One-pot synthesis of tetrahydrobenzo[*a*]xanthen-11-one derivatives catalyzed by ruthenium chloride hydrate as a homogeneous catalyst

Khalil Tabatabaeian, Alireza Khorshidi, Manouchehr Mamaghani, Ali Dadashi, and Milad Khoshnood Jalali

Abstract: Three-component cyclocondensation of β-naphthol, aldehydes, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) was catalyzed efficiently by ruthenium chloride hydrate under mild reaction conditions to afford 12-aryl or alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives in good to excellent yields.

Key words: ruthenium, one-pot synthesis, tetrahydrobenzo[*a*]xanthen-11-one.

Résumé : La cyclocondensation à trois composants du β-naphtol, d'aldéhydes et de 5,5-diméthylcyclohexane-1,3-dione (dimédone) est catalysée d'une façon efficace par l'hydrate du chlorure de ruthénium, dans des conditions douces, pour conduire à la formation de dérivés 12-aryl- ou 12-alkyl- de la 8,9,10,12-tétrahydrobenzo[*a*]xanthén-11-one, avec des rendements allant de bons à excellents.

Mots-clés : ruthénium, synthèse monotope, tétrahydrobenzo[*a*]xanthén-11-one.

[Traduit par la Rédaction]

Introduction

In recent years, multicomponent reactions (MCRs) have attracted great attention from research groups working in medicinal chemistry, drug discovery, and materials science as they furnish the desired products in a single operation without isolating the intermediates. Simple procedures, facile execution, atom economy, and high selectivity are among the described advantages of multicomponent reactions.[1–5]

Developing ways to synthesize xanthenes and benzoxanthenes has been of considerable interest because these compounds possess antiviral,[6] antibacterial,[7] and anti-inflammatory properties.[8] Such compounds are also utilized for antagonism of the paralyzing action of zoxazolamine,[9] and can also be employed as dyes,[10] as pH-sensitive fluorescent materials for the visualization of biomolecules,[11] and in cancer therapy.[12] In addition, these heterocyclic compounds are structural key units in several natural products.[13] Xanthone derivatives are also found abundantly in a variety of natural products and exhibit various biological properties.[14,15] Synthetic tetrahydrobenzo[*a*]xanthen-11-ones have been prepared through three-component reaction of β-naphthol, aldehydes, and 1,3-dicarbonyl compounds in the presence of catalysts such as $BF_3{\cdot}Et_2O$,[16] $NaHSO_4{\cdot}SiO_2$,[17] strontium triflate ($Sr(OTf)_2$),[18] *p*-toluenesulfonic acid (pTSA),[19] indium trichloride ($InCl_3$),[20] phosphorous pentoxide (P_2O_5),[20] I_2,[21] tetrabutylammonium fluoride (TBAF),[22] HBF_4-SiO_2,[23] dodecatungstophosphoric acid ($H_3PW_{12}O_{40}$),[24] ceric ammonium nitrate (CAN),[25] 2,4,6-trichloro-1,3,5-triazine (TCT),[26] and $HClO_4$-SiO_2.[27] Several of these methodologies, however, suffer from severe drawbacks including long reaction times and toxic solvents,[16–18,22] the use of expensive reagents,[19] drastic conditions for catalyst preparation,[27] the use of a toxic catalyst,[21] and the requirement of a large or stoichiometric amount of catalysts.[20] Therefore, to avoid these limitations, the discovery of a new and efficient catalyst for preparation of these important molecules is of prime interest.

Recently, we have been involved in the study of the catalytic activity of ruthenium towards organic reactions such as the condensation of indoles and aldehydes,[28] oxidation of aromatic and heteroaromatic compounds,[29] double-conjugate 1,4-addition to enones,[30] nucleophilic addition to epoxides,[31] oxidative trimerization of indoles,[32] and Michael addition of indoles to hormone steroids.[33] As a matter of fact, many organic transformations that involve ruthenium species as catalyst are known and well-documented.[34–36] In continuation of our investigation in this context, hereby, we introduce a simple and efficient method for the synthesis of tetrahydrobenzo[*a*]xanthen-11-ones from one-pot condensation of β-naphthol, aldehydes, and dimedone in the presence of ruthenium chloride hydrate under mild reaction conditions.

Results and discussion

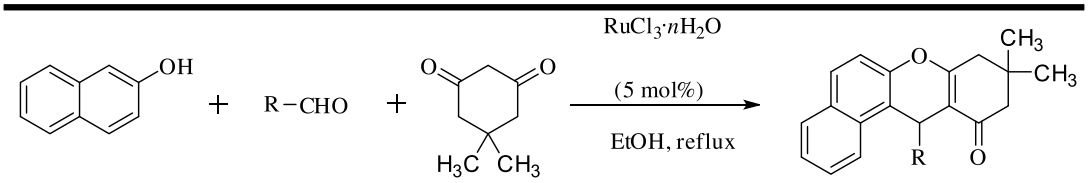
Typical results of the ruthenium-catalyzed cyclocondensation of β-naphthol, aldehydes, and 5,5-dimethylcyclohexane-1,3-dione are shown in Table 1. In an optimized procedure, with respect to the catalyst concentration, choice of solvent,

Received 6 November 2010. Accepted 15 February 2011. Published at www.nrcresearchpress.com/cjc on 5 May 2011.

K. Tabatabaeian, A. Khorshidi, M. Mamaghani, A. Dadashi, and M.K. Jalali. Department of Chemistry, Faculty of Sciences, University of Guilan, P. O. Box 41335-1914, Iran.

Corresponding author: K. Tabatabaeian (e-mail: Taba@guilan.ac.ir).

Table 1. $RuCl_3 \cdot nH_2O$ catalyzed synthesis of 12-aryl or alkyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones.



1 **2** **3** (**4a – 4m**)

Entry	R	Time (min)	Product	Yield (%)[a]	Mp (°C) Found	Mp (°C) Reported
1	C_6H_5	30	**4a**	88[b]	148–151	149–150
2	4-$NO_2C_6H_4$	30	**4b**	92[b]	177–180	178–180
3	3-$NO_2C_6H_4$	35	**4c**	86[b]	169–171	168–170
4	4-ClC_6H_4	30	**4d**	92[b]	187–189	188–189
5	2-ClC_6H_4	45	**4e**	86[b]	177–180	179–180
6	2,4-$Cl_2C_6H_3$	35	**4f**	85[b]	178–181	178–180
7	4-$CH_3C_6H_4$	50	**4g**	88[b]	175–177	176–177
8	4-OHC_6H_4	55	**4h**	85[b]	151–153	151–152
9	4-$OCH_3C_6H_4$	55	**4i**	86[b]	206–208	206–207
10	2-OH-3-$OCH_3C_6H_3$	45	**4j**	84[b]	214–216	213–215
11	3,4-$(CH_3O)_2C_6H_3$	50	**4k**	82	201–204	—
12	4-SCH_3-C_6H_4	50	**4l**	86	209–211	—
13	$(CH_3)_2CH$	70	**4m**	75[b]	116–119	116–117

Note: All products were characterized by ^1H NMR, ^{13}C NMR, and IR data.

[a]Isolated yields.

[b]Identified by comparison with authentic samples.[21, 20, 17, 27]

temperature, and time, the treatment of benzaldehyde (1 mmol), β-naphthol (1 mmol), and dimedone (1.2 mmol) in the presence of $RuCl_3 \cdot nH_2O$ catalyst (5 mol%) in ethanol (2.5 mL) at 80 °C for 30 min gave the corresponding tetrahydrobenzo[*a*]xanthen-11-one as a precipitate, which was easily purified (see Experimental) (product **4a**, 88% yield).

To evaluate the generality of the process, we also examined the reaction of β-naphthol and 5,5-dimethylcyclohexane-1,3-dione with a variety of aromatic aldehydes (Table 1, entries 2–12). Both aromatic aldehydes bearing electron-withdrawing and electron-donating groups afforded corresponding tetrahydrobenzo[*a*]xanthen-11-one derivatives in high yields (82%–92%). It is also noteworthy that the electronic properties of the aromatic ring have an effect on the time of this nucleophilic addition reaction. Aromatic aldehydes with electron-withdrawing groups reacted, somehow, faster than the aromatic aldehydes with electron-donating groups. An aliphatic aldehyde (Table 1, entry 13), however, showed a longer reaction time and lower yield. Although the precise mechanism of the reaction awaits further studies, a plausible mechanism for this transformation, which rationalizes the formation of products, is outlined in Scheme 1. By referring to the literature,[16,17] we proposed that after prior activation of the carbonyl group of aldehyde by Ru^{III} (intermediate **1**), nucleophilic attack from C_1 of β-naphthol provides an *ortho*-quinone methide intermediate (*o*-QM, intermediate **2**). After subsequent attack of dimedone to the *o*-QM and loss of water, intermediate **3** undergoes dehydration to afford the desired product **4**.

A comparison between the present results and other reported methods in this context is shown in Table 2.

As it is shown, operational simplicity and higher efficiency of our protocol covers the expensive cost of ruthenium chloride hydrate. Moreover, reusability of the catalyst was also studied to minimize costs and inorganic waste. As it is shown in Table 3, after four times, the reused catalyst showed only a 4% decrease in the yield of desired product.

To improve efficiency, we carried out this reaction under microwave irradiation. As it is shown in Table 4, this method affords the desired products in excellent yields in rather short times.

Conclusion

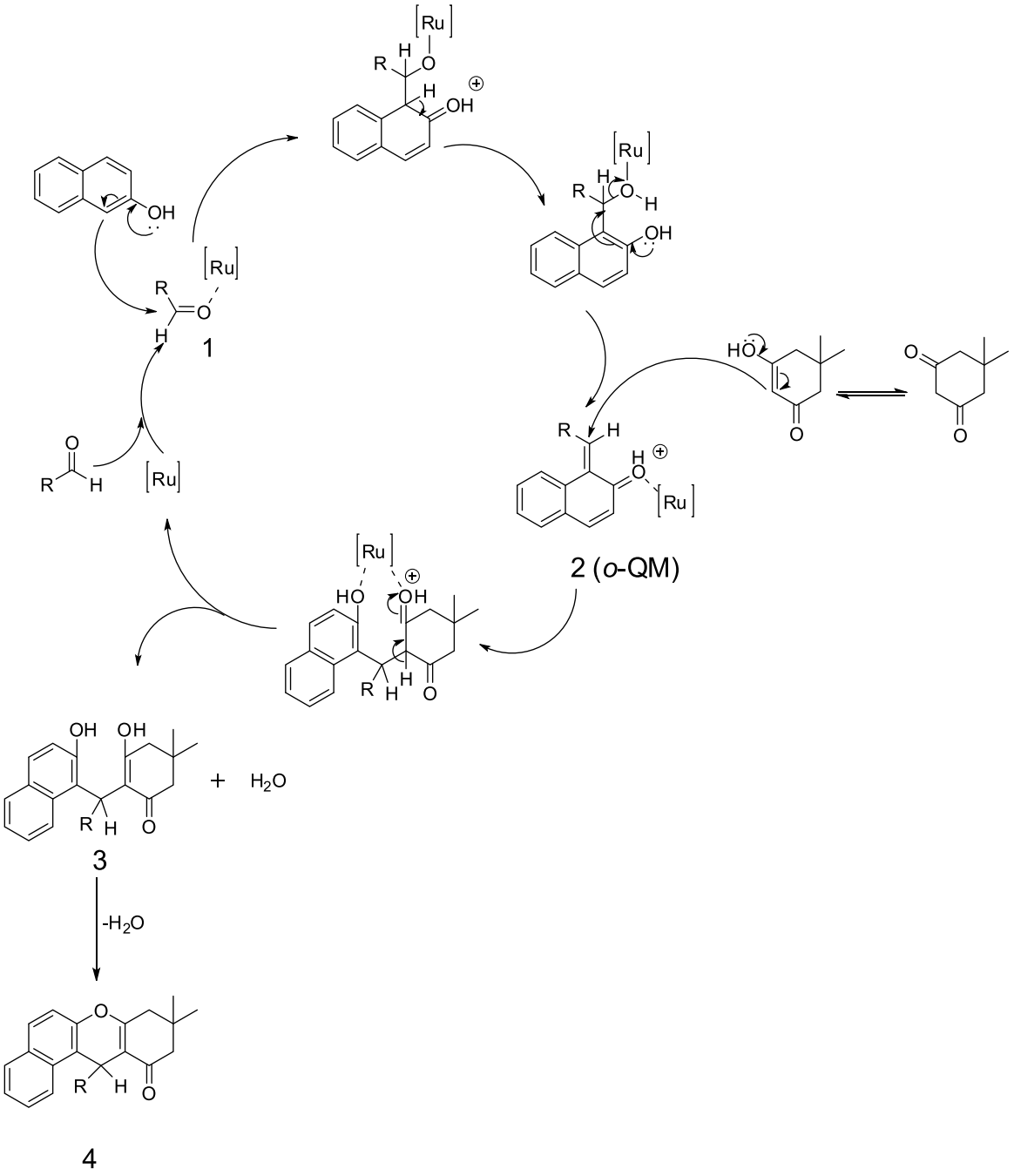
In brief, we have reported a convenient synthesis of tetrahydrobenzo[*a*]xanthen-11-ones by using $RuCl_3 \cdot nH_2O$ as a homogeneous catalyst. The unique feature of the reaction is that the corresponding tetrahydrobenzo[*a*]xanthen-11-ones are insoluble in the reaction solvent and this leads to an easy workup along with high yields (75%–92%). In all cases, simple filtration of the reaction mixture and rinsing with cold ethanol provided spectroscopically pure products. Several merits, such as efficiency, mild reaction conditions, short reaction times, high yields of products, easy workup procedure, low catalyst loading, reusability of the catalyst, and use of ethanol as an eco-friendly solvent, make this protocol a useful and attractive process for the synthesis of tetrahydrobenzo [*a*]xanthen-11-ones.

Experimental

General

All products were characterized by spectroscopic data (IR, ^1H NMR, ^{13}C NMR). IR spectra were recorded on a Shimadzu

Scheme 1. Proposed mechanistic pathway for the formation of tetrahydrobenzo[*a*]xanthen-11-one derivatives under ruthenium catalysis.



FTIR-8400S spectrophotometer. ^{1}H NMR spectra were measured on a Bruker DRX-400 Avance spectrometer. ^{13}C NMR spectra were obtained on a Bruker DRX-100 Avance spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in parts per million downfield from trimethylsilane (TMS) as the internal standard. Melting points were measured on a BÜCHI Melting Point B-540 and are uncorrected.

Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. Microwave irradiation was performed in a LBP125 microwave oven.

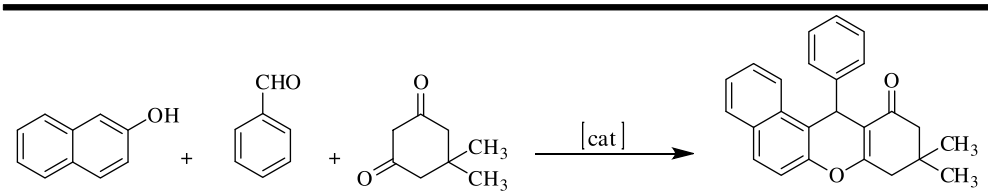
Materials

All the reagents were purchased from Merck and used without further purification.

Typical experimental procedure

To a mixture of β-naphthol (144.17 mg, 1 mmol), benzaldehyde (106.13 mg, 1 mmol), and dimedone (168.22 mg, 1.2 mmol) in ethanol (2.5 mL), $RuCl_3{\cdot}nH_2O$ (10.71 mg, 0.05 mmol) was added and the mixture was refluxed in an oil bath at 80 °C for 30 min, which yielded a precipitate. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, as

Table 2. Comparison of our results with those obtained by other groups in the reaction of β-naphthol, benzaldehyde, and dimedone.



Entry	Catalyst	Concentration of catalyst (mol %)	Solvent	Temperature (°C)	Time (min)	Yield (%)	References
1	$NaHSO_4{\cdot}SiO_2$	56	$ClCH_2CH_2Cl$	80	240	87	17
2	$Sr(OTf)_2$	10	$ClCH_2CH_2Cl$	80	300	85	18
3	pTSA	10	[bmim]BF_4	80	180	90	19
4	$InCl_3$	30	—	120	30	84	20
5	P_2O_5	20	—	120	40	76	20
6	I_2	10	—	60	75	90	21
7	HBF_4-SiO_2	10	—	80	65	91	23
8	$H_3PW_{12}O_{40}$	5	—	60	70	86	24
9	TCT	5	—	80	50	90	26
10	$HClO_4$-SiO_2	5	—	80	72	89	27
11	$RuCl_3{\cdot}nH_2O$	5	C_2H_5OH	80	30	88	—

Table 3. Reusability of the catalyst in the reaction of β-naphthol, benzaldehyde, and dimedone in the presence of $RuCl_3{\cdot}nH_2O$ (5 mol%).

Run No.	Yield (%)
1	88
2	88
3	86
4	84

Table 4. Ru^{III}-catalyzed synthesis of tetrahydrobenzo[*a*]xanthen-11-one derivatives under microwave irradiation.

Entry	R	Time (min)	Product	Yield (%)
1	C_6H_5	4	**4a**	88
2	4-$NO_2C_6H_4$	2	**4b**	90
3	4-ClC_6H_4	3	**4d**	93
4	4-$CH_3C_6H_4$	5	**4g**	87
5	$(CH_3)_2CH$	7	**4m**	78

indicated by TLC, the precipitate was filtered off and rinsed with cold ethanol. The solid was dried under vacuum to afford the desired compound in pure form (311.78 mg, 88%). The same procedure was also used for the other products listed in Table 1. To reuse the catalyst, after filtration, substrates were added into solution and the same procedure was repeated. For microwave reactions, irradiation was conducted in an open vessel at 50 °C in a 500 W microwave oven (Table 4).

12-(3,4-Dimethoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (4k)

Solid; mp 201–204 °C. IR (KBr, cm^{-1}) ν: 3070, 2960, 1644, 1590, 1371, 1260, 1220, 1140, 1020, 817. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 7.93 (d, 1H, J = 8.8 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 8.4 Hz), 7.48 (t, 1H, J = 7.2 Hz), 7.36 (t, 1H, J = 7.2 Hz), 7.18 (d, 1H, J = 8.8 Hz), 6.69 (d, 1H, J = 7.6 Hz), 6.59 (d, 1H, J = 7.6 Hz), 6.50 (s, 1H), 5.64 (s, 1H), 3.68 (s, 3H), 3.57 (s, 3H), 2.54 (s, 2H), 2.42 (d, 1H, J = 16.4 Hz), 2.27 (d, 1H, J = 16.4 Hz), 1.09 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, ppm) δ: 196.2, 162.8, 153.6, 142.1, 136.0, 133.5, 130.2, 129.0, 128.2, 127.1, 126.8, 125.4, 124.3, 123.5, 116.9, 116.4, 115.8, 113.2, 112.4, 53.7, 53.4, 49.6, 40.2, 32.7, 31.2, 27.8, 26.0. Anal. calcd. for $C_{27}H_{26}O_4$: C 78.24, H 6.32; found: C 78.25, H 6.34.

9,9-Dimethyl-12-(4-methylthiophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (4l)

Solid; mp 209–211 °C. IR (KBr, cm^{-1}) ν : 3050, 2960, 1642, 1593, 1372, 1220, 1180, 1020, 800. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, ppm) δ: 7.93 (d, 1H, J = 8.4 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 8.8 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.41 (t, 1H, J = 7.2 Hz), 7.19 (d, 1H, J = 8.4 Hz), 7.08 (d, 2H, J = 7.6 Hz), 6.98 (d, 2H, J = 7.6 Hz), 5.66 (s, 1H), 2.56 (s, 2H), 2.50 (s, 3H), 2.38 (d, 1H, J = 16.4 Hz), 2.28 (d, 1H, J = 16.4 Hz), 1.12 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, ppm) δ: 196.7, 163.2, 154.1, 147.2, 136.2, 133.7, 132.1, 131.8, 130.1, 129.4, 127.9, 126.3, 124.3, 123.5, 117.8, 116.2, 113.7, 50.6, 40.8, 33.9, 31.9, 28.3, 26.6, 25.4. Anal. calcd. for $C_{26}H_{24}O_2S$: C 77.97, H 6.04; found: C 77.98, H 6.05.

Acknowledgement

Partial support of this work by the Research Council of the University of Guilan is gratefully acknowledged.

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