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ORIGINAL PAPER

An efficient TBHP/TBAI-mediated protocol for the synthesis of 4*H*-chromen-4-ones from chroman-4-ones via oxidative C–C bond formation

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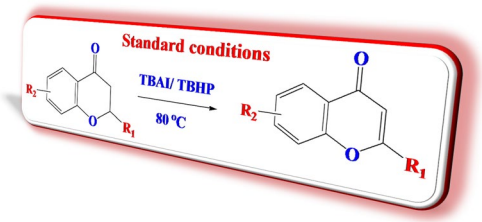
Abstract

A transition metal-free and efficient TBHP/TBAI-mediated protocol has been developed for the synthesis of 4*H*-chromen-4-ones from chroman-4-ones via oxidative C–C bond formation. It proceeds in the presence of a catalytic amount of tetrabutylammonium iodide and oxidant *tert*-butyl hydroperoxide (TBHP, 5–6 M in decane) to afford the corresponding products in good to excellent yields. Furthermore, it has been observed that an increase in the concentration of TBHP to 30 mol % drastically increases the yield of 4*H*-chromen-4-ones, any further increase will lead to a decrease in percent yield. The mechanism of this reaction involves the generation of tertiary butoxide radical initially which by oxidative single-electron transformation is converted to iodochroman-4-one. Later the hydrogen iodide is removed from iodochroman-4-one to give the desired product, i.e. 4*H*-chromen-4-ones. Moreover, this is a rare example of the *n*-Bu_4NI/TBHP-mediated C–C bond through dehydrogenative reaction.

Graphic abstract



Keywords *tert*-Butyl hydroperoxide · 4*H*-Chromen-4-ones · C–C bond formation · Chroman-4-ones

Introduction

Recently, scientific interest has increased towards 4*H*-chromen-4-ones moiety because they are an important component of pharmacophores of a number of biologically active molecules having a synthetic or natural origin and many of them have useful medicinal applications [1–4]. They have a number of biological activities such as anti-cancer [5, 6], antioxidant [7, 8], anti-ulcer [9], antifungal [10], anti-inflammatory [11], anti-HIV [12, 13], wound healing [14], and immune stimulatory [15]. Also, they possess enzymatic inhibition properties towards different systems such as oxidoreductase, kinase, lipoxygenase and cyclooxygenase

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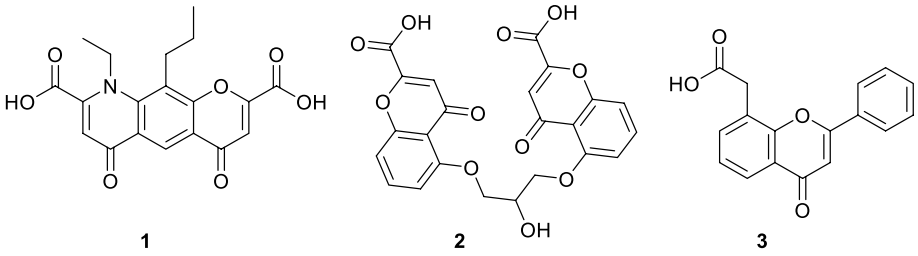
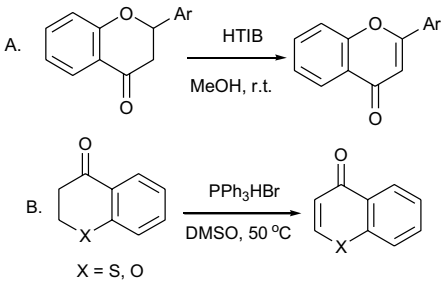
Fig. 1 Examples of currently marketed chromone-based drugs

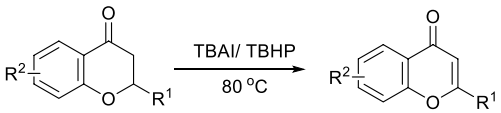


Scheme 1

Previous work



Present work

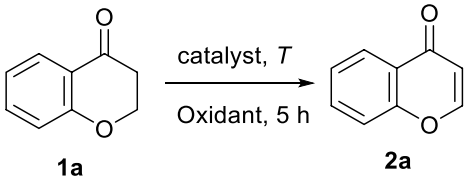


[16, 17]. It is considered as a privileged structure in drug development [18]. For example, nedocromil (**1**) and moglycate (**2**) are known anti-inflammatory drugs and flavone-8-acetic acid (**3**) is used as an anti-cancer drug (Fig. 1).

Although synthetic approaches to this family of compounds have been extensively investigated in the past decades [5, 6], specifically they are synthesized directly from chroman-4-ones by dehydrogenation using HTIB as oxidant [19] and PPh_3·HBr–DMSO mediated efficiently and chemoselective transformation of synthesis of chroman-4-one derivatives [20] (Scheme 1). However, these methods suffer from poor substituent tolerance or low chemical yields, expensive reagents, and restricted substrate scope [21]. Therefore, the synthesis of chroman-4-ones under mild conditions is still desirable for further study in this area.

On the other hand, readily available and nontoxic organocatalytic synthesis is highly attractive for chemical synthesis from environmental and economic points of view. Therefore, the development of the TBAI/TBHP-mediated oxidative C–C bond formation method is one of the valuable goals for the preparation of various 4*H*-chromen-4-ones. These findings are in conjunction with our recent results on the oxidative functionalization of C–H bonds of methyl arenes and ethers [15]. We herein report a new and simple route for the synthesis of 4*H*-chromen-4-ones derivatives via dehydrogenation of chroman-4-one derivative using TBHP/TBAI-mediated condition.

Table 1 Optimization of reaction conditions



Entry	Catalyst (mol %)	Oxidant (eq.)	*T*/°C	Solvent	Yield/%[c]
1	*n*-Bu_4NI (20)	TBHP (3)[a]	80	–	72
2	*n*-Bu_4NI (20)	TBPB (3)	80	–	31
3	*n*-Bu_4NI (20)	H_2O_2 (3)	80	–	49
4	*n*-Bu_4NI (20)	DDQ (3)	80	–	27
5	*n*-Bu_4NI (20)	$K_2S_2O_8$ (3)	80	–	< 10
6	*n*-Bu_4NCl (20)	TBHP (3)[a]	80	–	Trace
7	*n*-Bu_4NBr (20)	TBHP (3)[a]	80	–	Trace
8	I_2 (20)	TBHP (3)[a]	80	–	Trace
9	KI (20)	TBHP (3)[a]	80	–	Trace
10	*n*-Bu_4NI (20)	TBHP (3)[b]	80	–	85
11	*n*-Bu_4NI (30)	TBHP (4)[b]	80	–	96
12	*n*-Bu_4NI (40)	TBHP (4)[b]	80	–	60
13	*n*-Bu_4NI (30)	TBHP (6)[b]	80	–	69
14	*n*-Bu_4NI (30)	TBHP (3)[b]	60	–	45
15	*n*-Bu_4NI (30)	TBHP (3)[b]	100	–	54
16	*n*-Bu_4NI (30)	TBHP (4)[b]	80	EtOAc	35
17	*n*-Bu_4NI (30)	TBHP (4)[b]	80	DMF	Trace
18	*n*-Bu_4NI (30)	TBHP (4)[b]	80	DMSO	Trace
19	*n*-Bu_4NI (30)	TBHP (4)[b]	80	*t*-BuOH	Trace

The reactions were carried out with **1a** (0.7 mmol), catalyst and oxidant were heated at 80 °C for 4 h

[a]TBHP (70% in water)

[b]TBHP (5–6 M solution in decane)

[c]Isolated yields

Results and discussion

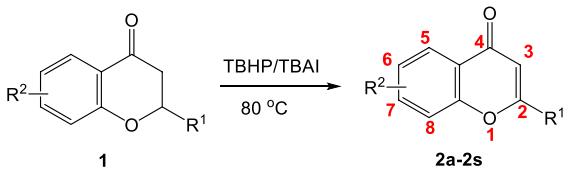
The reaction conditions were optimized with chroman-4-one (**1a**) using tetrabutylammonium iodide (TBAI, 20 mol %) and *tert*-butyl hydroperoxide (TBHP, 3 eq., 70% in water) at 80 °C for 4 h. The desired product **2a** was synthesized with a yield of up to 72% (Table 1, entry

1). Next, reaction conditions were optimized to increase the yield. Thus, various catalysts and oxidants including TBHP (5–6 M in decane) were tested and the results are summarized in Table 1. As indicated in Table 1, other oxidants such as TBPB, H_2O_2, DDQ, and $K_2S_2O_8$ and other catalysts such as *n*-Bu_4NCl, *n*-Bu_4NBr, I_2, and KI were proven to be ineffective for this transformation (Table 1, entries 2–9). While, when the authors used TBHP in decane instead of TBHP in water, surprisingly the product yield increased from 72 to 85%. For increasing the quantity of TBAI and TBHP, an increasing amount of TBAI from 20 to 30 mol % and TBHP (5–6 M in decane) 3 eq. to 4 eq. was used. A drastic increase in the product yield was observed which increased from 85 to 96% (Table 1, entry 10). Further, an increase in the quantity of TBAI to 40 mol % and TBHP to 6 eq. led to a decrease in the product yield (Table 1, entries 11, 12). Once we had established a suitable oxidant and catalyst for the oxidation of chroman-4-one, then we focused on the change of temperature with different solvents. Increasing or decreasing temperature resulted in lower yields (Table 1, entries 13, 14). Finally, various solvents were also examined, but no better yields were obtained (Table 1, entries 15–18).

With the optimized reaction conditions (Table 1, entry 11), the generality and scope of this oxidative C–C bond formation reaction was investigated. First, the authors had attempted the reactions with substituted chroman-4-ones and results are summarized in Table 2. It was found that chroman-4-ones substituted with electron-releasing groups such as $–CH_3$, and –OH at 7-position and electron-withdrawing groups such as –Cl, at 7-position and $–CO_2CH_3$ at 6-position proceeded quite efficiently and gave the corresponding products in good yields (Table 2, **2b**–**2e**).

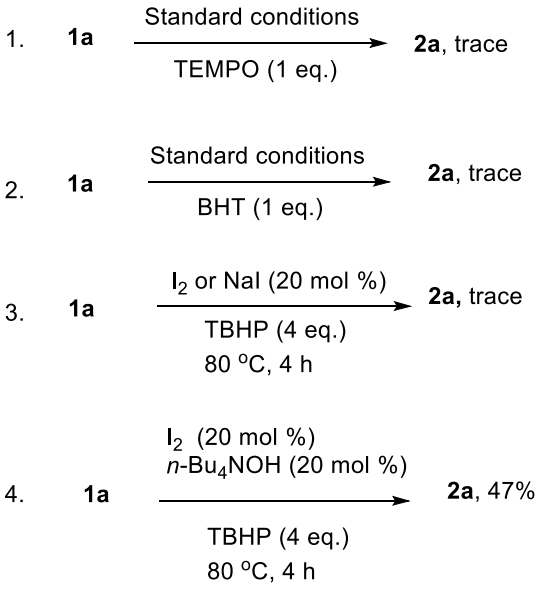
Furthermore, the authors carried out the reaction with 2-methylchroman-4-ones and 2-phenylchroman-4-ones (flavanones) under optimized reaction conditions and the results are summarized in Table 2. As shown in Table 2, 2-methylchroman-4-ones and 2-phenylchroman-4-ones (flavanones) having electron-donating and electron-withdrawing groups underwent smooth dehydrogenation to

Table 2 Scope for the synthesis of 4*H*-1-chromen-4-ones (reaction conditions: **1** (0.7 mmol), TBAI (30 mol %), TBHP (4 eq.), 80 °C, 4 h, isolated yields)

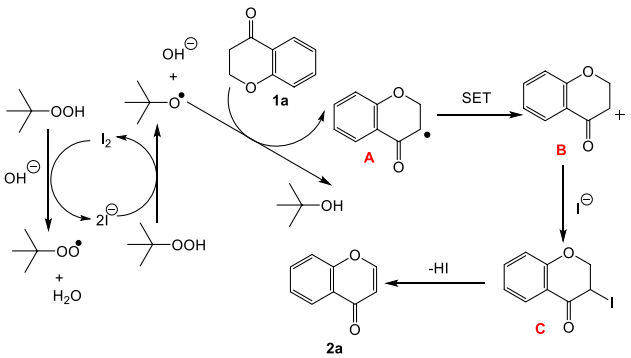


Comp.	R^1	R^2	Yield/%	Observed m.p./°C	Literature m.p./°C	References
2a	H	H	96	54–56	55–58	[22]
2b	H	6-CH_3	86	204–206	206–208	[20]
2c	H	6-Cl	88	148–150	–	–
2d	H	7-$COOCH_3$	76	156–158	156–157	[23]
2e	CH_3	H	76	74–75	72–73	[24]
2f	CH_3	6-CH_3	79	102–104	100	[25]
2g	CH_3	7-Cl	73	116–118	114–115	[26]
2h	Ph	H	95	95–96	–	–
2i	Ph	6-OH	86	180–182	–	–
2j	Ph	6-CH_3	86	120–122	122–124	[27]
2k	Ph	6-OCH_3	89	106–108	105–106	[28]
2l	Ph	6-Cl	85	158–160	159–160	[25]
2m	Ph	6-$COOCH_3$	74	180–182	180–181	[27]
2n	$PhCH_3$	H	79	115–117	114–115	[29]
2o	$PhOCH_3$	H	73	138–140	134–136	[30]
2p	$PhNO_2$	H	84	244–246	240	[26]
2q	PhCl	H	86	170–172	168–170	[26]
2r	PhF	H	88	164–166	165–167	[29]
2s	PhBr	H	79	178–180	178–181	[27]

Scheme 2



Scheme 3



produce the corresponding 2-methyl-4*H*-chromen-4-ones (Table 2, **2e**–**2g**) and 2-phenyl-4*H*-chromen-4-ones (flavones) (Table 2, **2h**–**2s**) in good to excellent yields.

Several control experiments were performed to gain insight into the mechanism (Scheme 2). Initially, when TEMPO and BHT were added, the reaction was significantly suppressed. This result indicated that a radical pathway may be involved in this reaction. Next, replacement of TBAI with I_2, NaI, or KI gave trace amounts of the products. However, the reaction in the presence of I_2/*n*-Bu_4NOH resulted in a 47% yield.

Based on the above observations as well as from the previous reports [31–34], a plausible mechanism for this oxidative transformation is illustrated in Scheme 3. Initially, TBHP is converted into tertiary butoxide radical catalytically with an aid of iodide anion and this radical traps the hydrogen from the chroman-4-one and generates radical cation **A** [31–34]. Subsequently, the hypothetic radical cation **A** is converted into carbocation intermediate **B** via oxidative single-electron transformation (SET) [31–34]. After that the carbocation **B** can also be attacked with iodide anion to form iodochroman-4-one **C**. Finally, hydrogen iodide is departed to yield the final products **2a**–**2s**.

Conclusion

In conclusion, the author has developed an efficient TBHP/TBAI-mediated protocol for the synthesis of 4*H*-chromen-4-ones from chroman-4-ones via oxidative C–C bond formation. This protocol provides a simple and green approach for the synthesis of 4*H*-chromen-4-ones and 2-phenylchromen-4-ones. Chroman-4-ones and 2-phenylchroman-4-ones with various functional groups proceeded smoothly to provide the corresponding products in good to excellent yields.

Experimental

All flavanone derivatives were prepared according to the literature procedure [35]. Melting points were recorded on a Mel-Temp melting point apparatus. Unless otherwise stated, all the materials were obtained from the commercial suppliers and are used without further purification. Chromatography was carried out on silica gel (100–200 mesh). All the reactions were monitored by thin-layer chromatography and the spots were visualized under UV light. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C using TMS as an internal standard. Chemical shifts are expressed in δ (ppm) and coupling constants J in Hertz (Hz). Mass spectra were recorded on an Agilent 1100 LC–MS. All yields refer to isolated ones.

General procedure for the synthesis of 4*H*-chromen-4-one

An oven-dried 50 cm^3 round bottom flask equipped with a magnetic stir bar was charged with chromanone **1a** (0.7 mmol), *n*-Bu_4NI [33, 34] (30 mol %), and aqueous solution of TBHP (5–6 M in decane, 4 equiv.) at room temperature. The reaction mixture was then refluxed at 80 °C for 5 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was admixed with ethyl acetate and transferred into a separating

funnel. The ethyl acetate layer was sequentially washed with 5% solution of sodium bicarbonate and brine solution. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The resulting residue was purified over a column of silica gel (100–200 mesh) to give **2a**–**2s** with petroleum ether/ethyl acetate as the eluent.

7-Chloro-4*H*-chromen-4-one (2c, $C_9H_5ClO_2$) M.p.: 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, 1H), 7.88 (d, $J = 6.0$ Hz, 1H), 7.64 (dd, 1H), 7.45 (d, 1H), 6.37 (d, $J = 6.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.4$, 155.4, 154.9, 134.0, 131.3, 125.8, 125.3, 120.0, 113.0 ppm; LC–MS: $m/z = 178$ ([M−2]).

2-Phenyl-4*H*-chromen-4-one (2h, $C_{15}H_{10}O_2$) M.p.: 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.27$ (q, $J = 9.6$ Hz, 1H), 7.97–7.95 (m, 2H), 7.72 (d, 1H), 7.62–7.55 (m, 4H), 7.44 (t, $J = 9.6$ Hz, 1H), 6.68 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 107.7$, 118.1, 124.0, 125.2-125.8, 126.3, 129.1, 131.6–131.9, 133.8, 156.3, 163.4, 178.5 ppm; LC–MS: $m/z = 223$ ($[M+H]^+$).

7-Hydroxy-2-phenyl -4*H*-chromen-4-one (2i, $C_{15}H_{10}O_3$) M.p.: 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$–7.96 (q, $J = 5.6$ Hz, 3H),7.57–7.54 (m, 4H), 7.36–7.34 (t, $J = 2.8$, 6.0 Hz, 2H), 6.88 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.5$, 163.4, 156.3, 133.8, 131.8, 129.1, 126.3, 125.5, 118.1, 124.0, 107.7 ppm; LC–MS: $m/z = 239$ ($[M+H]^+$).

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