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SO_4^{2-}/SnO_2-Catalyzed C3-Alkylation of 4-Hydroxycoumarin with Secondary Benzyl Alcohols and *O*-Alkylation with *O*-Acetyl Compounds

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ABSTRACT

Sulfated tin oxide (STO) has been found to be an efficient reusable solid superacid catalyst for C3-alkylation and *O*-alkylation of 4-hydroxycoumarins with benzylic, allylic alcohols/and corresponding acetates respectively, in acetic acid under reflux conditions with good yield of products.

Keywords: C-C and C-O Bond Formations; Sulfated Tin Oxide (STO); Reusability; 4-Hydroxy Coumarin; Secondary Benzyl Alcohol; Secondary Benzyl *O*-Acetate

1. Introduction

Coumarin is a privileged scaffold among heterocyclic and are known to possess a wide range of biological activities including antibiotic, anti-malarial, antifungal, antiviral, and cytotoxic [1-8]. In particular, the 4-hydroxycoumarins and its derivatives (3-alkylated) have evoked a great deal of interest due to their utility as "anticoagulant rodenticides as well as antithrombotic agents" such as warfarin, brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen [9] (**Figure 1**) and also as nonpeptide human immunodeficiency virus (HIV) protease inhibitors [10].

The C3 or *O*-alkylation of 4-hydroxycoumarin (formation of new C-C and C-O bond) is undoubtedly one of the most important and challenging reactions in synthetic chemistry due to its pharmaceutical utility as mentioned above and also can be diversified to synthesize 3,4-substitued compounds [11-14].

Although there are several reports about the C3-alkylation of 4-hydroxycoumarins, most of them need organic halides or boronic acid as substrates by Pd-catalyzed C-C bond formation or base mediated alkylation reactions [15-19]. From the synthetic point of view, alcohols are an attractive source compared to the corresponding halides or boronic acid because of easy availability of starting materials and the generation of water as the only side product.

Alternatively, the alkylation can also be performed under acidic conditions with alcohols as alkylating agents, which is not well explored. A few methods that have been reported for the C3-alkylation of 4-hydroxycoumarin so far with alcohols including strong acids, such as HCl, H_2SO_4, etc. [20-22], $Yb(OTf)_3$ [23], $FeCl_3{\cdot}6H_2O$ [24], Amberlite IR-120 [25], molecular iodine [26], $Bi(OTf)_3$ [27], $Fe(ClO_4)_3{\cdot}xH_2O$ [28], TMSOTf [29], $Bi(NO_3)_3{\cdot}5H_2O$/Ionic liquid system [30], Ir-Sn bimetallic system [31]. However, processes involving conventional acids, are inherently associated with problems such as high toxicity, corrosion, catalyst waste and difficulty in separation and recovery. Some of these catalytic systems have several limitations such as longer reaction times, lack of reusability, poor yields, as well.

Therefore, the development of a new efficient, catalytic method for the direct C3-alkylation of hydroxylcoumarin using alcohols is of greater importance and highly desirable.

In recent years, non-polluting and efficient catalytic technologies are much required, considering that environmental restrictions on emissions are covered in several legislations throughout the world. The substitution of homogeneous liquid acids by heterogeneous solid superacids as catalysts is expected to ease their separation from reaction mixture, less corrosion, allowing continuous operation as well as regeneration and neutralization of the catalyst and lowering the cost of process installation and maintenance [32,33]. Sulfated metal oxides with

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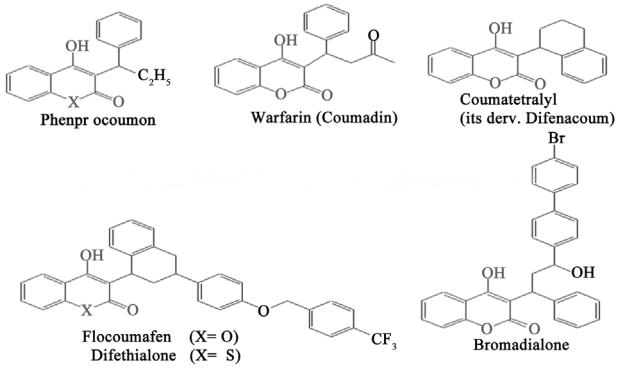


Figure 1. Prominet 3-(benzyl)-substituted 4-hydroxy coumarins.

both Brønsted and Lewis acid sites are widely used as solid super acid catalysts [34,35]. Sulfated metal oxides are stable to moisture, air and heat [36]. They are easy to prepare and environmentally benign [37].

However, in past few years, considerable attention has been given to sulphated tin oxide (hereafter, STO) which is known to possess strongest surface acidic sites [38-41]. STO was found to be efficient and suitable in Mukaiyama aldol condensation reactions, particularly for benzoylation, transesterfication of keto esters, various gas phase reactions, such as hydration, dehydration, alkylation, isomerization, esterification and polymerization reactions, biodiesel production, *β*-acetamido ketones and aryl dibenzo [*a.j*]xanthenes, 2,4,5-Triaryl-1*H*-imidazole, 2,4-diphenyl-4,6,7, 8-tetrahydro chromen-5-one [42-50].

The catalyst can be repeatedly used without sacrificing its catalytic activity, thus rendering heterogeneous character. Moreover, to our knowledge, STO has not yet been explored as a catalyst for the C3- and *O*-alkylation of 4-hydroxycoumarins.

In continuation of our interest in developing novel synthetic methodologies, particularly carbon-carbon, carbon-heteroatom bond formations [51-57], here in we report our brief findings for a highly efficient method for the C-C bond and C-O bond formation *via* STO catalyzed C3-alkylation and *O*-alkylation reactions of 4-hydroxycoumarins with 2^0 benzylic alchols and benzyl *O*-acetates, respectively.

2. Result and Discussion

Initially, the reaction of 4-hydroxycoumarin (**1**, 1 mmol) and 4-methoxy-1-phenylethanol (**2b**, 1.1 mmol) in the presence of STO was chosen as model reaction to develop optimum reaction conditions (**Table 1**).

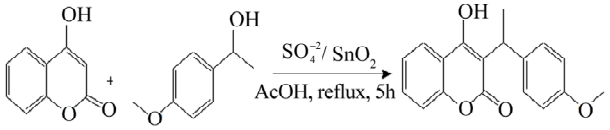
It is evident that the reaction does not progress at RT/reflux (**Table 1**, entry 9) or in the absence of catalyst. Next, different solvents were screened. We found that a remarkable solvent effect, as acetic acid proved to be the suitable solvent for obtaining good yields under reflux conditions for 5 h (**Table 1**, entry 6). Other solvents such as MeOH, EtOH, CH_3CN, IPA gave no product or considerably decreased yields of the products (**Table 1**, entries 1-4). Toluene gave moderate yield, although it took longer reaction time.

A catalytic amount of STO (10 mol%) was sufficient to afford the desired product in good yield. No significant improvements in yields were observed on increasing the catalyst loading (**Table 1**, entry 8). When the reaction was catalyzed by 5 mol% STO, the reaction time was prolonged to 20 h and the desired product (**3b**) was obtained with only 60% (**Table 1**, entry 7). The catalyst could be reused for at least three cycles after activation at 400˚C - 500˚C for 1 h; there was a slight decrease in activity after the third use in the model reaction forming **3b** (72%). Thus, the most suitable reaction conditions for the formation of **3b** were established (**Table 1**, entry 6).

With the optimized reaction conditions in hand (10 mol% STO, AcOH, reflux), we then evaluated the scope of the benzylation of 4-hydroxycoumarin 1 using a variety of structurally divergent reactants and the results are summarized in **Table 2**.

We obtained the corresponding C3-alkylated products in 68% - 81% yields, after 5 h (entries 1-3, **Table 2**). The reaction gave higher yields when benzylic alcohols bear electron-donating groups such as methoxy (entry 2, **Table 2**). When nitro group containing benzylic alcohol was introduced instead of bromo- or methoxy, the reaction did not proceed at all. Intrigued by these results, we adapted this protocol to synthesize an anti-coagulant compound, Coumatetralyl (C, Scheme 1; 3d, **Table 2**) in 70% yield using 4-hydroxycoumarin with 1, 2, 3, 4-

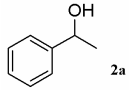
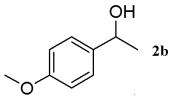
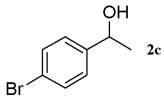
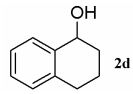
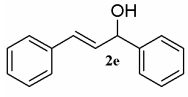
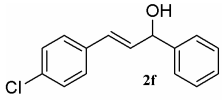
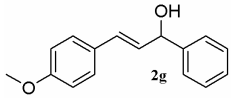
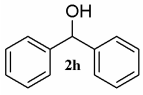
Table 1. Screening for the reaction conditions[a].



Entry	Cat. (mol%)[a]	Solvent	Temp	Time (h)	Yield[b] (%)
1	10	MeOH	Reflux	1	0
2	10	EtOH	Reflux	1	0
3	10	CH_3CN	Reflux	1	0
4	10	IPA	Reflux	1	0
5	10	Toluene	Reflux	10	50
6	10	AcOH	Reflux	5	75
7	5	AcOH	Reflux	20	60
8	20	AcOH	Reflux	5	75
9	0	AcOH	Reflux	24	0

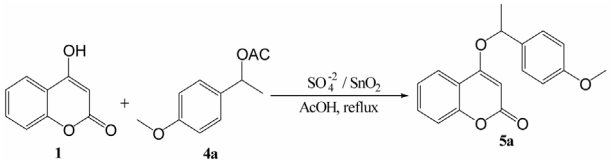
[a]1.0 mmol **1(a)**, 1.2 mmol **2(b)**, cat. SO_4^{-2} /SnO_2 in 10 mL solvent. [b]Isolated yield.

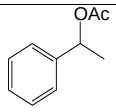
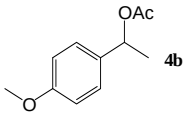
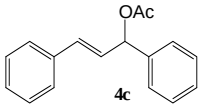
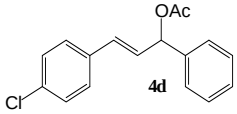
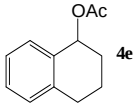
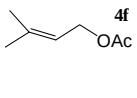
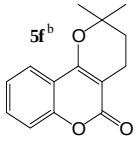
Table 2. C3-alkylation of 4-hydroxycomarin with various alcohols.

Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1		3a	5	72
2		3b	5	75
3		3c	5	68
4		3d	5.5	70
5		3e	6	81
6		3f	6	78
7		3g	6	70
8		3h	20	0

[a]Isolated yields after column chromatography.

Table 3. *O*-allkylation of 4-hydroxycomarin (1) with various acetates.



Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1		5a	4	67
2		5b	4	78
3		5c	5	73
4		5d	5	70
5		5e	6	82
6		 5f[b]	5	65

[a]Isolated yidlds after column chromatography, [b]Intramolecular cyclization.

tetrahydro-1-napthanol (2d). Moreover, we performed this reaction with substituted allylic alcohols (entries 5-7 and 9, **Table 2**) and excellent yields were obtained. When primary benzyl alcohols were used, they failed to give the expected product. These results clearly demonstrate that the direct C3-alkylation of 4-hydroxycoumarin was successful only with secondary benzylic alcohols. Reaction of benzhydrol (2 h) with 4-hydroxycoumarin did not proceed even after refluxing for 20 h (entry 8, **Table 2**).

After successful C3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols (new C-C bond formation), we turned our attention to test the feasibility of secondary benzyl acetates (prepared instantly for the purpose) reacting with 4-hydroxycoumarin under the above optimized conditions to generate novel compounds (5a-e) moderate to good yields (67% - 82%) in the specified time (**Table 3**). This strategy is successfully applied to new C-O bond formation reaction using STO catalysis.

Unexpectedly, when prenyl acetate (4f) was reacted with 4-hydroxycoumarin, we isolated pyranocoumarin in good yield (entry 6, **Table 3**) instead of expected *O*-alkylated product. This method provides a mild and straightforward route to multi-substituted pyranocoumarins [58-60].

The proposed mechanism of this reaction may tentatively be visualized to occur via a tandem sequence of reactions as depicted in **Figure 2** involving removal of water molecule as by-product via formation of stabilized carbocation to act as the alkylating species, derived from alcohol (or else by formation of dimeric ether) in presence of STO using its Bronsted acidic site (C3-Alkylation). Enolic hydroxyl group is activated by Sn metal via Lewis acid catalysis to make the 3-position more nucleophilic. Whereas, in case of *O*-alkylation, activation of carbonyl functionality of acetate making it as leaving group by Sn *via* Lewis acid catalysis and then the formed stabilized carbocation reacts with enolic hydroxide leaving AcOH as byproduct.

3. Conclusions

In summary, in this preliminary communication, we have

successfully employed STO as an efficient catalyst to promote C3-benzylation of 4-hydroxycoumarin using secondary benzyl alcohols such as benzylic and allylic alcohols, and also *O*-alkylation using secondary benzyl acetates. The advantages of this protocol are broad scope, mild conditions, use of inexpensive reusable catalyst, and simplicity of operation since water and acetic acid (solvent) are the only side products, respectively. This method also provides a mild and straightforward route to multi-substituted pyranocoumarins.

Further exploration of the full applicability for the STO catalyzed C3-alkylation and *O*-alkylation using structurally and electronically divergent substrates with substituted 4-hydroxy coumarins, their scope, limitations and biological activity studies is currently underway.

4. Experimental

STO was prepared according to the literature report [45]. All melting points were determined on an Electrothermal Gallenkamp apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini Spectrometer 300 MHz. IR spectra were recorded on Nicolet Fourier Transform spectrometer. Mass spectra were obtained on a 7070H or VG Autospec Mass spectrometer using LSIMS technique. Thin-layer chromatography (TLC) was performed on GF-25U (Anal. Tech) plates and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 100 - 200 mesh.

General experimental procedure for the C3-alkylation of 4-hydroxycoumarins: to a mixture of 4-hydroxycoumarin (1, 1.0 mmol) and secondary benzyl alcohol (2a-h, 1.1 mmol) in acetic acid (10 mL), STO (0.1 mmol) was added and the reaction mixture was stirred for the given time (see **Table 2**) at reflux temperature. After completion of the reaction (monitored by TLC), the reaction mixture was added into water. Adjusted to pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding C3-alkylated 4-hydroxycoumarin (3a-g).

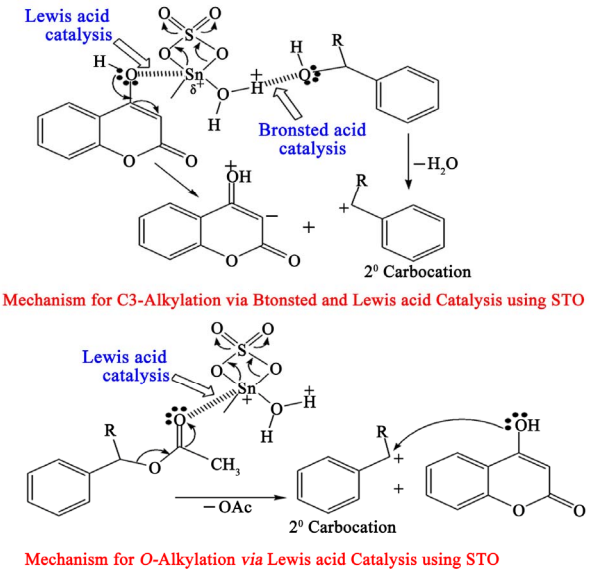


Figure 2. Mechanism for C and *O*-alkylation using STO.

General experimental procedure for the *O*-alkylation of 4-hydroxycoumarins: To a mixture of 4-hydroxycoumarin (1, 1.0 mmol) and secondary *O*-acetyl compound (4a-f, 1.1 mmol) in acetic acid (10 mL), STO (0.1 mmol) was added and the reaction mixture was stirred for the given time (see **Table 3**) at reflux temperature. After completion of the reaction (monitored by TLC), to the reaction mixture was added into water. Adjust pH neutral with sodium carbonate and extracted in ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by silica gel column with petroleum ether/ethyl acetate (1:3) as eluent to afford the corresponding *O*-alkylated 4-hydroxycoumarin (5a-f).

Spectral data for known compounds: 3a,[27] 3b,[26] 3c,[27] 3d,[31] 3e,[30] 3g[26].

Characterization data for new compounds: 3-((E)-3-(4-chlorophenyl)-1-phenylallyl)-4-hydroxy-2H-chromen-2-one (3f): Pale yellow solid, mp: 168˚C - 171˚C. IR (KBr): *v* 3327, 1674, 1626, 1611, 1494, 1393, 1200, 756 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 - 7.72 (m, 2H), 7.57 - 7.28 (m, 11H), 6.78 - 6.68 (m, 1H), 6.48 (d, J = 16.4 Hz, 1H), 5.46 (d, J = 6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 160.9, 152.5, 140.1, 136.2, 133.7, 132.2, 1130.0, 128.7, 128.2, 127.9, 127.6, 126.6, 124.1, 123.2, 116.5, 115.8, 106.5, 44.0 ppm. MS (ESI): *m/z* (rel. abund.%) 389 (M^+, 100), 391 (M^+, 30) ($[M+1]^+$).

4-(1-Phenylethoxy)-2H-chromen-2-one (5a). Off white solid; mp: 214˚C - 218˚C. IR (KBr): *v* 1669, 1621, 1492, 1401, 1218, 1168, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 12.4 Hz, 1H), 7.64 - 7.43 (m, 5H), 7.64 - 7.42 (m, 2H), 7.23 (dd, J = 10.8 Hz, 1H), 5.99 (br s, 1H), 4.74 (q, J = 9.6 Hz, 1H), 1.68 (d, J = 9.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 160.0, 152.6, 141.8, 132.1, 129.8, 127.7, 127.5, 123.9, 123.0, 116.3, 116.2, 110.3, 34.8, 16.8 ppm. MS (ESI): *m/z* (rel. abund.%) 267.3 ($[M+1]^+$, 100).

4-(1-(4-methoxyphenyl) ethoxy)-2H-chromen-2-one (5b): Off white solid. mp: 180˚C - 184˚C. IR (KBr): 1673, 1628, 1514, 1249 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, J = 8.8 Hz, 1H), 7.48 - 7.52 (m, 2H), 7.41 (d, J = 11.2 Hz, 1H), 7.26 - 7.22 (m, 2H), 6.99 (d, J = 4 Hz, 2H), 6.04 (s, 1H), 4.65 (q, J = 10 Hz, 1H), 3.79 (s, 3H), 1.60 (d, J = 9.6 Hz, 3H). ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 159.1, 152.3, 133.1, 131.7, 128.5, 123.8, 122.6, 116.2, 116.1, 114.9, 110.0, 55.3,

33.6, 16.8 ppm. MS (ESI): *m/z* (rel. abund.%) 297.2 ($[M+1]^+$, 100).

4-((E)-1,3-diphenylallyloxy)-2H-chromen-2-one (5c): Pale yellow solid, mp: 132˚C - 136˚C. IR (KBr): *v* 1678, 1626, 1613, 1501, 1394, 1203, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.24 - 7.64 (m, 12H), 6.94 (br, s 1H), 6.67 (dd, J = 6.4, 9.6 Hz, 1H), 6.52 (d, J = 16.4 Hz, 1H), 5.47 (d, J = 5.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 161.5, 152.4, 139.7, 136.3, 133.9, 132.4, 129.2, 128.7, 128.2, 128.7, 127.7, 126.4, 124.4, 123.1, 116.5, 115.7, 106.4, 43.5 ppm. MS (ESI): *m/z* (rel. abund.%) 355.0 ($[M+1]^+$, 100).

4-((E)-3-(4-chlorophenyl)-1-phenylallyloxy)-2H-chromen-2-one (5d): Pale yellow solid, mp: 154˚C - 158˚C. IR (KBr): 1676, 1629, 1616, 1502, 1398, 1210, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (dd, J = 8, 14.8 Hz, 1H), 7.41 - 7.14 (m, 12H), 6.78 - 6.67 (m, 1H), 6.48 (d, J = 16.4 Hz, 1H), 6.41 - 6.35 (m, 1H), 5.44 (dd, J = 5.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 161.1, 152.8, 139.7, 136.2, 133.7, 132.4, 129.6, 128.4, 128.1, 128.0, 127.8, 126.5, 124.1, 123.3, 116.7, 115.6, 106.5, 43.9 ppm. MS (ESI): *m/z* (rel. abund.%) 387 (M^-,100), 389 (M^-, 30) ($[M-1]^-$).

4-(1,2,3,4-tetrahydronaphthalen-4-yloxy)-2H-chromen-2-one (5e): Off white solid, mp: 178˚C - 180˚C. IR (KBr): 2938, 1674, 1628, 1389, 1214, 1148, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, J = 12.8 Hz, 1H), 7.52 (t, 1H), 7.34 - 7.21 (m, 6H), 5.78 (s, 1H), 4.60 (t, J = 10 Hz, 1H), 2.93 (t, J = 8.8 Hz, 2H), 2.25 - 2.20 (m, 1H), 1.94-1.80 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 160.3, 152.6, 138.1, 134.7, 132.0, 130.7, 129.4, 128.3, 127.8, 124.1, 123.3, 116.4, 116.1, 109.4, 36.5, 30.3, 29.8, 22.1 ppm. MS (ESI): *m/z* (rel. abund.%) 293 ($[M+1]^+$, 100).

3,4-dihydro-2,2-dimethylpyrano[3,2-c]chromen-5(2H)-one (5f): Semi solid. IR (KBr): 1721, 1636, 1614, 1497, 1451, 1383, 1276, 1203, 1171, 1118, 1016, 764, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (dd, J = 10 Hz, 1H), 7.61 - 7.57 (m, 1H), 7.39 - 7.30 (m, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.87 (t, J = 6.4 Hz, 2H) 1.47 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.03, 60.1, 150.3, 128.4, 125.5, 121.6, 117.4, 100, 78.2, 35.5, 27.7, 15.8 ppm. MS (ESI): *m/z* (rel. abund.%) 231.3 ($[M+1]^+$, 100).

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