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An Efficient One-Pot Synthesis of Tetrahydrobenzo Xanthen-11-one Derivatives Catalyzed by P_2O_5 under Solvent Free Conditions

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The present study highlights the catalytic activity of P_2O_5 for the one pot synthesis of tetrahydrobenzoxanthen-11-one derivatives from dimedone and various aromatic aldehydes under solvent free conditions. The present methodology offers several advantages such as clean and mild reaction, short reaction time, low environmental impact, wide substrate scope, high yield and purity.

Keywords: P_2O_5, One-pot synthesis, Solvent free conditions, Xanthene.

INTRODUCTION

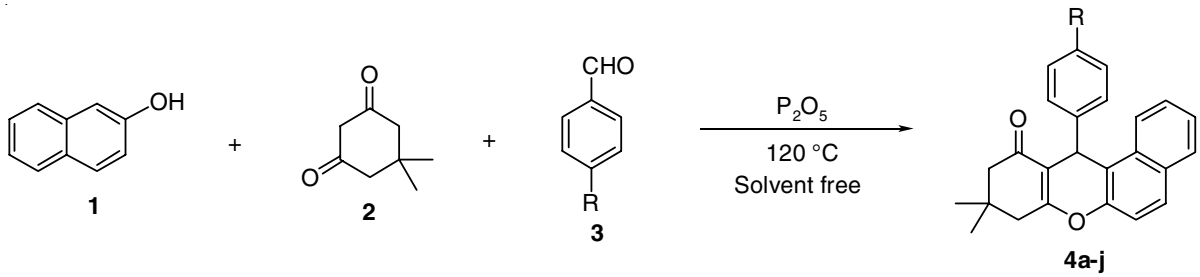
Xanthene derivatives are very important class of organic molecules because they have a wide range of biological and pharmaceutical properties such as antibacterial [1], antiviral [2], antiinflammatory [3], antidepressant, antimalarial agents and these are being utilized as antagonists [4] for paralyzing action of zoxazolamine [5] and in photodynamic therapy [6]. Furthermore, these compounds can be used as dyes in laser technologies [7] and pH sensitive fluorescent materials for visualization of biomolecules [8]. In particular, xanthene diones constitute a key structural motif in a number of natural products [9] and have been used as versatile synthons because of inherent reactivity of inbuilt pyran ring [10]. Synthesis of xanthene diones is a continuing hot topic because these moieties are active pharmaceutical ingredients (API's) and also valuable reactive intermediates for both synthetic and medicinal chemists.

A survey of the literature reveals that various methods have been reported for the preparation of xanthenes and substituted xanthenes. The classical method for the synthesis of tetrahydrobenzo xanthen-11-one derivatives involves the condensation of appropriate active methylene compounds with various substituted aromatic aldehydes. For this purpose, two molecules of dimedone (5,5-dimethylcyclohexane-1,3-dione) was reacted with various aromatic aldehydes [11] by using different Lewis acid catalysts such as triethyl benzyl ammonium chloride [12], *p*-dodecylbenzenesulfonic acid [13], diammonium hydrogen phosphate [14] under various conditions, sulfonic acid under ultrasonic irradiation [15], ionic liquids [16], Ambedrlyst-1s [17], $NaHSO_4$-SiO_2 or silica chloride [18], phosphomolybdic acid supported on silica gel [19], nano-sized MCM-41-SO_3H under ultrasonic irradiation [20], sulfonic acid on silica gel [21], Dowex-50W ion exchange resin under solvent-free conditions [22] $HClO_4$-SiO_2 [23], ZnO and ZnO-acetyl chloride [24] and heteropoly acid supported MCM-41 [25].

However, the methods reported serve their best but they still suffer from certain drawbacks such as long reaction times, low yields, use of toxic transition metals as catalysts, use of hazardous organic solvents and tedious workup procedures. Keeping the above facts in mind and as a part of our ongoing research, herein we report the first time use P_2O_5 for the efficient synthesis of tetrahydrobenzo xanthen-11-one derivatives. This method offers advantages such as short reaction time, easy to work-up procedure and excellent yields (**Scheme-I**).

EXPERIMENTAL

Synthesis of tetrahydrobenzo xanthen-11-one derivatives: A mixture of 5,5-dimethyl-1,3-cyclohexanediones, substituted aromatic aldehyde, 2-naphthol and P_2O_5 as catalyst was stirred at 120 °C in the oil bath. The reaction was monitored by TLC. The reaction was cooled to room temperature after completion of the reaction. The solid product was filtered, washed with hot water and finally recrystallized from ethanol. All the synthesized products were characterized by IR, NMR and mass spectroscopic data for their structure and their melting points were compared with authentic samples.



Scheme-I: Synthesis of xanthenes catalyzed by P_2O_5 under solvent free conditions

Spectral data for selected compounds

9,10-Dihydro-9,9-dimethyl-12-phenyl-8*H*-benzo[a]-xanthen-11(12*H*)-one (4a): IR (KBr, ν_{max}, cm^{-1}): 3148, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 4H, $2CH_2$), δ 4.30 (s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 6H, $2CH_3$), MS (*m/z*): 354 [M+].

9,10-Dihydro-9,9-dimethyl-12-*p*-tolyl-8*H*-benzo[a]-xanthen-11(12*H*)-one (4b): IR (KBr, ν_{max}, cm^{-1}): 3146, 3112, 1732; ^{1}H NMR (DMSO-d_6): δ 2.15-2.27 (s, 4H, $2CH_2$), δ 4.82 (s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.9 (s, 9H, $3CH_3$), MS (*m/z*): 369 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-hydroxyphenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4c): IR (KBr, ν_{max}, cm^{-1}): 3251, 3136, 3112, 1722; ^{1}H NMR (DMSO-d_6): δ 2.25-2.27 (s, 4H, $2CH_2$), δ 4.26 (s, 1H), 6.4-7.5 (m, 12H, Ar-H), 2.9 (s, 9H, $3CH_3$), 11.2 (s, 1H, OH), MS (*m/z*): 371 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-methoxyphenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4d): IR (KBr, ν_{max}, cm^{-1}): 3138, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 4H, $2CH_2$), δ 4.30(s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 9H, $3CH_3$), MS (*m/z*): 384 [M+].

9,10-Dihydro-9,9-dimethyl-12-[4-(dimethylamino)-phenyl]-8*H*-benzo[a]xanthen-11(12*H*)-one (4e): IR (KBr, ν_{max}, cm^{-1}): 3248, 3112, 1726; ^{1}H NMR (DMSO-d_6): δ 2.15-2.24 (s, 4H, $2CH_2$), δ 4.30(s, 1H), 6.6-7.7 (m, 12H, Ar-H), 2.28 (s, 12H, $4CH_3$), MS (*m/z*): 398 [M+].

9,10-Dihydro-9,9-dimethyl-12-[4-(diethylamino)-phenyl]-8*H*-benzo[a]xanthen-11(12*H*)-one (4f): IR (KBr, ν_{max}, cm^{-1}): 3148, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 8H, $4CH_2$), δ 4.30(s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 12H, $4CH_3$), MS (*m/z*): 426 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-bromophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4g): IR (KBr, ν_{max}, cm^{-1}): 3138, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 4H, $2CH_2$), δ 4.32(s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 6H, $2CH_3$), MS (*m/z*): 434 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-fluorophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4h): IR (KBr, ν_{max}, cm^{-1}): 3158, 3130, 1725; ^{1}H NMR (DMSO-d_6): δ 2.25-2.64 (s, 4H, $2CH_2$), δ 4.38 (s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 6H, $2CH_3$), MS (*m/z*): 372 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-nitrophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4i): IR (KBr, ν_{max}, cm^{-1}): 3148, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 4H, $2CH_2$), δ 4.30 (s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 6H, $2CH_3$), MS (*m/z*): 414 [M+].

9,10-Dihydro-9,9-dimethyl-12-(4-isopropylphenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (4j): IR (KBr, ν_{max}, cm^{-1}): 3148, 3110, 1728; ^{1}H NMR (DMSO-d_6): δ 2.05-2.14 (s, 4H, $2CH_2$), δ 4.30 (s, 1H), 6.5-7.5 (m, 12H, Ar-H), 2.8 (s, 6H, $4CH_3$), 3.2 (d, 6H, $2CH_3$), 3.5 (q, 1H, CH), MS (*m/z*): 397 [M+].

RESULTS AND DISCUSSION

Literature survey revealed that there are few reports on the use of P_2O_5 as a catalyst in the synthesis of tetrahydrobenzo-xanthen-11-one derivatives under solvent-free reaction [26,27]. In continuation of our interest in the area of clean synthesis under solvent-free conditions for the development of new synthetic methodologies herein, we reported a simple, efficient and one-pot reaction of dimedone, 2-naphthol and aldehydes using P_2O_5 at 120 °C for the preparation of tetrahydrobenzo-xanthen-11-one derivatives (**4a-j)** in high yields (**Scheme-I**). The different reaction time carried out in presence of P_2O_5 catalyst, percentage of the yield and melting points are presented in Table-1.

TABLE-1
REACTION OF DIFFERENT SUBSTRATE
UNDER OPTIMIZED CONDITION

Entry	R	Time (min)	Yield (%)	m.p. (°C)
4a	H	5	95	202-204
4b	$-CH_3$	15	85	215-217
4c	-OH	30	90	220-222
4d	$-OCH_3$	30	80	230-232
4e	$-NMe_2$	15	90	224-226
4f	$-NEt_2$	15	90	224-226
4g	-Br	20	91	230-232
4h	-F	12	92	223-225
4i	$-NO_2$	15	95	219-221
4j	$CH(CH_3)_2$	25	88	238-239

Initially, a blank reaction with benzaldehyde, dimedone and 2-naphthol (mol ratio 1:1:1) at 120 °C without P_2O_5 was performed in order to establish the real effectiveness of the catalyst and the results showed that the desired product was not formed even after 12 h of heating. We then focused on optimizing the catalyst loading percentage. In order to evaluate the most appropriate catalytic percentage, a model reaction using benzaldehyde and dimedone (mole ratio 1:2) was carried out using 0, 5, 10, 15 and 20 mol % of P_2O_5 at different temperatures under solvent-free conditions (Table-2). It was found that 15 mol % of P_2O_5 showed a maximum yield in minimum time at 120 °C (Table-3).

Conclusion

In the present work, it is found that P_2O_5 is the most efficient catalyst with respect to the reaction time and temperature and exhibited broad applicability in terms of yields.

TABLE-2
EFFECT OF TEMPERATURE ON RATE OF REACTION

Entry	Temperature (± 5 °C)	Yield (%)
1	40	10
2	60	49
3	80	76
4	120	96

Reaction conditions: 2-Naphthol (20 mmol); dimedone (20 mmol); benzaldehyde (20 mmol); P_2O_5 = 10 % weight of substrate; time = 15 min).

TABLE-3
EFFECT OF CATALYST ON SYNTHESIS OF TETRAHYDROBENZO XANTHEN-11-ONE DERIVATIVES

Entry	Catalyst (%)	Yield (%)	Time (min)
1	0	0	24 h
2	5	89	18
3	10	96	15
4	15	95	16
5	20	94	20

Reaction conditions: 2-Naphthol (20 mmol); dimedone (20 mmol); benzaldehyde (20 mmol); temp. = 120 °C, time = 15-30 min (reaction completion on TLC)

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