convergent construction of complex molecular skeletons from common staring materials in one-pot synthesis [20–24]. In addition, organic reactions that were performed under solvent-free conditions may lead to high efficiency and selectivity, reduction of cost, easy separation and purification, and eco-friendliness [25–27]. Therefore, if a one-pot MCR could be carried out under solvent-free conditions, it may be most efficient and eco-friendly.

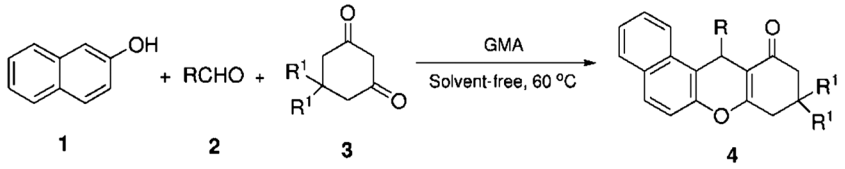
During the past decade, methanesulfonic acid (GMA) has been reported as an inexpensive, readily biodegradable, nontoxic, commercially available, and environmentally benign catalyst for various organic transformations [28–32]. In the lights of our success in developing several catalytic system for organic reactions [33–38], herein, we wish to report a novel and high yielding solvent-free method for the preparation of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives in the presence of GMA (Scheme 1).

RESULTS AND DISCUSSION

In a preliminary study, 4-chlorobenzaldehyde (**1q**) was treated with 2-naphthol (**2**) and 5,5-dimethyl-1,3-cyclohexanedione in the presence of 10 mol % of GMA. The reaction went to completion in 30 min at 60°C under solvent-free conditions, and the product 12-(4-chloro-phenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo [*a*]xanth-en-11-one (**4q**) was obtained in 97% yield. In the absence of catalyst, the desired product could not be obtained under similar reaction conditions, even after a long time (2 h).

To explore the scope and limitations of this protocol, a range of aldehydes were reacted with 2-naphthol and 5,5-dimethyl-1,3-cyclo-hexanedione under the above-mentioned conditions. The results are displayed in Table 1.

Scheme 1. Synthesis of tetrahydrobenzo[*a*]xanthen-11-ones catalyzed by GMA.



As it can be seen from Table 1, when aromatic aldehydes were applied, all reactions proceed efficiently and the corresponding products were obtained in high to excellent yields. The electronic effects and the nature of the substituents on the aldehydes show some effects in terms of yields and reaction times. With aromatic aldehydes with electron-withdrawing groups as substrates, the reaction time was shorter and the reaction proceeded well at faster rate compared with aromatic aldehydes with electron-donating groups. Aliphatic aldehydes also afforded the desired products in slightly lower yields and required longer reaction times. Also, the same reaction when carried out by replacing 5,5-dimethyl-1,3-cyclo-hexanedione with cyclohexane-1,3-dione the similar results were obtained.

Finally, to ascertain the effectiveness of this catalyst relative to those previously used, the synthesis of **4q** was considered as a representative example (Table 2). As demonstrated in Table 2, GMA is an equally or more efficient catalyst for this three-component reaction in terms of the reaction temperature, rate, and yields of product.

In conclusion, we have provided an efficient three-component route using readily available starting materials for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives catalyzed by GMA. This new strategy has some advantages, such as high yields of products, short reaction time, solvent-free conditions, and inexpensive and the use of readily available catalyst.

EXPERIMENTAL

Infrared (IR) spectra were obtained with a Shimadzu FTIR-8900 spectrometer with KBr plates. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian 400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on Vario EL III CHNOS elemental analyzer.

Representative procedure for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one. A mixture of 4-chlorobenzaldehyde (2 mmol), 2-naphthol (2mmol), 5,5-dimethyl-1,3-cyclohexanedione (2.5 mmol), and GMA (19 mg, 0.2 mmol) was heated at 60°C. The completion of reaction was monitored by thin-layer chromatography, and then the mixture was cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3× 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and the resulting

Table 1

Scope for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-ones catalyzed by GMA.

					m.p. (°C)	
Entry	R	R^1	Time (min)	Yield (%)[a]	Found	Reported
a	Ph	H	35	88	190–191	192–193 [8]
b	4-MeC_6H_4	H	35	90	205–206	206–207 [8]
c	3,4-$Me_2C_6H_3$	H	30	86	175–176	174–175 [14]
d	4-$MeOC_6H_4$	H	35	89	180–181	181–182 [8]
e	2-ClC_6H_4	H	40	87	244–246	243–245 [8]
f	3-ClC_6H_4	H	30	92	211–212	210–211 [8]
g	4-ClC_6H_4	H	30	93	208–210	208–209 [8]
h	3-$NO_2C_6H_4$	H	30	94	235–236	234–235 [8]
i	4-$NO_2C_6H_4$	H	30	92	236–237	236–237 [8]
j	CH_3CH_2	H	50	74	Oil	Oil [13]
k	C_6H_{11}	H	50	72	185–186	186–187 [13]
l	Ph	Me	30	91	150–151	151–152 [8]
m	4-MeC_6H_4	Me	35	90	175–176	176–177 [8]
n	4-$MeOC_6H_4$	Me	35	89	205–206	206–207 [8]
o	4-OHC_6H_4	Me	40	88	209–211	210 [14]
p	3,4-$Cl_2C_6H_3$	Me	35	91	181–182	
q	4-ClC_6H_4	Me	30	97	185–187	185–186 [8]
r	4-$NO_2C_6H_4$	Me	30	92	175–176	176–177 [8]
s	CH_3CH_2	Me	50	78	Oil	Oil [14]
t	$(CH_3)_2CH$	Me	50	75	115–116	116–117 [8]

[a]Isolated yields.

Table 2

Comparison of the efficiency of GMA with other catalysts for the synthesis of **4q**.

Entry	Catalyst	Reaction condition	Time (min)	Yield (%)	References
1	Cyanuric chloride	Solvent free, 80°C	30	92	[8]
2	$NaHSO_4{\cdot}SiO_2$	1,2-Dichloroethane, reflux	300	91	[9]
3	I_2	Solvent free, 60°C	60	95	[10]
4	Tungstophosphoric acid	Solvent free, 60°C	60	92	[11]
5	$HClO_4$-SiO_2	Solvent free, 80°C	60	95	[12]
6	$Sr(OTf)_2$	1,2-Dichloroethane, 80°C	300	88	[13]
7	Cerium ammonium nitrate	Solvent free, 120°C	30	92	[14]
8	*p*-Toluenesulfonic acid	[bmin]BF_4, 80°C	120	85	[15]
9	Caro's acid–silica gel	Solvent free, 60°C	30	90	[16]
10	Tetrabutylammonium fluoride	H_2O, reflux	210	92	[17]
11	$InCl_3$	Solvent free, 120°C	30	80	[18]
12	P_2O_5	Solvent free, 120°C	40	76	[18]
13	$HClO_4/SiO_2$	Solvent free, 80°C	60	95	[19]
14	GMA	Solvent free, 60°C	30	97	This work

product was purified by silica gel column chromatography (10% ethyl acetate in *n*-hexane as eluent) to afford pure product. The spectral and analytical data of some representative compounds are given below.

12-(4-Chlorophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (3g). This compound was obtained as yellow needles, m. p. 208–210°C. IR: 3087, 2869, 1664, 1616, 1488, 1458, 1382, 1359, 1201, 1172, 1128, 1085, 1012, 958, 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93–2.10 (m, 2H), 2.32–2.43 (m, 2H), 2.65–2.80 (m, 2H), 5.65 (s, 1H), 7.05–7.50 (m, 7H), 7.78–7.88 (m, 3H). *Anal.* Calcd. for $C_{23}H_{17}ClO_2$: C, 76.56; H, 4.75. Found: C, 76.65; H, 4.90.

12-(4-Hydroxyphenyl)-9,9-dimethyl-8,9,10,12-tetra-hydrobenzo [*a*]xanthen-11-one (3o). This compound was obtained as yellow needles, m.p. 209–211°C. IR: 3411, 3149, 2952, 1651, 1595, 1512, 1465, 1398, 1228, 1143, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.12 (s, 3H), 2.21 (d, J = 16.0 Hz, 1H), 2.31 (d, J = 16.0 Hz, 1H), 2.57 (s, 2H), 5.45 (s, 1H), 5.60 (s, 1H), 6.54 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.30–7.46 (m, 2H), 7.70–7.92 (m, 3H). *Anal*. Calcd. for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.20; H, 6.18.

12-(3,4-Dichlorophenyl)-9,9-dimethyl-8,9,10,12-tetra-hydrobenzo [*a*]xanthen-11-one (3p). This compound was obtained as yellow needles, m.p. 181–182°C; IR: 3134, 2960, 1649, 1618, 1596, 1465, 1398, 1234, 1199, 1164, 1026, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.12 (s, 3H), 2.16–2.29 (m, 2H), 2.57 (s, 2H), 5.67 (s, 1H), 7.18–7.48 (m, 5H), 7.78–7.85 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H); *Anal*. Calcd. for $C_{25}H_{20}C_{12}O_2$: C, 70.93; H, 4.76. Found: C, 70.85; H, 4.94.

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