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Copper(I)-Catalyzed 3-Position Methylation of Coumarins by Using Di-*tert*-butyl Peroxide as the Methylation Reagents

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The copper-catalyzed methylation of coumarin by using di-*tert*-butyl peroxide (DTBP) has been described. The reaction provides direct access to a wide range of 3-methylcoumarins in moderate to good yields. In this procedure, it is noteworthy that DTBP was employed not only as the oxidant, but also as the methyl source.

Keywords CuCl, di-*tert*-butyl peroxide, methylation, coumarin

Introduction

Coumarins are an important class of natural products that display a diverse range of biological activities[1] and they are also widely used in organic materials due to their good optical properties.[2] Recently, simple coumarins have been used successfully in transition-metal-catalyzed direct C—H bond activation reactions with different nucleophiles.[3]

Metal-catalyzed methylation reactions have been developed for the magical methyl effect.[4] In 2008, Li and co-workers[5] firstly reported palladium-catalyzed methylation of arenes by using peroxides. In the past decade, organic peroxides were widely used in Csp_3-H bond activation processes, especially in the cross-dehyodrgenative coupling reactions.[6] In these reactions, organic peroxides were usually used as H-acceptors to activate C—H bonds. Thus metal-catalyzed cross-dehydrogenative coupling/cyclization of activated alkenes with methylic C—H bonds for the synthesis of heterocycles has also been developed.[7] Recently, copper-catalyzed *N*-methylation and *O*-methylation have been reported by using peroxides.[8]

In our previous studies, we reported the direct trifluoromethylation of coumarins.[9] Herein we report a novel, selective and efficient method for 3-position methylation of coumarins by using peroxides.

Results and Discussion

When the model reaction of coumarin (**1a**) with di-*tert*-butyl peroxide (DTBP) (**2a**) was performed at 100 ℃ in chlorobenzene in the presence of CuCl, no reaction took place (Table 1, Entry 17). However, the reaction proceeded to afford the desired product 3-methylcoumarin (**3a**) in modiate yield at 140 ℃ (Table 1, Entry 1). Followed by screening different Cu salt such as CuI, CuO, $Cu(OAc)_2$•H_2O (Table 1, Entries 2—4), the results showed that CuCl works well for the reaction. Reaction time screening showed that 10 h was the best (Entries 6—10). Solvent screening showed that MeCN, DMSO, DMF and THF were not effective at all (Entries 13—16).

A control experiment revealed that 18% of product was detected in the absence of any catalyst (Table 1, Entries 5).

Other than the above-mentioned factors, the effects of peroxides were also investigated (Table 1, Entries 9, 11, 12), and the optimal reaction conditions were determined to be DTBP as peroxides and CuCl as catalyst in chlorobenzene at 140 ℃ for 10 h under air.

To explore the scope of the copper-catalyzed methylation of coumarin, we examined a variety of coumarins including electron-withdrawing group and electron-donating group (Table 2). It was found that coumarins bearing electron-donating groups like methyl and methoxy on the phenyl ring afforded the expected 3-methylcoumarins in 50%—58% yields (Table 2, Entries 1—10). On the contrary, coumarins bearing electron-withdrawing groups like Cl and NO_2 on the phenyl ring gave the products in good yields (Table 2, Entries 11—13). In addition, 4-methyl coumarins also gave the products in good yield (Table 2, Entries 14—16).

The plausible mechanism for the CuCl-catalyzed methylation reaction of coumarin (**1**) with DTBP (**2a**) was proposed in Scheme 1. DTBP produced the *tert*-butoxy radical, which converted to the methyl radical by releasing 1 equiv. of acetone. Then, methyl radical derived from **2a** selectively added to the 3-position of **1** to form intermediate radical **4**, which was oxidized by

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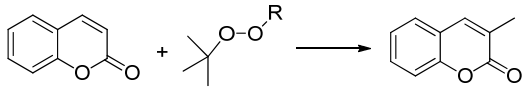
Table 1 Optimization of the reaction conditions[a]



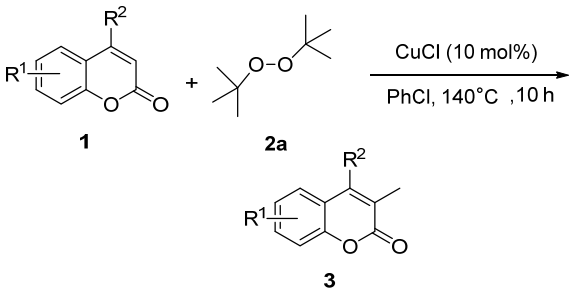
Entry	Catalyst	Solvent	Peroxide	Time/h	Yield[b]/%
1	CuCl	PhCl	DTBP	24	51
2	CuI	PhCl	DTBP	24	46
3	$Cu(OAc)_2$	PhCl	DTBP	24	50
4	CuO	PhCl	DTBP	24	47
5	—	PhCl	DTBP	24	18
6	CuCl	PhCl	DTBP	1	N.D.[c]
7	CuCl	PhCl	DTBP	4	20
8	CuCl	PhCl	DTBP	8	43
9	CuCl	PhCl	DTBP	10	53
10	CuCl	PhCl	DTBP	12	51
11	CuCl	PhCl	TBPB	10	48
12	CuCl	PhCl	TBHP	10	N.D.[c]
13	CuCl	MeCN	DTBP	10	N.D.[c]
14	CuCl	DMSO	DTBP	10	N.D.[c]
15	CuCl	DMF	DTBP	10	N.D.[c]
16	CuCl	THF	DTBP	10	N.D.[c]
17[e]	CuCl	PhCl	DTBP	10	N.R.[d]
18[f]	CuCl	PhCl	DTBP	10	32

[a] Reaction conditions: Coumarin (**1a**) (1.0 mmol), catalyst (10 mol%), and peroxide (**2**) (4.0 mmol, 4 equiv.) (DTBP = di-*tert*-butyl peroxide, TBPB = *tert*-butyl peroxybenzoate, TBHP = tert-butyl hydroperoxide) in PhCl (3 mL) at 140 ℃ for 10 h under air. [b] Isolated yield. [c] N.D. means not detected. [d] N.R. means no reaction. [e] At 100 ℃. [f] At 120 ℃.

Cu(II) to form carbocation **5**. Finally deprotonation of **5** gave the product **3**.

Finally, the control experiment was performed (Scheme 2). When the radical-trapping reagent 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) was added to coumarins (**1a**) and DTBP (**2a**), the reaction was completely suppressed. In addition, the TEMPO-CH_3 adduct **A** was detected by LC-MS, which could indicate that this methylation involves free radical intermediates.

Table 2 Reactions of coumarins (**1a**) and DTBP (**2a**)[a]



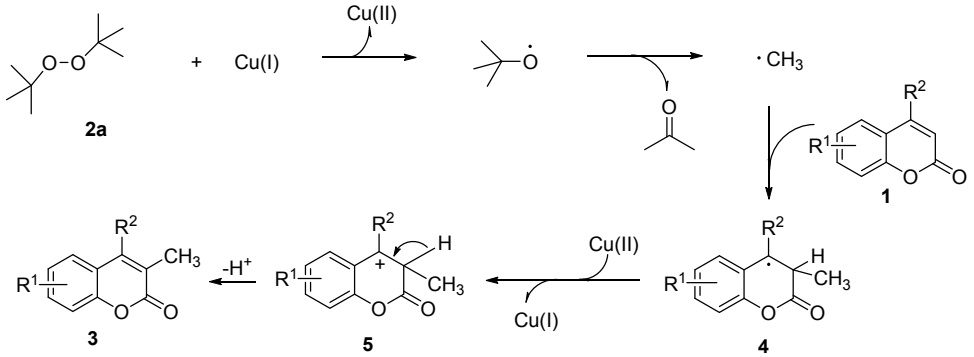
Entry	R^1	R^2	Product	Yield[b]/%
1	H	H	**3a**	53
2	6-Me	H	**3b**	50
3	7-Me	H	**3c**	52
4	6-MeO	H	**3d**	56
5	7-MeO	H	**3e**	58
6	7-CH_3COO	H	**3f**	55
7	8-Me	H	**3g**	53
8	6,8-di Me	H	**3h**	51
9	5,8-di Me	H	**3i**	50
10	7,8-di Me	H	**3j**	58
11	6-Cl	H	**3k**	66
12	7-Cl	H	**3l**	64
13	6-NO_2	H	**3m**	68
14	6-Me	4-Me	**3n**	65
15	5,7-di-MeO	4-Me	**3o**	62
16	7-CH_3COO	4-Me	**3p**	68
17	H	4-MeO	**3q**	60

[a] Reaction conditions: Coumarin (**1**) (1.0 mmol), CuCl (10 mol%), and peroxide (**2a**) (4.0 mmol, 4 equiv.) in PhCl (3 mL) at 140 ℃ for 10 h under air. [b] Isolated yield.

Conclusions

In conclusion, a novel method for 3-position methylation of coumarins was developed through the radical

Scheme 1 Plausible mechanism for reactions of coumarins (**1**) and DTBP (**2a**) catalyzed by Cu(I)



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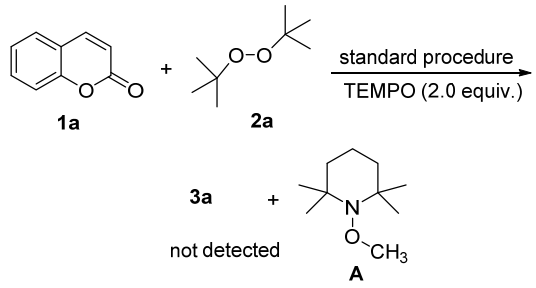
Scheme 2 Radical capture experiment



reaction of coumarins with DTBP catalyzed by CuCl. This procedure tolerated a series of functional groups, avoided the use of poisonous methyl iodide and provided a facile and straightforward way for the synthesis of 3-methylcoumarins.

Experimental

General

Column chromatography was performed with silica gel (300−400 mesh) and analytical TLC on silica 60-F 254. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ on an Inova-400 MHz spectrometer and chemical shifts (δ) reported relative to internal TMS. HRMS was recorded on a Micromass OA-TOF instrument. All reagents were used directly as obtained commercially.

General procedure for the synthesis of 3-amino-4-cyano-substituted isoquinoline-1(2*H*)-ones (3a−3z)

A glassware with a magnetic stirring bar was charged with coumarins **1** (1.0 mmol), CuCl (10 mol%), DTBP **2** (4 mmol, 4 equiv.) and PhCl (3 mL). The reaction mixture was stirred at 140 ℃ for 10 h under air. After cooling to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford 3-methylcoumarins **3**.

3-Methyl-2*H*-chromen-2-one (3a)[10] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 53% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.48−7.41 (m, 2H), 7.30 (d, J=8.3 Hz, 1H), 7.27−7.23 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 153.9, 140.0, 131.2, 127.7, 126.5, 125.0, 120.3, 117.1, 17.9. MS calcd for $C_{10}H_8O_2$ $[M+1]^+$: 161; found 161.

3,6-Dimethyl-2*H*-chromen-2-one (3b)[11] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 50% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.26 (dd, J=8.5, 1.7 Hz, 1H), 7.20−7.18 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 152.1, 139.9, 134.6, 132.1, 127.5, 126.3, 120.0, 116.8, 21.5, 17.9. MS calcd for $C_{11}H_{10}O_2$ $[M+1]^+$: 175; found 175.

3,7-Dimethyl-2*H*-chromen-one (3c)[11] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 52% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (s, 1H), 7.31 (d, J=7.9 Hz, 1H), 7.13 (s, 1H), 7.08 (d, J=7.9 Hz, 1H), 2.45 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 154.1, 142.3, 140.0, 127.4, 126.2, 125.3, 117.9, 117.4, 22.4, 17.9. MS calcd for $C_{11}H_{10}O_2$ $[M+1]^+$: 175; found 175.

6-Methoxy-3-methyl-2*H*-chromen-2-one (3d)[11] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 56% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (s, 1H), 7.23 (d, J=9.0 Hz, 1H), 7.03 (dd, J=9.0, 2.9 Hz, 1H), 6.85 (d, J=2.9 Hz, 1H), 3.84 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.1, 156.7, 148.4, 139.8, 126.9, 120.7, 118.7, 118.1, 110.0, 56.5, 18.0. MS calcd for $C_{11}H_{10}O_3$ $[M+1]^+$: 191; found 191.

7-Methoxy-3-methyl-2*H*-chromen-2-one (3e)[12] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 58% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.33 (d, J=8.6 Hz, 1H), 6.86−6.83 (m, 2H), 3.88 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 162.5, 155.7, 140.1, 128.6, 123.0, 114.0, 113.2, 101.3, 56.5, 17.8. MS calcd for $C_{11}H_{10}O_3$ $[M+1]^+$: 191; found 191.

3-Methyl-2-oxo-2*H*-chromen-7-yl acetate (3f)[13] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶16 to 1∶4) afforded the title product in 55% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.10 (s, 1H), 7.04−7.02 (m, 1H), 2.34 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 162.6, 154.5, 152.8, 139.4, 128.4, 126.0, 118.2, 110.7, 21.9, 17.9. MS calcd for $C_{12}H_{10}O_4$ $[M+1]^+$: 219; found 219.

3,8-Dimethyl-2*H*-chromen-one (3g)[14] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶32 to 1∶20) afforded the title product in 53% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 7.32 (d, J=7.3 Hz, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.18−7.14 (m, 1H), 2.47 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 152.4, 140.4, 132.6, 126.6, 126.1, 125.4, 124.6, 120.1, 17.9, 16.2. MS calcd for $C_{11}H_{10}O_2$ $[M+1]^+$: 175; found 175.

3,6,8-Trimethyl-2*H*-chromen-2-one (3h) Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶32 to 1∶20) afforded the title product in 51% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.14 (s, 1H), 7.04 (s, 1H), 2.43 (s, 3H), 2.37 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 150.5, 140.4, 134.1, 133.7, 126.2, 126.0, 125.2, 119.8, 21.5, 17.9, 16.1. HRMS calcd for $C_{12}H_{12}O_2$ $[M+Na]^+$: 211.0732; found 211.2225.

3,5,8-Trimethyl-2*H*-chromen-2-one (3i)[15] Column chromatography on silica gel (ethyl acetate/petro-

leum ether 1∶32 to 1∶20) afforded the title product in 50% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.18 (d, J=7.6 Hz, 1H), 6.97 (d, J=7.6 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 152.7, 137.3, 133.1, 132.2, 125.7, 125.3, 124.2, 118.7, 18.9, 18.1, 16.1. MS calcd for $C_{12}H_{12}O_2$ $[M+1]^+$: 189; found 189.

3,7,8-Trimethyl-2*H*-chromen-2-one (3j) Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶32 to 1∶20) afforded the title product in 58% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.15 (d, J=7.9 Hz, 1H), 7.06 (d, J=7.9 Hz, 1H), 2.38 (d, J=3.8 Hz, 6H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 152.4, 140.8, 140.6, 126.4, 124.9, 124.7, 124.5, 118.1, 21.0, 17.7, 12.2. HRMS calcd for $C_{12}H_{12}O_2$ $[M+Na]^+$: 211.0732; found 211.2225.

6-Chloro-3-methyl-2*H*-chromen-2-one (3k)[11] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 66% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.42−7.40 (m, 2H), 7.28−7.24 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 152.3, 138.7, 131.1, 130.2, 128.0, 127.0, 121.4, 118.6, 21.0, 18.0. MS calcd for $C_{10}H_7ClO_2$ $[M+1]^+$: 195; found 195.

7-Chloro-3-methyl-2*H*-chromen-2-one (3l) Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶32 to 1∶20) afforded the title product in 64% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (s, 3H), 7.36−7.28 (m, 2H), 7.23−7.21 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 154.1, 139.2, 136.9, 128.5, 126.6, 125.6, 118.8, 117.4, 17.9. MS calcd for $C_{10}H_7ClO_2$ $[M+1]^+$: 195; found 195.

3-Methyl-6-nitro-2*H*-chromen-2-one (3m) Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶16 to 1∶8) afforded the title product in 68% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J=2.5 Hz, 1H), 8.35 (dd, J=9.0, 2.6 Hz, 1H), 7.62 (s, 1H), 7.46 (d, J=9.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.3, 157.5, 138.6, 129.3, 126.1, 123.6, 121.4, 120.4, 118.4, 18.1. MS calcd for $C_{10}H_7NO_4$ $[M+1]^+$: 206; found 206.

3,4,6-Trimethyl-2*H*-chromen-2-one (3n)[16] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 65% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (s, 1H), 7.27−7.25 (m, 1H), 7.19 (d, J=8.4 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 150.9, 146.7, 134.3, 132.1, 125.0, 122.9, 121.0, 117.2, 21.9, 15.8, 14.2. HRMS calcd for $C_{12}H_{12}O_2$ $[M+Na]^+$: 211.0727; found 211.0825.

5,7-Dimethoxy-3,4,-dimethyl-2*H*-chromen-2-one (3o)[17] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶16 to 1∶8) afforded the title product in 62% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.44 (d, J=2.5 Hz, 1H), 6.32 (d, J=2.5 Hz, 1H), 3.86 (d, J=8.3 Hz, 6H), 2.56 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 162.3, 159.4, 155.8, 149.3, 118.5, 106.3, 96.4, 93.8, 56.5, 56.4, 20.3, 13.8. MS calcd for $C_{10}H_7ClO_2$ $[M+1]^+$: 221; found 221.

3,4-Dimethyl-2-oxo-2*H*-chromen-7-yl acetate (3p)[17] Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶16 to 1∶4) afforded the title product in 68% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, J=8.6 Hz, 1H), 7.10−7.05 (m, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 162.5, 153.3, 152.7, 146.3, 125.9, 122.5, 119.2, 118.6, 110.8, 21.0, 15.9, 14.2. MS calcd for $C_{13}H_{12}O_4$ $[M+1]^+$: 233; found 233.

4-Methoxy-3-methyl-2*H*-chromen-2-one (3q) Column chromatography on silica gel (ethyl acetate/petroleum ether 1∶20) afforded the title product in 56% isolated yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (dd, J=7.9, 1.5 Hz, 1H), 7.53−7.49 (m, 1H), 7.34 (dd, J=8,3, 0.7 Hz, 1H), 7.33−7.28 (m, 1H), 4.02 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 164.4, 153.1, 132.0, 124.8, 123.7, 118.0, 117.4, 113.2, 62.0, 11.4. MS calcd for $C_{11}H_{10}O_3$ $[M+1]^+$: 191; found 191.

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