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Syntheses of 3-Chloro-7-[(Chlorocarbonyl)Methoxy]-4-Methylcoumarin

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SYNTHESES OF 3-CHLORO-7-[(CHLOROCARBONYL)METHOXY]-4-METHYLCOUMARIN

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ABSTRACT: Two efficient syntheses of 3-chloro-7-[(chlorocarbonyl)methoxy]-4-methylcoumarin are described, one utilizing traditional chemistry starting from 3-chloro-7-hydroxy-4-methylcoumarin, while the other uses a novel reagent, sulfuryl chloride/thionyl chloride, in a one-pot reaction starting from 7-(carboxymethoxy)-4-methylcoumarin.

Naturally occurring materials have proven to be a valuable source of novel agents that exhibit antineoplastic activity[1-4]. Due to the unique structural features typical of these compounds, developing suitable methodologies for their quantitative analysis in biological fluids often presents a formidable challenge. Many of the natural products that are presently undergoing evaluation as candidate anticancer drugs possess aliphatic hydroxyl substituents[1], thereby presenting sites for chemical modification to facilitate their determination. Within

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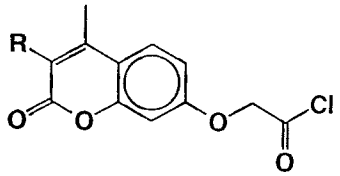


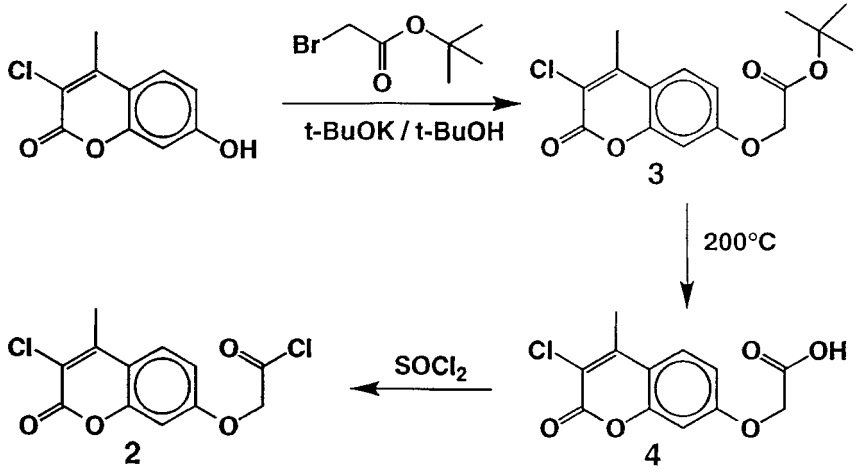
1 R = H

2 R = Cl

this context, 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin **1**[5] was assessed as a fluorescent precolumn derivatizing reagent for the liquid chromatographic analysis of hydroxylated natural products. However, in our hands, the reported synthesis of **1**[5] persistently lead to the production of a minor (<2%), but highly fluorescent impurity, which we subsequently determined to be 3-chloro-7-[(chlorocarbonyl)-methoxy]-4-methylcoumarin **2**. A search of the literature revealed that **2** had not been previously reported. Accordingly, our attention was directed toward the synthesis of **2** on a preparative scale, recognizing that derivatives of hydroxylated compounds with **2** could potentially be detected with much greater sensitivity than derivatives with **1**.

Repeated attempts to apply Karlsson's strategy for the synthesis of **1**[5] to the preparation of **2** were unsuccessful. However, a three-step synthesis of **2** was devised (Route 1) and satisfactorily performed. The first step is essentially a Williamson ether synthesis. Using *tert*-butanol as the solvent, commercially available 3-chloro-7-hydroxy-4-methylcoumarin was reacted with *tert*-butyl α-bromoacetate in the presence of potassium *tert*-butoxide to give a 77% yield of 3-chloro-7-[(1,1-dimethylethoxy)carbonyl)methoxy]-4-methylcoumarin **3**.

ROUTE 1



Classically used as a protecting group for carboxylic acids, the base-stable *tert*-butyl carboxylate can be cleaved under mildly acidic conditions[6-8]. Alternatively, deprotection may be accomplished by simply applying heat to induce a pyrolytic rearrangement, affording the desired product acid and gaseous 2-methylpropene as by-product[9]. When solid **3** was heated briefly to 200°C, the corresponding carboxylic acid **4** was produced in 95% isolated yield. Finally, the reaction of **4** with thionyl chloride yielded **2**.

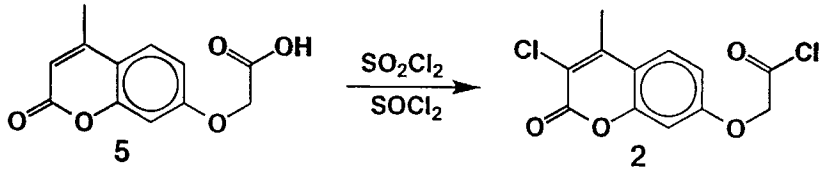
Each of the reactions in this three-step sequence were performed at least three times. The *average* yield for the first, second and third steps were 79%, 92% and 85%, respectively, thus giving an *average* overall isolated yield of 62% for the method. The key to the synthetic strategy was to employ *tert*-butyl α-bromoacetate as the means to introduce the carboxymethoxy group as a protected

functionality. This promoted the efficient isolation of reaction intermediates, thereby ensuring a final product of high purity, and facilitating the preparation of **2** in gram quantities.

The second synthetic route to **2** resulted from consideration of the source of the contaminant (**2**) observed upon application of Karlsson's method for the preparation of **1**. In this procedure, thionyl chloride was used to effect halo-de-hydroxylation of the carboxylic acid group. However, commercial reagent grade thionyl chloride is known to contain a small quantity of sulfuryl chloride (1-2%), a potent chlorinating agent[10] that has been used specifically for α-chlorinating carbonyl compounds[11], cyclohex-2-enones[12] and sulfoxides[13]. Evidently, attempted purification of the reagent by distillation is ineffective in removing the sulfuryl chloride. Therefore, the introduction of a chlorine atom at an activated position on 7-(carboxymethoxy)-4-methylcoumarin **5** by the action of sulfuryl chloride is not unexpected. To demonstrate that chlorination of the coumarin at position 3 was due to the presence of sulfuryl chloride, and not the result of sequential chlorination by thionyl chloride, the reaction was performed with increasing sub-equimolar quantities of sulfuryl chloride added to thionyl chloride. This resulted in a concomitant increase in the proportion of **2** relative to **1** in the reaction mixtures. With this preliminary evidence suggesting that sulfuryl chloride selectively introduces a chlorine atom at the 3-position of the coumarin, a convenient single-step synthesis of **2** was envisioned (Route 2).

Using thionyl chloride as the solvent, **5** was reacted with an equimolar amount of sulfuryl chloride. This interesting one-pot synthesis allowed the

ROUTE 2



simultaneous but independent creation of two very dissimilar functional groups, namely an α-chloro lactone from chlorination of the pyranone portion of the coumarin and an acyl chloride upon chlorination of the aryloxyacetic acid moiety. The reaction proceeded smoothly to afford **2** in 57% isolated yield.

In summary, 3-chloro-7-[(chlorocarbonyl)methoxy]-4-methylcoumarin **2**, which was desired for the fluorescent labelling of primary and secondary hydroxyl groups, was observed as a highly fluorescent contaminant in the preparation of the known derivatization reagent 7-[(chlorocarbonyl)methoxy]-4-methylcoumarin **1**. Two synthetic routes to **2** have been developed, both of which are convenient methods for preparing gram quantities of this new reagent. One route utilizes traditional chemistry starting from 3-chloro-4-methyl-7-hydroxycoumarin, while the other uses a new and interesting reagent, sulfuryl chloride/thionyl chloride, in a novel one-pot reaction starting from 7-(carboxymethoxy)-4-methylcoumarin.

EXPERIMENTAL

Analytical reagent grade 3-chloro-4-methyl-7-hydroxycoumarin, 2-methyl-2-propanol, *tert*-butyl α-bromoacetate, potassium *tert*-butoxide, toluene, acetone,

thionyl chloride, hexane, 7-(carboxymethoxy)-4-methylcoumarin, and sulfuryl chloride were purchased from Aldrich Chemical Company (Milwaukee, WI), and used as received. All other chemicals were obtained from commercial sources in grades appropriate for direct use. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN). Melting points were determined on a MEL-TEMP II apparatus (Laboratory Devices, Holliston, MA) and are uncorrected. ^{1}H-NMR spectra were acquired using a Varian VXR-500 S spectrometer, at 25°C. Samples were dissolved in deuterated solvents (ca. 3 mg in 1.0 ml), and the residual ^{1}H signal of the solvent was used as an internal reference in determining relative chemical shift (δ) values. ^{13}C-NMR spectra were acquired in the presence of broad-band decoupling at 11 Tesla. Nominal resolution (electron-ionization, 70 eV) mass spectra and exact mass measurements were obtained using a Finnigan MAT 90 high resolution mass spectrometer. Samples were introduced into the ion source *via* the solids' direct exposure (high temperature) probe. Exact mass measurements were performed on selected *m/z* values of samples at a static resolution of ca. 6000, using perfluorokerosene (PFK) as an internal standard.

Route 1

3-Chloro-7-[(1,1-dimethylethoxy)carbonyl)methoxy]-4-methylcoumarin (3). To a flask containing 3-chloro-4-methyl-7-hydroxycoumarin (648 mg, 3.08 mmol) was added 2-methyl-2-propanol (20 ml). The resulting mixture was heated to reflux and stirred for 30 minutes to effect dissolution. Heating was discontinued,

and *tert*-butyl bromoacetate (1 ml, 6.16 mmol) was added dropwise with stirring. Following dropwise addition of potassium *tert*-butoxide (3.24 ml of a 1.0 M solution in *tert*-butyl alcohol, 3.24 mmol), the reaction mixture was heated to reflux for 4 hours. The cooled reaction mixture was then concentrated under reduced pressure to give a white, pasty mass. Toluene (67 ml) was added, and the resulting mixture was washed three times with 5% aqueous sodium hydroxide and three times with 1 M aqueous potassium chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure to give 769 mg of **3** as white crystals (2.37 mmol, 77%) mp 128-129°C. ^{1}H-NMR (CD_2Cl_2): δ 7.59 (d ($^3J_{HH}$=9.1 Hz),1H), 6.94 (dd,1H), 6.79 (d, ($^4J_{HH}$=2.6 Hz),1H), 4.56 (s,2H), 2.56 (s,3H), 1.48 (s,9H). ^{13}C-NMR (^{1}H-decoupled; CD_2Cl_2): δ 16.36, 28.08, 66.11, 83.07, 101.85, 113.20, 114.25, 118,35, 126.57, 148.34, 153.28, 157.30, 161.12, 167.22. Mass spectrum (electron-ionization, 70 eV) *m/z* (% relative abundance): 324 ($M^{+\cdot}$, 39), 268 (98), 223 (43), 137 (29), 57 (100). HRMS: *m/z* 324.0754 (calculated for $C_{16}H_{17}O_5{}^{35}Cl$: 324.0765). **Analysis.** Calculated for $C_{16}H_{17}O_5Cl$: C, 59.17; H, 5.28; Cl, 10.92. Found: C, 59.13; H, 5.29; Cl, 11.56.

7-(Carboxymethoxy)-3-chloro-4-methylcoumarin (4). The *tert*-butyl ester of 7-(carboxymethoxy)-3-chloro-4-methylcoumarin (**3**) (761 mg, 2.35 mmol) was placed in a flask and warmed in an oil bath from ambient temperature to 210°C over a period of 15 minutes. After the ester melted, stirring was begun as heating continued. The evolution of 2-methylpropene began at 190°C and became most vigorous at 200°C. Once the temperature attained 205°C, cessation

of 2-methylpropene production was quickly followed by solidification of the reaction mixture. Upon reaching a temperature of 210°C, heating was discontinued and the cooled reaction product was dissolved in a minimum amount of refluxing acetone (25 ml), to which water (30 ml) was added until the solution became turbid. Upon cooling, white crystals formed, which were isolated by filtration to give 600 mg of crystalline **4** (2.24 mmol, 95%) mp 208-210°C. ^{1}H-NMR (acetone-d_6): δ 7.78 (d ($^3J_{HH}$=8.8 Hz),1H), 7.04 (dd,1H), 6.95 (d ($^4J_{HH}$=2.5 Hz),1H), 4.90 (s,2H), 2.58 (s,3H). ^{13}C-NMR (^{1}H-decoupled; acetone-d_6): δ 16.23, 65.54, 102.30, 113.71, 114.52, 118.22, 127.58, 149.09, 153.87, 157.10, 161.97, 169.46. Mass spectrum (electron-ionization, 70 eV) *m/z* (% relative abundance): 268 ($M^{+\cdot}$, 100), 210 (19), 181 (46), 137 (10), 89 (13). HRMS: *m/z* 268.0107 (calculated for $C_{12}H_9O_5{}^{35}Cl$: 268.0138). **Analysis.** Calculated for $C_{12}H_9O_5Cl$: C, 53.65; H, 3.38; Cl, 13.20. Found: C, 53.37; H, 3.43; Cl, 13.74.

3-Chloro-7-[(chlorocarbonyl)methoxy]-4-methylcoumarin (2). To 7-(carboxymethoxy)-3-chloro-4-methylcoumarin (**4**) (101 mg, 0.38 mmol) was added thionyl chloride (1.5 ml, 20.6 mmol). The resulting mixture was stirred and heated to reflux for 1 h. Heating was discontinued and the reaction mixture, a clear yellow-green solution, was stirred at ambient temperature for an additional 18 h. Hexane (8 ml) was then added to the reaction mixture, and the resulting precipitate was collected on a fritted disc filter, which was washed with an additional 10 ml of hexane. The slightly bluish-white solid was then freed of solvent *in vacuo*, yielding 91 mg of crystals of **2** (0.32 mmol, 83%) mp 151-

153°C. ^{1}H-NMR (CD_2Cl_2): δ 7.63 (d ($^3J_{HH}$=9.0 Hz),1H), 6.96 (dd,1H), 6.85 (d ($^4J_{HH}$=2.7 Hz),1H), 5.09 (s,2H), 2.56 (s,3H). ^{13}C-NMR (^{1}H-decoupled; CD_2Cl_2): δ 16.41, 72.63, 102.39, 112.89, 115.24, 119.13, 126.96, 148.12, 153.19, 157.06, 159.63, 170.03. Mass spectrum (electron-ionization, 70 eV) *m/z* (% relative abundance): 286 ($M^{+\cdot}$, 100), 223 (65), 210 (31), 181 (23), 165 (16), 137 (20). HRMS: *m/z* 285.9797 (calculated for $C_{12}H_8O_4{}^{35}Cl_2$: 285.9800).

Route 2

3-Chloro-7-[(chlorocarbonyl)methoxy]-4-methylcoumarin (2). To 7-(carboxymethoxy)-4-methylcoumarin (213.0 mg, 0.91 mmol) was added 3.0 ml of a 3% (v/v) solution of sulfuryl chloride in thionyl chloride. The resulting stirred mixture was heated to and maintained at reflux for 1 hour. Heating was discontinued and the reaction mixture was stirred for an additional 16 hours at ambient temperature. Hexane (30 ml) was added to the clear, light brown solution. The resulting mixture was cooled to and maintained at 5°C for 4 hours. The resulting precipitate was collected by filtration and freed of solvent *in vacuo*, yielding 149.3 mg of crystals of **2** (0.52 mmol, 57%) mp 149-151°C. ^{1}H-NMR (CD_2Cl_2): δ 7.64 (d ($^3J_{HH}$=9.1 Hz),1H), 6.96 (dd,1H), 6.86 (d ($^4J_{HH}$=2.6 Hz),1H), 5.09 (s,2H), 2.57 (s,3H). Mass spectrum (electron-ionization, 70 eV) *m/z* (% relative abundance): 286 ($M^{+\cdot}$, 100), 223 (67), 210 (46), 181 (27), 165 (20), 137 (22). HRMS: *m/z* 285.9810 (calculated for $C_{12}H_8O_4{}^{35}Cl_2$: 285.9800).

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