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Synthesis of 6- and 7-alkoxy-4-methylcoumarins from corresponding hydroxy coumarins and their conversion into 6- and 7-alkoxy-4-formylcoumarin derivatives

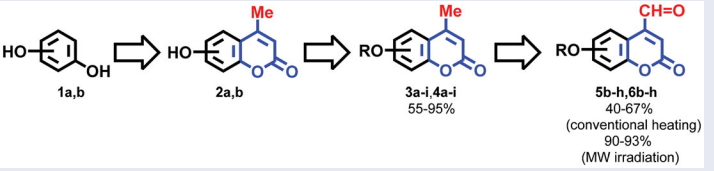
Vu Ngoc Toan[a,b] and Nguyen Dinh Thanh[b]

[a]Institute for Chemistry and Materials, Vietnam Academy of Military Science and Technology, Hanoi, Vietnam; [b]Faculty of Chemistry, VNU University of Science (Vietnam National University), Hanoi, Vietnam

ABSTRACT

Hydroxy derivatives of 4-methyl-2*H*-chromen-2-one were prepared from hydroquinone and resorcinol through their reaction with ethyl acetoacetate. These hydroxy coumarins were then converted into corresponding alkoxy derivatives by reaction with alkyl halides. The yields of 6- and 7-alkoxy-4-methylcoumarins **3a–i** and **4a–i** were 55−95%. Oxidation of these compounds by selenium dioxide under conventional and microwave-assisted heating conditions produced corresponding 4-formyl compounds **5b–h** and **6b–h** with yields of 40−67% and 90−93%, respectively. Several 6- and 7-alkoxy-4-methylcoumarins **3a–i**, **4a–i** and nearly all 6- and 7-alkoxy-4-formylcoumarins **5b–h**, **6b–h** are novel compounds.

GRAPHICAL ABSTRACT



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4-Formylcoumarin; 4-methylcoumarin; microwave-assisted; Riley's oxidation; Williamson ether synthesis

Introduction

Derivatives of coumarin (2*H*-chromen-2-one) found in many applications as fragrances, pharmaceuticals and agrochemicals. Some 4-methylcoumarin derivatives were also useful as anticancer,[1] inflammatory,[2] antioxidant,[3,4] and cytotoxic[4] agents. The functionalization of coumarin ring by formyl group facilitated the synthesis of various compounds that carry this ring based on the properties of the formyl group, such as thiosemicarbazones,[5,6] coumarin-substituted benzothiazole derivatives,[7] coumarin Schiff bases,[8] etc. Their 7-methoxy- and 7-ethoxy derivatives remained as the most selective inhibitors for the coumarin 7-hydroxylase (Coh) enzyme.[9] Literatures have described several pathways for the synthesis of alkoxy coumarins by Pechmann

CONTACT Nguyen Dinh Thanh nguyendinhthanh@hus.edu.vn Faculty of Chemistry, VNU University of Science (Vietnam National University), 19 Le Thanh Tong, Hoan Kiem, Hanoi, Vietnam.

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reaction[10] of substituted phenols with donated electron and methyl or ethyl acetoacetate in the presence of protonic acid (conc. H_2SO_4),[11] Lewis acids (boron trifluoride dihydrate,[12] $AlCl_3$, $ZnCl_2$,[10,13] $ZnCl_2/Al_2O_3$,[14] $ZrCl_4$[15] etc.), zirconyl chloride octahydrate,[16] dehydrating agents (P_2O_5) or montmorillonite clay,[17] and ionic liquids, such as phosphorus oxychloride in 1-butyl-3-methyl-imidazolium chloride ([bmim]Cl), 1-butyl-3-methylimidazolium bromide ([bmim]Br), and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), phosphoric acid and imidazolium dihydrogen phosphate,[18] [bmim]Cl.2$AlCl_3$,[19] (and lastly) Selectfluor™ [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate)].[20] There were also literatures regarding the synthesis of the alkoxy coumarins through Williamson ether synthesis. Several known alkoxy 4-methylcoumarins were prepared by Pechmann of different alkoxy phenols, such as 6-methoxy-4-methylcoumarin from 3-methoxyphenol,[16] 6-ethoxy-4-methylcoumarin from 6-ethoxyphenol,[4] 7-methoxy-4-methylcoumarin from 3-methoxyphenol,[19] and 7-ethoxy-4-methylcoumarin from 3-ethoxyphenol.[20]

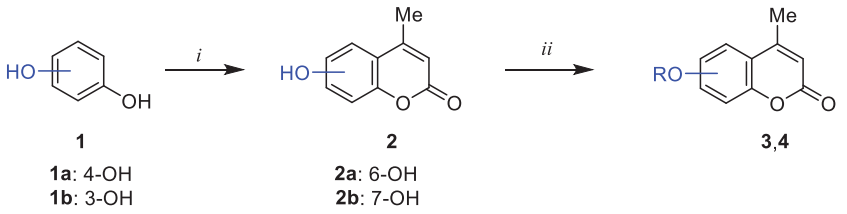
It is well known that the formyl group could be introduced on benzene moiety when coumarins bearing the hydroxy group on this aromatic ring (so-called hydroxycoumarins) by reaction with hexamethylenetetramine in hot acetic acid (Sommelet reaction)[21] or on 2*H*-pyran-2-one moiety in positions 3 or 4. A series of substituted 3-formylcoumarins were prepared from 3-cyanocoumarinsby reduction of 3-cyanocoumarins with Raney nickel in formic acid.[22] Other preparation methods for these aldehydes included reaction of trimethylsilyl propiolate esters of salicylaldehydes with DABCO in THF,[23] dibromination of 3-methylcoumarin with subsequent hydrolysis in AcONa/AcOH (for preparation of 7-butoxy-3-formylcoumarin),[24,25] Rosenmund reduction of some coumarin-3-carbonyl chlorides,[26] or through unusual rearrangement of 2-morpholino-3-cyanochromenes.[27] 7-Dialkyl- and diarylaminocoumarins could also react with Vilsmeier reagent to give 3-formyl derivatives.[28] 3-Methylcoumarin and its 6-chloro- and 6-bromo-substituted derivatives can be converted into corresponding 3-carbaldehydes by selenium dioxide oxidation under microwave-assisted conditions.[29]

4-Methyl coumarins could be converted into 4-formylcoumarins using different oxidizing agents with good yields.[30–32] Holiyachi et al.[33] reported that substituted 4-formylcoumarins could be prepared from corresponding 4-bromomethylcoumarins by using excesses DMSO in presence of base (TEA/Na2CO3) under heating conditions (Kornblum's oxidation).[34,35] In this protocol, some substituted 4-formylcoumarins were synthesized with different substituents on benzene ring, including 6- or 7-methyl, 6-methoxy, 7-hydroxy, 5,7-dimethyl, 6-chloro, and 6-bromo groups, with yields of 84−91% and solvent DMSO did not be recycled.[33] Lin et al. examined the two-step synthetic path for substituted 4-formylcoumarins[36] by hydrolysis of corresponding 7-methyl- and 7-hydroxy-4-chloromethylcoumarins and subsequent oxidation of the obtained coumarin alcohols with manganese dioxide as oxidant under reflux in THF. In Lin's protocol, 4-methyl group on coumarin ring should be converted into 4-chloromethyl first. Methyl group in methyl arenes and methyl heteroarenes could be oxidized directly into formyl one by using the selenium dioxide-mediated oxidation (Riley's oxidation).[37,38] Razzak Mahmood Kubba et al. also obtained 4-formyl-7-hydroxycoumarin with yield of 35% by SeO_2-oxidation of 7-hydroxy-4-methylcoumarin.[39] Ito and Kaoru used selenium dioxide in xylene as the specific oxidizing agent in cases of 7-substituted

4-methylcoumarins (with substituents being H, Me, NEt_2, Ac, OH) for 8 h under reflux in yields of 27−75%.[30,32] Tanakao et al. prepared 4-formyl-7-methoxycoumarin with yield of 26% by using SeO_2-oxidation in dry chlorobenzene for 20 h.[40] Gonçalves et al. converted 6-methoxy-4-methyl-2-oxo-2*H*-benzo[*h*]benzopyran into 4-formyl derivative (with yield of 79%) by heating the compound with selenium dioxide in chlorobenzene under reflux for until 36 h.[41] El Azab et al. prepared 4-formyl-6-hydroxycoumarin from corresponding 6-hydroxy-4-methylcoumarin using SeO_2 in DMF in the presence of glacial AcOH (with catalytic amount)[42] by using conventional and microwave-assisted heating methods with yields of 85 and 97%, respectively. Wang et al. performed the SeO_2-oxidation of 6,7-dimethoxy-4-methylcoumarin in xylene to produce corresponding 4-formyl coumarin with yield of 91%.[43] Buechi et al. synthesized 5-benzyloxy-7-methoxy- and 5,7-dibenzyloxy-4-formylcoumarins in yields of 93% from corresponding 4-methyl derivatives using resublimed selenium dioxide in xylene for 6 hrs. Gabr prepared three 4-formyl coumarin derivatives including 6,8-dichloro-, 6,8-dimethoxy-7-methyl and 7-amino-4-formylcoumarins with yields of 72, 87, and 51%, respectively, from corresponding 4-methyl derivatives by SeO_2-oxidation in xylene for 24 h.[44] Bray et al. prepared 6-(*tert*-butyldimethylsilyloxy)-4-formyl-7-methylcoumarin with yield of 78% by heating 4-methyl derivative and SeO_2 in xylenes at 100 °C.[45] Moorthy et al. synthesized 6- and 7-fluoro-, 6- and 7-chloro-, 7-bromo- and unsubstituted 4-formylcoumarins with yields of 58−87% by melting corresponding 4-methylcoumarins with SeO_2 at 160−170 °C for 1 h.[46] Until now there has been no publication for the synthesis of 4-formylcoumarins having alkoxy groups on benzene ring directly from corresponding alkoxy 4-methylcoumarins, except report from Wu F. and coworkers.[47] In their article, the synthesis of several substituted 4-formylcoumarin (with 7-methyl and 7-methoxy groups) were described but the complete physical and spectral data for the synthesized aldehydes were not included. Thus, in this article, we have reported the synthesis of some 6- or 7-alkoxy-4-methylcoumarins and their oxidation into corresponding 4-formylcoumarins by using activated SeO_2 under conventional and microwave-assisted heating methods. We hoped that these synthesized substituted 4-formyl coumarins will be important initial materials for further studies in the synthesis of compounds with coumarin ring. The synthesis of substituted 4-formylcoumarins created the opportunity to functionalize the coumarin ring and facilitate the transform associated with this heterocycle.

Results and discussions

We have provided the synthetic pathway of alkoxy 4-formylcoumarins derived from 6- and 7-hydroxy-4-methylcoumarins (Scheme 1). Hydroxycoumarins were easily obtained from corresponding dihydroxy benzene (hydroquinone and resorcinol); the former was transformed into ether using Williamson ether synthesis, followed by an oxidation reaction using selenium dioxide as an oxidant. 6-Hydroxy-4-methylcoumarin (**2a**) and 7-hydroxy-4-methylcoumarin (**2b**) needed for this study were prepared from hydroquinone (**1a**) or resorcinol (**1b**), respectively, by Pechmann reaction with ethyl acetoacetate in the presence of concentrated sulfuric acid as catalyst according to Russell's procedure.[11] Next, these 6- and 7-hydroxy-4-methylcoumarins (**2a** and **2b**) would be



1

1a: 4-OH
1b: 3-OH

2

2a: 6-OH
2b: 7-OH

3,4

3a: RO =	6-OCH_3	**4a**: RO =	7-OCH_3
3b:	6-OCH_2CH_3	**4b**:	7-OCH_2CH_3
3c:	6-$OCH_2CH_2CH_3$	**4c**:	7-$OCH_2CH_2CH_3$
3d:	6-$OCH(CH_3)_2$	**4d**:	7-$OCH_2(CH_3)_2$
3e:	6-$OCH_2(CH_2)_2CH_3$	**4e**:	7-$OCH_2(CH_2)_2CH_3$
3f:	6-$OCH_2CH(CH_3)_2$	**4f**:	7-$OCH_2CH(CH_3)_2$
3g:	6-$OCH_2(CH_2)_3CH_3$	**4g**:	7-$OCH_2(CH_2)_3CH_3$
3h:	6-$OCH_2CH_2CH(CH_3)_2$	**4h**:	7-$OCH_2CH_2CH(CH_3)_2$
3i:	6-$OCH_2CH{=}CH_2$	**4i**:	7-$OCH_2CH{=}CH_2$

Scheme 1. Synthetic path for 6- and 7-alkoxy-4-methylcoumarins from corresponding 6- or 7-hydroxycoumarins. Reaction conditions: (i) 1. Ethyl acetoacetate, 85% H_2SO_4, 10–25 °C, 24 h; 2. 5% NaOH solution, then 20% H_2SO_4 solution;[11] (ii) see Tables 1 and 2.

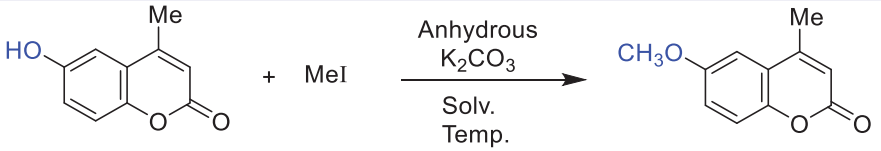
converted into corresponding various 6- or 7-alkoxy-4-methylcoumarins (**3a–i**, **4a–i**) by bimolecular nucleophilic substitution reaction of corresponding hydroxy-4-methylcoumarins with appropriate alkyl iodides or bromides (Williamson′s ether synthesis).

First, we have examined the influences of the bases and solvents on the reaction times and the yield of the ether products. Reaction of 6-hydroxy-4-methylcoumarin with methyl iodide was chosen as the model reaction (Table 1). The bases used in Williamson ether synthesis of phenols (in this research they were 6- and 7-hydroxy-4-methylcoumarins) could be potassium carbonate, sodium carbonate, sodium hydroxide, and sodium hydride.[48–50] It is known that coumarin ring readily opened in the presence of strong bases (also strong nucleophiles), such as NaOH,[51] NaOEt (in abs. ethanol, under reflux),[52] NaH (in THF at $-30 \div -40$ °C),[53] or NaH in THF in the presence of methyl iodide at room temperature or under reflux.[54] Thus, these bases were not used in our research, and only K_2CO_3 and Na_2CO_3 were chosen as base in examining the above-mentioned model reaction. We conducted preliminary investigations of the influences of sodium and potassium carbonates as basic catalyst and acetone as solvent on the yield of ether **3a**. We found that the use of Na_2CO_3 instead K_2CO_3 caused yield of **3a** to decrease (yield of 70% with Na_2CO_3 *v.s.* yield of 87% with K_2CO_3 for 6 h under reflux). The lower yield could be due to the lower basicity of the Na_2CO_3 in comparison with K_2CO_3.[55]

The solvents used for these investigations were dried solvents, such as acetone, acetonitrile, DMF, and DMSO. The influence of these solvents on the yield of 6-methoxy-4-methylcoumarin **2a** were evaluated. In these processes, anhydrous potassium carbonate was used to promote Williamson ether reaction. The obtained results were listed in Table 1.

The results in Table 1 showed that the use of acetone as a solvent was more appropriate for this reaction, resulting in higher yields of **3a** (87 and 90 for 6 and 12 h under reflux, Entries 1 and 2, respectively), whereas acetonitrile (Entries 4 and 5) gave lower yields of **3a** (84 and 85% for 6 and 12 h, respectively) depending on the reaction time. The remaining solvents, DMF (Entries 6, 7, and 8), and DMSO (Entries 9,10) also gave

Table 1. Optimization of solvent conditions for the synthesis of methoxy ether of 6-hydroxy-4-methylcoumarin (**3a**).



2a **3a**

Entry	Solvents[a]	Reaction time (h)[b]	Reaction temp. (°C)[c]	Yield of 6**a** (%)[d]
1	Acetone	6	56	87
2	Acetone	**16**	**56**	**90**
3	Acetone	24	56	92
4	Acetonitrile	6	82	84
5	Acetonitrile	12	82	85
6	DMF	6	100	66
7	DMF	12	100	69
8	DMF	24	100	64
9	DMSO	6	100	57
10	DMSO	12	100	56

[a]Volumes of reaction solvents: Acetone, 20 mL, Acetonitrile, 20 mL, DMF, 15 mL, DMSO, 15 mL;
[b]Reaction was monitored based on the disappearance of **2a** by TLC (toluene/ethyl acetate = 1:2 by volume);
[c]At boiling point of reaction solvent, except DMF, DMSO: reaction temperature was 70 °C;
[d]Isolated yields.
The bold values mean the optimal reaction conditions in this synthetic study.

lower yields. DMF and DMSO gave lower yields relative to the solubility of the products and were difficult to handle. The removal of DMF or DMSO from reaction mixture was difficult even at reduced pressure, and on a workup of reaction mixtures, most of the product was lost with DMF-water or DMSO-water mixtures. The product yields in these cases were about 64−69% and 56−57%, respectively. Conversely, the use of dried acetone or acetonitrile as the solvent for this reaction held several advantages, and both solvents gave remarkable and similar yields (Entries 1−5). Acetone could easily be removed from the reaction mixture in vacuum due to its low boiling point, and its removal would not affect product yields, even with temperature-sensitive products (ethers **3i** and **4i**, for reactions of allyl bromide with **2a** in Entries 8 and 18, respectively, in Table 2). Extending the reaction time (from 24 h to 36 h, Entries 1−3) increased the yields unremarkably, 90 vs. 92% (Entries 2 and 3).[55]

Therefore, the optimal reaction conditions were dried acetone as a solvent, anhydrous K_2CO_3 as a base, and the reaction time of 24 hours at a temperature of 56 °C. These conditions were used in the synthesis of other ethers **3b–i** and **4a–i**. In case of alkyl chloride or alkyl bromide, a small amount of KI (1 mol%) was supplemented to the reaction mixture in order to promote the S_N2 process. The obtained results were listed in Table 2. Yields of 6- and 7-alkoxy-4-methylcoumarins **3a–i** and **4a–i** were 55−95%.

Almost all obtained 6- and 7-alkoxycoumarins in this study are novel compounds, and their structures were confirmed by spectroscopic methods. IR spectra of compounds **3a–i** and **4a–i** displayed characteristic absorption bands at 1737−1708 cm^{-1} (C=O lactone), 1293−1242 cm^{-1} and 1170−1142 cm^{-1} (C−O−C group in lactone and ether functional groups). ^1H NMR showed chemical shifts at 7.66−6.17 ppm (coumarin protons) and 4.03−0.88 ppm (protons in the alkoxy group). Methylene group attached to oxygen atom had signal at about 4.07−4.00 ppm. ^{13}C NMR

Table 2. Synthesis of 6-alkoxy- and 7-alkoxy-4-methylcoumarins (**3a–i, 4a–i**).

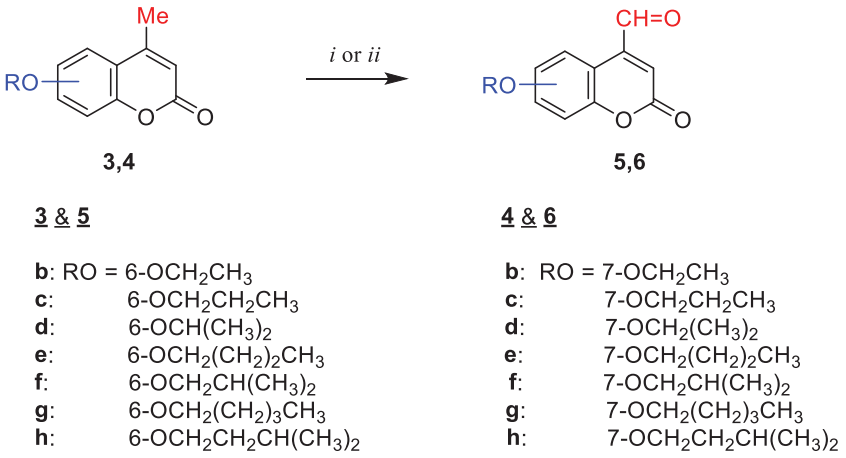
Entry	R		Reaction time (h)[a,b]	Yield (%)[c]
1	6-Methoxy	**3a**	16	92
2	6-Ethoxy	**3b**	16	85
3	6-Propoxy	**3c**	16	75
4	6-Isopropoxy	**3d**	16	60
5	6-Butoxy	**3e**	12	85
6	6-Isobutoxy	**3f**	12	75
7	6-Pentoxy	**3g**	12	84
8	6-Isopentoxy	**3h**	12	79
9	6-Allyloxy	**3i**	12	85
10	7-Methoxy	**4a**	18	90
11	7-Ethoxy	**4b**	18	85
12	7-Propoxy	**4c**	15	70
13	7-Isopropoxy	**4d**	15	75
14	7-Butoxy	**4e**	12	55
15	7-Isobutoxy	**4f**	12	57
16	7-Pentoxy	**4g**	12	95
17	7-Isopentoxy	**4h**	12	82
18	7-Allyloxy	**4i**	12	87

Note: [a]Reaction conditions: R−Cl, R−Br or R−I, K_2CO_3, acetone, under reflux;
[b]In cases of chlorides and bromides, KI (1 mol%) was added;
[c]Isolated yields.

spectra displayed resonance signals of carbon atoms in molecules, for examples, at 160.6−101.1 ppm (carbon atoms in the coumarin component, except C=O lactone atom), 162.2−159.9 ppm (carbon atom in C=O lactone group), 30.7−10.7 ppm (carbon atoms in the alkoxy group, except methylene carbon atom attached to oxygen) depending on their positions in carbon alkyl chain, and 74.3−64.2 ppm (methylene carbon atom attached to oxygen).

Methyl group on position 4 of 6- and 7-alkoxy-4-methylcoumarins was converted into formyl group by oxidation using activated selenium dioxide as selective oxidant. The solvent used in this oxidation was xylene (Riley's oxidation)[37] according to modified literature procedure.[32] It is known that microwave irradiation accelerates the reactions.[56] As such, besides the conventional heating method, in this study we also performed the SeO_2-oxidation reaction under microwave-assisted conditions. The synthetic pathways for 6- and 7-alkoxy-4-formylcoumarins **5b–h** and **6b–h** were represented in Scheme 2, including the conventional and microwave-assisted heating methods. In the former, the reaction mixture was heated under reflux for 24 hours and the yields of aldehydes **5b–h** and **6b–h** achieved were 40−67%. In the latter, the reaction mixture was heated under microwave-assisted heating conditions for 30−40 min and the yields of these aldehydes obtained were 90−93% (Table 3). The reaction time was dramatically reduced for each substitution from 24 h in conventional heating method to 30−45 min under microwave irradiation conditions. Solvent volume was also reduced from 10 mL in conventional heating method to 2 mL under microwave irradiation conditions. Microwave-assisted reactions were conducted in reaction vessels with reflux condenser in a microwave reactor. We found that SeO2 oxidation carried out under microwave-assisted conditions had some advantages over traditional method: reaction time was shorter (30 vs. 24 hours), product yields were higher (90−93% vs. 40−67%), and solvent amounts were smaller (2 vs. 10 mL, less than 5 times.

IR spectra of these aldehyde compounds **5b–h** and **6b–h** displayed characteristic absorption bands for functional groups that are present in the molecule.



Scheme 2. Synthetic path for substituted 6-alkoxy- and 7-alkoxycoumarins. Reaction conditions: (i) activated SeO_2, xylene, for 24 h under reflux conditions; (ii) activated SeO2, xylene, under microwave-assisted reflux conditions for 30−45 min.

Table 3. Synthesis of 6-alkoxy- and 7-alkoxy-4-formylcoumarins **5b–h, 6b–h**.

			Conventional heating procedure (Method A)		Microwave-assisted heating procedure (Method B)[a]	
Entry	R		Reaction time (h)	Yield (%)[b]	Reaction time (min)	Yield (%)[b]
1	6-Ethoxy	**5b**	24	65	30	90
2	6-Propoxy	**5c**	24	67	30	93
3	6-Isopropoxy	**5d**	24	50	30	92
4	6-Butoxy	**5e**	24	41	45	91
5	6-Isobutoxy	**5f**	24	40	45	92
6	6-Pentoxy	**5g**	24	62	45	90
7	6-Isopentoxy	**5h**	24	50	45	90
8	7-Ethoxy	**6b**	24	60	30	92
9	7-Propoxy	**6c**	24	50[b]	30	91
10	7-Isopropoxy	**6d**	24	60	30	90
11	7-Butoxy	**6e**	24	50[c]	45	92
12	7-Isobutoxy	**6f**	24	46	45	92
13	7-Pentoxy	**6g**	24	40	45	91
14	7-Isopentoxy	**6h**	24	40	45	91

Note: [a]At microwave power of 450 W;
[b]isolated yield.

Intense absorption bands characterized the stretching vibration for these functional groups, for examples, in region at 1737−1712 cm^{-1} ($\nu_{C=O}$ lactone), 1710−1700 cm^{-1} ($\nu_{C=O}$ aldehyde), 1270−1243 cm^{-1} and 1151−1145 cm^{-1} (ν_{COC} lactone and ether). The benzene ring of coumarin had some characteristic absorption bands for aromatic C=C bonds in region at 1540−1480 cm^{-1}. ^{1}H NMR spectra exhibited chemical shifts in accordance with the structure of compounds **5b–h** and **6b–h**. Protons of coumarin ring had chemical shifts in region at $\delta = 8.00-6.33$ ppm with the splitting pattern in agreement with the substitution on benzene ring of coumarins. Proton of the formyl group gave resonance signal at $\delta = 10.1-10.2$ ppm, while alkyl protons had chemical shifts in region at $\delta = 1.94-0.84$ ppm. ^{13}C NMR spectra displayed resonance signals of carbon atoms that are present in the molecule, with the C atoms in the aldehyde group

showing a resonance signal of nearly 193.8 ppm, the C atoms within coumarin showing signal at $\delta = 155-109$ ppm, and the C-alkyl atoms showing signal at $\delta = 20-10$ ppm.

Conclusion

6-Alkoxy- and 7-alkoxy-4-methylcoumarins were readily prepared by Williamson ether synthesis from corresponding 6- or 7-hydroxy-4-methylcoumarins using acetone as solvent and potassium carbonate as base. The yields of 6- and 7-alkoxy-4-methylcoumarins **3a–i** and **4a–i** were 55−95%. The 4-methyl group of these compounds were converted into 4-formyl functional group by oxidation using activated selenium dioxide as oxidant under conventional and microwave-assisted heating conditions. The yields of 6- and 7-alkoxy-4-formylcoumarins **5b–h** and **6b–h** were 40−67% and 90−93%, respectively. Almost all 6- and 7-alkoxy coumarins **3a–i** and **4a–i** and 6- and 7-alkoxy-4-formylcoumarins **5b–h** and **6b–h** are novel compounds and were characterized by spectral (IR, NMR and mass) methods.

Experimental

Melting points were determined by open capillary method on STUART SMP3 (BIBBY STERILIN, UK). The IR spectra were recorded on FT-IR Affinity-1S Spectrometer (Shimadzu, Japan) in KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded on Avance AV500 Spectrometer (Bruker, Germany) at 500 MHz and 125 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts, δ, are given in parts per million (ppm), and spin multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). Coupling constants, *J*, are expressed in hertz (Hz); ESI-mass spectra were recorded on LC-MS LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) or Agilent 6310 Ion Trap (Agilent Technologies Inc., USA) in methanol/dichloromethane or methanol using ESI method. The analytical thin-layer chromatography (TLC) was performed on silica gel 60 WF_{254} aluminum sheets (Merck, Germany) and was visualized with UV light or by iodine vapor. Chemical reagents in high purity were purchased from the Merck Chemical Company (in Viet Nam). All materials were of reagent grade for organic synthesis. The reaction was monitored by thin-layer chromatographic method (solvent system was toluene/ethyl acetate = 1:2 by volume). 4-Methyl-6-hydroxy-2*H*-chromen-2-one (**2a**), 4-methyl-7-hydroxy-2*H*-chromen-2-one (**2b**) were prepared according to literature procedure [11] from hydroquinone (**1a**) and resorcinol (**1b**), respectively. Synthetic procedures and analytical data (IR, ^{1}H, ^{13}C NMR, ESI-MS, ESI-HRMS, and elemental analysis) for compounds, **3a–i**, **4a–i**, **5b–h**, and **6b–h** can be found via the "Supplementary Material" of this article's webpage.

General procedure for synthesis of 6-alkoxy- and 7-alkoxy-4-methylcoumarins (3a–i,4a–i)

To the suspension of 4-methyl-6- or 7-hydroxy-2H-chromen-2-ones (**2a** or **2b**, 0.02 mol), respectively, in dry appropriate solvent (Tables 1 and 2) was added anhydrous

potassium carbonate (0.04 mol, 5.5 g). The mixture was heated under reflux for 10 min with stirring. Appropriate alkyl bromide or alkyl iodide was added and reaction mixture continued to heat under reflux for appropriate time (Tables 1 and 2). Solvent was removed completely under reduced pressure. Water (20 mL) was added to residue in order to dissolve inorganic salts. The precipitate was filtered, washed with water until pH 7, crystallized from 96% ethanol to yield the title compounds **3a–i**, and **4a–i**. Synthesis of several typical compounds was described below.

4-Methyl-6-ethoxycoumarin (3b)

From **2a** (0.02 mol, 3.52 g), ethyl iodide (0.024 mol, 1.93 mL). Yield: 3.47 g (85%) of **3b** as pale-yellow crystals. M.p.: 116−117.5 °C (from 96% ethanol), ref.:[4] 161–162 °C (from 96% ethanol). IR (KBr), ν (cm^{-1}) 1715 ($\nu_{C=O}$ lactone), 1572, 1485 ($\nu_{C=C}$ arene), 1165 &1067 (ν_{COC} lactone); ^{1}H NMR (500 MHz, DMSO-d_6, ppm), δ (ppm): 7.27 (d, J = 9.0 Hz, 1H, H-8), 7.16 (dd, J = 9.0, 2.5 Hz, 1H, H-7), 7.11 (d, J = 2.5 Hz, 1H, H-5), 6.34 (s, 1H, H-3), 4.07 (q, J = 7.0 Hz, 2H, 6-O**CH$_2$**CH$_3$), 2.39 (s, 3H, 4-CH$_3$), 1.35 (t, J = 7.0 Hz, 3H, 6-OCH$_2$**CH$_3$**); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 160.3 (C=O lactone), 155.3 (C-6), 153.4 (C-8a), 147.6 (C-4), 120.5 (C-5), 119.7 (C-7), 117.8 (C-8), 115.1 (C-4a), 109.2 (C-3), 64.2 (6-O**CH$_2$**CH$_3$), 18.6 (4-CH$_3$), 15.0 (6-OCH$_2$**CH$_3$**); ESI-MS: $C_{12}H_{12}O_3$, calc. for M = 204.1 Da, found: m/z 204.2 ($[M]^+$); ESI/HRMS: calcd. for M + H = 205.0865 Da, found: m/z 205.0873 ($[M+H]^+$, 100%); Elemental anal. for $C_{12}H_{12}O_3$, calcd.: C, 70.58; H, 5.92%; found: C, 70.33; H, 5.81%.

General procedure for synthesis of 6- and 7-alkoxy-4-formylcoumarins (5b–h,6b–h)

Method A. Conventional heating procedure

To the solution of appropriate 6- or 7-alkoxycoumarins (**3b–h**, **4b–h**) (2 mmol) in dry xylene (10 mL) was added activated selenium dioxide (3 mmol, 333 mg). The mixture was boiled (at boiling point of solvent) under reflux for 24 h with stirring. The hot reaction mixture was filtered, the filtrate was cooled in ice bath, and the separated product was filtered, crystallized from toluene to afford the title compounds (**5b–h**, **6b–h**).

Method B. Microwave-assisted heating procedure

To the solution of appropriate 6- or 7-alkoxycoumarins (**3b–h**, **4b–h**) (2 mmol) in dry xylene (2 mL) was added activated selenium dioxide (3 mmol, 333 mg). The mixture was heated under microwave-assisted reflux conditions at power of 450 W for 30−45 min (Table 3). The hot reaction mixture was filtered, the filtrate was cooled in ice bath, and the separated product was filtered, crystallized from toluene to afford the title compounds (**5b–h**, **6b–h**).

4-Formyl-6-ethoxycoumarin (5b)

From **3b** (2 mmol, 408 mg). Yield: 283 mg (65%, method A), 392 mg (90%, method B) of **5b** as yellow crystals. M.p.: 167−168 °C (from toluene). IR (KBr), ν cm^{-1}: 1736 ($\nu_{C=O}$ lactone), 1708 ($\nu_{C=O}$ aldehyde), 1565, 1430 ($\nu_{C=C}$ arene), 1243 &1054 (ν_{COC}

lactone); ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 10.15 (s, 4-CHO), 7.96 (d, $J = 3.0$ Hz, 1H, H-5), 7.40 (d, $J = 9.0$ Hz, 1H, H-8), 7.27 (dd, $J = 9.5$, 3.0 Hz, 1H, H-7), 7.16 (s, H, 1H, H-3), 4.09 (q, $J = 7.0$ Hz, 2H, 6-O**CH$_2$**CH$_3$), 1.37 (t, $J = 7.0$ Hz, 3H, 6-OCH$_2$**CH$_3$**); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 193.6 (4-CHO), 160.1 (C= O lactone), 155.0 (C-6), 148.2 (C-4), 143.0 (C-8a), 125.3 (C-4a), 119.9 (C-7), 117.3 (C-8), 109.1 (C-3), 63.7 (6-O**CH$_2$**CH$_3$), 14.5 (6-OCH$_2$**CH$_3$**); ESI-MS: $C_{12}H_{10}O_4$, calcd. for M + H = 219.07 Da, M + Na = 241.05 Da, found: *m/z* 219.15 ([M + H]$^+$), 241.11 ([M + Na]$^+$); ESI-MS: calcd. for M + H = 219.0657 Da, found: *m/z* 219.0685 ([M + H]$^+$, 100%); ESI-HRMS: calcd. for M + H = 219.0657 Da, found: *m/z* 219.0661 ([M + H]$^+$, 100%); Elemental anal. for $C_{12}H_{10}O_4$, calcd.: C, 69.46; H, 5.30%; found: C, 69.57; H, 5.41%.

Disclosure statement

No potential conflict of interest was reported by the author(s). Vu Ngoc Toan is principal author, Nguyen Dinh Thanh is corresponding author.

ORCID

Vu Ngoc Toan http://orcid.org/0000-0002-4424-7078
Nguyen Dinh Thanh http://orcid.org/0000-0002-2267-1775

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