Tetrahedron 64 (2008) 11666–11672

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solid-supported acid-catalyzed C3-alkylation of 4-hydroxycoumarins with secondary benzyl alcohols: access to 3,4-disubstituted coumarins via Pd-coupling

Ch. Raji Reddy [a,*], B. Srikanth [a], N. Narsimha Rao [a], Dong-Soo Shin [b]

[a] Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500007, India
[b] Department of Chemistry, Changwon National University, Changwon 641-773, South Korea

ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form
12 September 2008
Accepted 8 October 2008
Available online 14 October 2008

Keywords:
Acid catalyst
Amberlite IR-120
Benzylation
Benzyl alcohol
Palladium coupling
3,4-Disubstituted coumarin

ABSTRACT

An efficient and operationally simple method for C3-alkylation of 4-hydroxycoumarins has been developed under acidic medium giving good yields of the products. In the present method, a reusable Amberlite® IR-120 (H^+ form) was used as an acid catalyst and secondary benzyl alcohols were used as alkylating agents. The obtained 3-alkylated-4-hydroxycoumarins offered an easy access for the synthesis of 3,4-disubstituted coumarins by way of Pd-catalyzed coupling reactions.

1. Introduction

Coumarin and its derivatives are one of the important classes of heterocyclic compounds and are known to possess a wide range of biological activities including anti-HIV, anti-biotic, anti-fungal, anti-bacterial, anti-viral, anti-cancer, anti-clotting activity, and especially as anti-coagulants.[1–8] Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represents a significant class of compounds as not only as biologically active compounds (Fig. 1),[9,10] but also serve as a useful scaffolds, which can be highly diversified in several ways to synthesize 3,4-substituted compounds.[11–14]

The existing methods for the synthesis of 3-substituted 4-hydroxycoumarins include direct synthesis of the target compound[15–18] or C3-alkylation/substitution of 4-hydroxy-coumarin.[19–28] The later method is gaining importance due to the prospect of generating more number of compounds using various alkylating/substituting agents. Although, there are several known methods for C3-alkylation/substitutions via Pd-catalyzed C–C bond formation or base mediated alkylation reactions, most of them generally required the suitable alkylating agents such as halo compounds, boronic acid, etc.[19–28] Alternatively, the alkylation can also be performed under acidic conditions with alcohols as

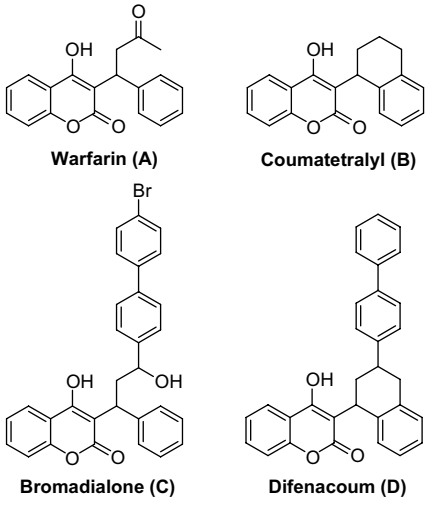
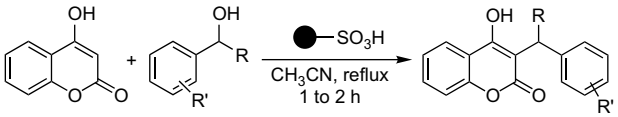


Figure 1.

* Corresponding author. Tel.: +91 40 27193128; fax: +91 40 27160512.
E-mail address: rajireddy@iict.res.in (Ch.R. Reddy).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.017

alkylating agents, which is not well explored. To the best of our knowledge, there is a limited number of examples known for the alkylation of 4-hydroxycoumarins with alcohols in the presence of strong acids, which include HCl, H_2SO_4,[29–31] etc. and recently $Yb(OTf)_3$.[32] From the synthetic point of view, alcohols are an attractive source compared to the corresponding halides and also can be obtained more easily. Hence, the development of a practical and economical method for direct C3-alkylation of 4-hydroxycoumarins using alcohols under acidic medium is highly desirable. In recent years, solid-supported acids have emerged as convenient and reusable catalysts to perform various useful organic transformations.[33] Furthermore, solid-supported acid catalysts are inexpensive, easy to handle, and are environmentally friendly. In continuation of our interest in acid-catalyzed reactions,[34–36] herein, we describe a convenient method for the C3-alkylation of 4-hydroxycoumarin using secondary benzyl alcohols as an alkylating agent in the presence of a solid-supported sulfonic acid catalyst (Amberlite IR-120) (Scheme 1).



R= aryl or alkyl or alkynyl
R'= H or 4-OMe

Scheme 1. Solid-supported acid-catalyzed C3-alkylation.

2. Results and discussions

First, the reaction of 4-hydroxycoumarin **1a** with benzhydrol **2a** was investigated in the presence various acid catalysts and the results are summarized in Table 1. It was found that the acid catalysts tested, such as $BF_3 \cdot OEt_2$ (5 mol %) and $MoCl_5$ (5 mol %) appeared to be effective at room temperature for this conversion (entries 1 and 2, Table 1). However, $ZnCl_2$ (5 mol %) was able to give only 43% of the desired product (entry 3, Table 1). The reaction proceeds efficiently with solid-supported catalysts such as Amberlite IR-120 (H^+) or polymer-supported *p*-toluenesulfonic acid (PS-*p*TSA) to give the C3-alkylated product in good yields at refluxing temperature (entries 4 and 5 Table 1). It is noteworthy to mention that the reaction does not progress at room temperature or in the absence of catalyst (entry 6, Table 1). Although, most of the tested catalysts were found to be effective, Amberlite IR-120 (H^+), for obvious reasons (being inexpensive, environmentally benign, reusable, and operationally simple) was chosen for further experiments.

To reveal the generality of this method, the scope of the reaction was investigated with various benzyl alcohols under optimized conditions (Amberlite IR-120, CH_3CN, reflux); Table 2. From the results of Table 2, the protocol has proven to be useful for benzylation of 4-hydroxycoumarins **1a** and **1b** with variety of secondary benzyl alcohols **2a**–**2g** (entries 1–8, Table 2). However, the reaction of 4-hydroxycoumarin **1a** with primary benzyl alcohol **2h** or non-benzylic alcohol **2i** failed to give the expected product after 24 h in the presence of Amberlite IR-120 in CH_3CN at reflux (entries 9 and 10, Table 2). The results from the above reactions clearly demonstrate that the direct C3-alkylation of 4-hydroxycoumarin was successful only with secondary benzylic alcohols, but not with the primary benzylic or non-benzylic alcohols.[34] Further, we have tested the efficiency of $BF_3 \cdot Et_2O$ in the alkylation of 4-hydroxycoumarin **1a** with a few other benzylic alcohols **2b**, **2d** and found that the reaction proceeded smoothly to give the corresponding C3-benzylated products **3b**, **3d** in good yields (entries 11 and 12, Table 2). Finally, the application of the present protocol was demonstrated by synthesizing an anti-coagulant compound, coumatetralyl (**B**), from benzylic alcohol **2j** in 72% yield (Scheme 2).[37]

The reusability of the catalyst was investigated and the observations are summarized in Table 3. After completion of the reaction of benzhydrol with **1a**, Amberlite IR-120 resin was filtered, evaporation of the filtrate gave the crude product, which was purified (86% yield) and the same catalyst was used[38] once again for the similar reaction to obtain 86% yield of the product in 2 h. The third and fourth runs were also successfully repeated using the same catalyst. However, the fifth and sixth runs took little longer time and the yield was also low when compared to first run (Table 3).

After successful C3-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols, to further diversify the obtained products, we turned our attention to substitute the hydroxyl group at C4-position to obtain 3,4-disubstituted coumarins. Having the advantage of enolic-OH at C4-position, the substitution was accomplished by adopting Pd-catalyzed cross-coupling reactions, which has proven to be a powerful reaction for C–C bond formation in organic synthesis.[28,39–42]

In order to show the Pd-catalyzed coupling reactions, compound **3a** was selected as a model substrate. To make the substrate ready for Pd-coupling reactions, compound **3a** was treated with $PhNTf_2$ and Et_3N at room temperature to give the triflate **4a** in 82% yield. Next, the triflate **4a** was subjected to various types of Pd-couplings such as Heck, Suzuki, Stille, and Sonogashira reactions to obtain the corresponding 3,4-disubstituted coumarins (Scheme 3).

As a first reaction, triflate **4a** was treated with ethyl acrylate in the presence of Pd(0)/Et_3N at 80 °C (Heck coupling conditions) to give the coupled product **5a** in 78% yield (entry 1, Table 4). Similarly, the reaction of **4a** with phenylboronic acid using Suzuki coupling conditions leads to the corresponding 4-phenyl-3-(diphenylmethyl)coumarin **5b** in 80% yield (entry 2, Table 4), Stille coupling of **4a** with allyl tributyltin gave the 4-allyl-3-(diphenylmethyl)coumarin **5c** in 75% yield (entry 3, Table 4). The coupling of **4a** with phenyl acetylene was also successful under Sonogashira reaction conditions to obtain **5d** in 77% yield (entry 4, Table 4). After the completion of Pd-catalyzed coupling reactions on **3a**, the possibility of similar reactions were tested on a structurally different substrate, coumarin derivative **3d**. Accordingly, compound **3d** was treated with phenylboronic acid under Suzuki coupling conditions and with allyl tributyltin under Stille reaction conditions. To our disappointment, both the reactions gave the inseparable complex mixture (based on TLC).[43]

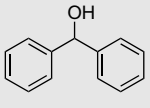
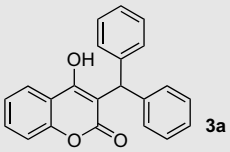
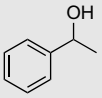
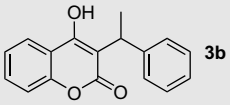
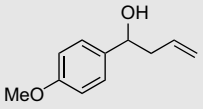
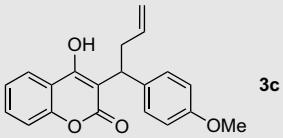
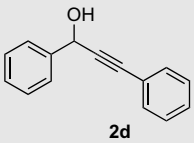
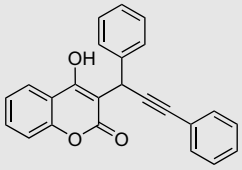
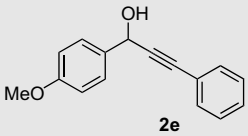
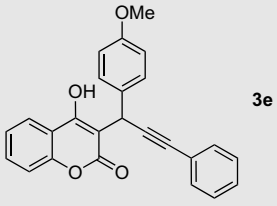
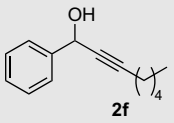
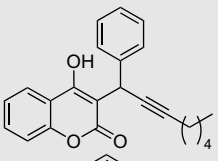
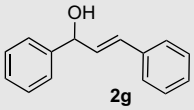
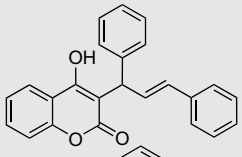
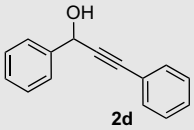
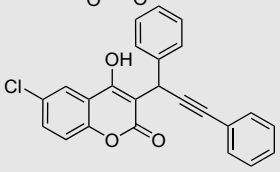
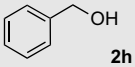
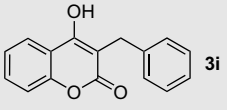
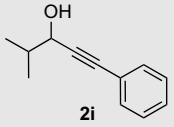
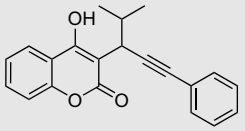
We have also demonstrated the amination of 3-substituted 4-hydroxycoumarin **3d** via its triflate with benzylamine and morpholine to obtain the corresponding 3-substituted 4-aminated coumarin derivatives **6a** and **6b** in 56% and 55% yields, respectively (for two steps, Scheme 4). Benzylamine was reacted smoothly at room temperature, whereas morpholine required heating (80 °C). The 3-propargylated 4-hydroxycoumarins are also useful in the synthesis of substituted furocoumarins,[32] a key structural motif in several natural products.

Table 1
Activity of various acids in the alkylation of 4-hydroxycoumarin (**1a**) with benzhydrol (**2a**)[a]

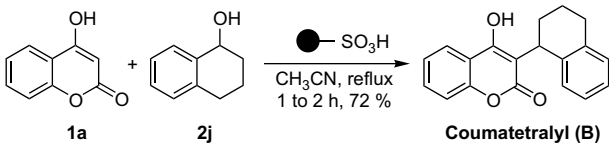
Entry	Acid	Time (h)/temperature	Yield[b] (%)
1	$BF_3 \cdot Et_2O$ (5 mol %)	2/rt	82
2	$MoCl_5$ (5 mol %)	1.5/rt	76
3	$ZnCl_2$ (5 mol %)	5/rt	43
4	PS-*p*TSA (50 mg/mmol)	1.5/reflux[c]	85
5	Amberlite IR-120 (50 mg/mmol)	2/reflux[c]	86
6	—	720/reflux	—

[a] All the reactions were carried out in CH_3CN.
[b] Isolated yields after column purification.
[c] No reaction at room temperature.

Table 2
C3-Alkylation of 4-hydroxycomarins **1a** and **1b** with benzylic alcohols

Entry	Benzylic alcohol	Time (h)	Product	Yield[a] (%)
1	 **2a**	2	 **3a**	86
2	 **2b**	2	 **3b**	81
3	 **2c**	2	 **3c**	78
4	 **2d**	2.5	 **3d**	84
5	 **2e**	2	 **3e**	83
6	 **2f**	2.5	 **3f**	79
7	 **2g**	3	 **3g**	78
8[b]	 **2d**	2	 **3h**	75
9	 **2h**	14	 **3i**	0[c]
10	 **2i**	14	 **3j**	0[c]
11[d]	**2b**	2	**3b**	78
12[d]	**2d**	1.5	**3d**	76

[a] Isolated yields after column chromatography.
[b] 7-Chloro-4-hydroxycoumarin (**1b**) was used.
[c] No reaction.
[d] $BF_3 \cdot Et_2O$ (5 mol %) was used as catalyst.

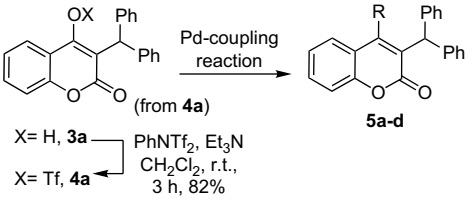


Scheme 2. Synthesis of coumatetralyl (**B**).

Table 3
Reusability of Amberlite IR-120 for the benzylation 4-hydroxycoumarin with benzhydrol[a]

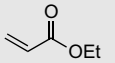
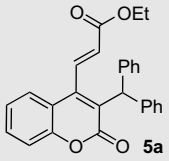
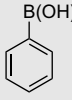
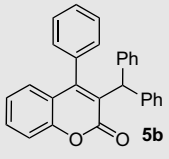
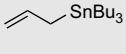
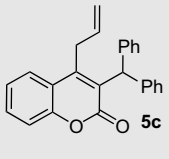
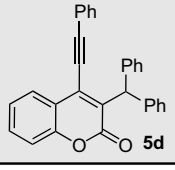
Run	1	2	3	4	5	6
Time (h)	2	2	2.5	2.5	3.5	3.5
Yield[b] (%)	86	86	83	82	78	72

[a] Reactions were carried out under refluxing in CH_3CN.
[b] Isolated yields after column purification.

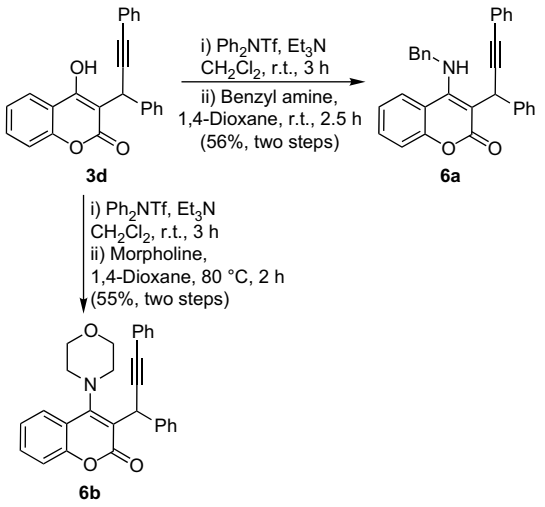


Scheme 3. Synthesis of 3,4-disubstituted coumarins.

Table 4
Palladium-catalyzed reactions of compound **4a**

Entry	Reagent	Reaction conditions	Product	Yield[a] (%)
1		$Pd(PPh_3)_4$, Et_3N, DMF, 100 °C, 10 h (Heck)	 **5a**	78
2		$Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O (1:1:0.3), reflux, 10 h (Suzuki)	 **5b**	80
3		$Pd(PPh_3)_4$, LiCl, 1,4-dioxane, 100 °C, 18 h (Stille)	 **5c**	75
4		$Pd(PPh_3)_4$, CuI, Et_3N, DMF, 70 °C, 12 h (Sonogashira)	 **5d**	77

[a] Isolated yields after column chromatography.



Scheme 4. Synthesis of 3-alkyl-4-aminated coumarin (**6**).

3. Conclusion

In summary, we have demonstrated the C3-benzylation of 4-hydroxycoumarin in the presence of Amberlite IR-120 using secondary benzyl alcohols. This method provides an advantage that the use of secondary benzyl alcohols as alkylating agents, which can be an attractive source. Furthermore, simplicity of operation and the use of inexpensive and recyclable catalyst are added advantages. Other acid catalysts $BF_3 \cdot Et_2O$, $MoCl_5$ (at room temperature), and PS-*p*TSA (at reflux) were also found to be effective in C3-benzylation for the first time. The present protocol was efficiently used for the synthesis of an anti-coagulant, coumatetralyl. The products obtained were successfully utilized in the preparation of 3,4-disubstituted coumarin derivatives via palladium coupling reactions. These significant results may find applications in the synthesis of diversified coumarins.

4. Experimental

4.1. General

All the solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683, Nicolet Nexus 670 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200 and Bruker AV-300 NMR spectrometer. Chemical shifts were reported in parts per million (ppm) with respect to internal TMS. Coupling constants (*J*) are quoted in hertz (Hz). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H or Agilent technologies LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system.

4.2. General experimental procedure for the C3-alkylation of 4-hydroxycoumarins (for 3a to 3h and B)

To a mixture of 4-hydroxycoumarin (1.0 mmol) and benzylic alcohol (1.0 mmol) in acetonitrile (10 mL), Amberlite IR-120 (H^+) (50 mg) was added and the reaction mixture was stirred for the given time (see Table 2) at refluxing temperature. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and the filtrate was evaporated in vacuo. The crude compound was purified by column chromatography (ethyl acetate in hexanes) to afford the corresponding C3-alkylated 4-hydroxycoumarin.

*4.2.1. 3-Benzhydryl-4-hydroxy-2H-chromen-2-one (**3a**)*

White solid; mp: 178–180 °C; R_f (30% EtOAc/hexanes) 0.3; IR (neat): ν_{max} 3264, 2921, 1672, 1623, 1209, 752, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (1H, dd, J=1.5, 7.5 Hz, Ar–H), 7.54 (1H, td, J=1.1, 8.3 Hz, Ar–H), 7.43–7.20 (12H, m, Ar–H), 6.27 (1H, s, OH), 5.98 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 160.8, 152.9, 140.1, 132.3, 129.6, 128.9, 128.0, 124.1, 123.3, 116.6, 116.1, 107.9, 47.5; HRMS (ESI): calcd for $C_{22}H_{16}O_3Na$: 351.0997 $(M+Na)^+$, found: 351.0999.

*4.2.2. 4-Hydroxy-3-(1-phenylethyl)-2H-chromen-2-one (**3b**)*

White solid; mp: 200–202 °C; R_f (30% EtOAc/hexanes) 0.3; IR (neat): ν_{max} 3227, 2925, 1671, 1624, 1392, 1215, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (1H, d, J=8.3 Hz, Ar–H), 7.57–7.18 (8H, m, Ar–H), 5.92 (1H, s, OH), 4.74 (1H, q, J=7.5 Hz, CH–Ar), 1.67 (3H, d, J=7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 152.1, 143.9, 131.0, 127.5, 127.0, 125.4, 123.2, 123.0, 116.3, 115.8, 109.6, 33.6, 16.3; HRMS (ESI): calcd for $C_{17}H_{14}O_3Na$: 289.0840 $(M+Na)^+$, found: 289.0842.

*4.2.3. 4-Hydroxy-3-(1-(4-methoxyphenyl)but-3-enyl)-2H-chromen-2-one (**3c**)*

Brown solid; mp: 58–60 °C; R_f (30% EtOAc/hexanes) 0.25; IR (neat): ν_{max} 3415, 2924, 1679, 1610, 1511, 1249, 1034, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (1H, dd, J=1.5, 8.3 Hz, Ar–H), 7.54–7.47 (1H, m, Ar–H), 7.41 (2H, d, J=9.0 Hz, Ar–H), 7.30–7.20 (2H, m, Ar–H), 6.95–6.90 (2H, m, Ar–H), 5.97–5.82 (1H, m, CH=CH_2), 5.13 (1H, dd, J=1.5, 17.3 Hz, CH_2=CH), 5.03 (1H, dd, J=1.5, 10.5 Hz, CH_2=CH), 4.66 (1H, t, J=7.5 Hz, CH–Ar), 3.80 (3H, s, OCH_3), 3.00–2.80 (2H, m, CH_2–CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 160.3, 159.1, 152.7, 136.1, 132.4, 131.9, 129.1, 123.9, 123.0, 117.3, 116.5, 116.2, 115.0, 108.7, 55.47, 39.3, 35.5; HRMS (ESI): calcd for $C_{20}H_{18}O_4Na$: 345.1102 $(M+Na)^+$, found 345.1098.

*4.2.4. 3-(1,3-Diphenylprop-2-ynyl)-4-hydroxy-2H-chromen-2-one (**3d**)[32]*

Brown solid; mp: 158–160 °C; R_f (30% EtOAc/hexanes) 0.3; IR (neat): ν_{max} 3329, 2924, 1672, 1625, 1491, 1205, 756, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.37 (1H, s, OH), 7.86 (1H, dd, J=1.5, 8.3 Hz, Ar–H), 7.61 (2H, d, J=6.7 Hz, Ar–H), 7.58–7.49 (3H, m, Ar–H), 7.42–7.24 (7H, m, Ar–H), 5.79 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 161.3, 152.9, 138.7, 132.5, 132.0, 129.4, 129.2, 128.7, 127.9, 127.3, 124.2, 123.6, 121.6, 116.7, 116.1, 105.1, 88.1, 86.6, 33.6; HRMS (ESI): calcd for $C_{24}H_{16}O_3Na$: 375.0997 $(M+Na)^+$, found: 375.0999.

*4.2.5. 4-Hydroxy-3-(1-(4-methoxyphenyl)-3-phenylprop-2-ynyl)-2H-chromen-2-one (**3e**)*

Viscous liquid; R_f (30% EtOAc/hexanes) 0.2; IR (neat): ν_{max} 3334, 2927, 1673, 1625, 1508, 1250, 1033, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.38 (1H, s, OH), 7.85 (1H, dd, J=1.5, 7.8 Hz, Ar–H), 7.58–7.46 (5H, m, Ar–H), 7.39–7.22 (5H, m, Ar–H), 6.93–6.84 (2H, m, Ar–H), 5.72 (1H, s, CH–Ar), 3.77 (3H, s, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.7, 161.1, 159.2, 152.7, 132.4, 131.9, 130.6, 129.2, 128.6, 128.4, 124.2, 123.5, 121.6, 116.6, 116.1, 114.5, 105.3, 87.6, 86.9, 55.4, 32.8; HRMS (ESI): calcd for $C_{25}H_{18}O_4Na$: 405.1102 $(M+Na)^+$, found: 405.1100.

*4.2.6. 4-Hydroxy-3-(1-phenyloct-2-ynyl)-2H-chromen-2-one (**3f**)*

Pale-yellow solid; mp: 90–92 °C; R_f (30% EtOAc/hexanes) 0.5; IR (neat): ν_{max} 3306, 2928, 1707, 1627, 1494, 1201, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.78 (1H, s, OH), 7.85 (1H, dd, J=1.4, 8.0 Hz, Ar–H), 7.58–7.46 (3H, m, Ar–H), 7.37–7.19 (5H, m, Ar–H), 5.48 (1H, t, J=2.2 Hz, CH), 2.34 (2H, dt, J=2.2, 7.3 Hz, CH_2C≡C), 1.69–1.50 (2H, m, CH_2–CH_2C≡C), 1.48–1.22 (4H, m, $C_2H_4CH_2$C≡C), 0.91 (3H, t, J=6.6 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.7, 161.2, 152.8, 139.4, 132.3, 128.9, 127.6, 127.2, 124.1, 123.5, 116.6, 116.2, 105.2, 89.4, 78.2, 33.1, 31.2, 28.3, 22.2, 18.9, 14.1; HRMS (ESI): calcd for $C_{23}H_{22}O_3Na$: 369.1466 $(M+Na)^+$, found: 369.1454.

*4.2.7. (E)-3-(1,3-Diphenylallyl)-4-hydroxy-2H-chromen-2-one (**3g**)[32]*

White solid; mp: 68–70 °C; R_f (30% EtOAc/hexanes) 0.2; IR (neat): ν_{max} 3026, 2923, 2853, 1665, 1608, 1493, 1204, 753, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (1H, d, J=7.8 Hz, Ar–H), 7.55–7.49 (1H, m, Ar–H), 7.42–7.23 (12H, m, Ar–H), 6.78 (1H, dd, J=6.6, 16.2 Hz, CH=CH), 6.52 (1H, d, J=15.9 Hz, CH=CH), 5.46 (1H, d, J=5.7 Hz, CH–CH=CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 161.1, 152.8, 139.8, 136.3, 134.0, 132.3, 129.4, 128.8, 128.3, 128.2, 127.8, 126.7, 126.6, 124.1, 123.3, 116.7, 116.0, 106.6, 44.2; HRMS(ESI): calcd for $C_{24}H_{18}O_3Na$: 377.1148 $(M+Na)^+$, found: 377.1145.

*4.2.8. 6-Chloro-3-(1,3-diphenylprop-2-ynyl)-4-hydroxy-2H-chromen-2-one (**3h**)*

Brown solid; mp: 145–147 °C; R_f (30% EtOAc/hexanes) 0.2; IR (neat): ν_{max} 3195, 2923, 2130, 1682, 1621, 1484, 1192, 822, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (1H, d, J=2.2 Hz, Ar–H), 7.60–7.44 (3H, m, Ar–H), 7.39–7.21 (9H, m, Ar–H), 5.71 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 159.7, 150.7, 138.8, 131.3, 131.2, 128.5, 127.9, 127.8, 127.6, 127.0, 126.3, 123.0, 117.6, 117.5, 106.3, 88.0, 82.6, 32.4; HRMS (ESI): calcd for $C_{24}H_{15}O_3ClNa$: 409.0607 $(M+Na)^+$, found: 409.0608.

*4.2.9. 4-Hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2H-chromen-2-one (coumatetralyl, **B**)*

White solid; mp: 188–190 °C; R_f (30% EtOAc/hexanes) 0.3; IR (neat): ν_{max} 3271, 2941, 1671, 1625, 1391, 1211, 1143, 745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.63 (1H, dd, J=1.4, 8.0 Hz, Ar–H), 7.49 (1H, td, J=1.4, 8.0 Hz, Ar–H), 7.35–7.12 (6H, m, Ar–H), 5.73 (1H, s, OH), 4.59 (1H, t, J=6.6 Hz, CH–Ar), 2.93 (2H, t, J=5.8 Hz, CH_2–Ar), 2.33–2.14 (1H, m, $CH_2CH_2CH_2$–Ar), 2.03–1.79 (3H, m, $CH_2CH_2CH_2$–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.1, 152.7, 138.3, 134.8, 132.0, 130.8, 129.8, 128.1, 127.6, 124.0, 123.1, 116.5, 116.3, 109.6, 36.6, 30.0, 29.5, 21.9; HRMS (ESI): calcd for $C_{19}H_{17}O_3$: 293.1172 $(M+H)^+$, found: 293.1175.

4.3. 3-Benzhydryl-2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (4a)

To a solution of **3a** (1 g, 3.04 mmol) and Et_3N (0.63 mL, 4.57 mmol) in dichloromethane was added *N*-phenyltriflimide (0.75 g, 3.35 mmol). The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated in vacuo and the crude compound was purified by column chromatography to afford the desired product **4a** (1.14 g, 82% yield). Viscous liquid; R_f (20% EtOAc/hexanes) 0.6; IR (neat): ν_{max} 3447, 3062, 1733, 1616, 1417, 1217, 1132, 893, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (1H, dd, J=1.5, 5.2 Hz, Ar–H), 7.61 (1H, dt, J=1.5, 7.5 Hz, Ar–H), 7.42–7.35 (2H, m, Ar–H), 7.33–7.20 (10H, m, Ar–H), 5.77 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 153.0, 152.5, 139.2, 133.3, 129.1, 128.5, 127.3, 125.1, 124.3, 123.7, 117.0, 115.2, 48.1; HRMS (ESI): calcd for $C_{23}H_{15}O_5F_3SNa$: 483.0490 $(M+Na)^+$, found: 483.0482.

4.4. (*E*)-Ethyl 3-(3-benzhydryl-2-oxo-2*H*-chromen-4-yl)acrylate (5a)

To a solution of **4a** (160 mg, 0.34 mmol) in DMF (5 mL) under nitrogen was added $Pd(PPh_3)_4$ (20 mg, 5 mol %). After stirring for 15 min at room temperature, ethyl acrylate (174 mg, 1.7 mmol) and Et_3N (0.15 mL, 1.04 mmol) were added. The reaction was stirred at 100 °C for 10 h and the mixture was concentrated in vacuo. The residue was dissolved in 20 mL of EtOAc and washed with water

(15 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of crude compound by flash chromatography affords the desired product **5a** (111 mg, 78% yield). Viscous liquid; R_f (20% EtOAc/hexanes) 0.5; IR (neat): ν_{max} 3430, 2924, 2854, 1722, 1601, 1383, 1176, 755, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.59–7.44 (2H, m, Ar–H), 7.39–7.19 (13H, m, Ar–H, CH=$CHCO_2Et$), 6.00 (1H, d, J=16.0 Hz, $CHCO_2Et$), 5.87 (1H, s, CH–Ar), 4.25 (2H, q, J=7.2 Hz, CH_2CH_3), 1.34 (3H, t, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 160.0, 153.0, 147.0, 140.7, 137.8, 131.8, 129.2, 128.7, 128.4, 128.0, 127.9, 127.0, 126.4, 124.4, 117.1, 61.3, 51.0, 14.4; HRMS: calcd for $C_{27}H_{23}O_4$: 411.1596 $(M+H)^+$, found: 411.1595.

4.5. 3-Benzhydryl-4-phenyl-2*H*-chromen-2-one (5b)

To a solution of **4a** (150 mg, 0.33 mmol) and phenylboronic acid (52 mg, 0.42 mmol) in toluene/ethanol/water (1:1:0.3, 11.5 mL) were added Na_2CO_3 (73.4 mg, 0.69 mmol) and $Pd(PPh_3)_4$ (7.6 mg, 0.007 mmol). The reaction mixture was stirred at refluxing temperature for 10 h and diluted with water (10 mL). The product was extracted into EtOAc (3×15 mL), dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by flash chromatography to get the desired product **5b** (101 mg, 80% yield). White solid; mp: 200–202 °C; R_f (20% EtOAc/hexanes) 0.6; IR (neat): ν_{max} 3430, 2924, 2854, 1727, 1599, 1447, 1052, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (3H, dd, J=1.5, 5.2 Hz, Ar–H), 7.43 (1H, dt, J=1.5, 7.5 Hz, Ar–H), 7.32 (1H, d, J=8.3 Hz, Ar–H), 7.26–7.05 (13H, m, Ar–H), 6.93 (1H, dd, J=1.5, 7.5 Hz, Ar–H), 5.17 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 153.3, 153.0, 141.3, 134.9, 131.2, 129.1, 129.0, 128.4, 128.3, 128.0, 127.9, 126.6, 124.1, 120.9, 116.5, 51.5; HRMS (ESI): calcd for $C_{28}H_{21}O_2$: 389.1541 $(M+H)^+$, found: 389.1535.

4.6. 4-Allyl-3-benzhydryl-2*H*-chromen-2-one (5c)

To a solution of **4a** (0.2 g, 0.43 mmol) in 1,4-dioxane (1.6 mL), LiCl (0.09 g, 2.17 mmol), allyl tributyltin (0.21 g, 0.65 mmol), and $Pd(PPh_3)_4$ (25 mg, 0.02 mmol) were consequently added. The reaction mixture was stirred at 100 °C for 18 h. The mixture was concentrated in vacuo and the crude product was purified by flash chromatography to afford **5c** (114.5 mg, 75% yield). Light-brown solid; mp: 160–161 °C; R_f (20% EtOAc/hexanes) 0.6; IR (neat): ν_{max} 3424, 2922, 2853, 1709, 1601, 1451, 1062, 752, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (1H, dd, J=0.7, 8.3 Hz, Ar–H), 7.49 (1H, dt, J=1.5, 7.5 Hz, Ar–H), 7.36–7.18 (12H, m, Ar–H), 5.94 (1H, s, CH), 5.73–5.28 (1H, m, CH=CH_2), 5.12–4.95 (2H, m, CH_2=CH), 3.66 (2H, d, J=6.0 Hz, CH_2CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 153.1, 149.6, 141.1, 132.7, 131.1, 129.1, 128.5, 128.4, 126.7, 125.6, 124.2, 119.9, 118.2, 116.9, 49.6, 33.3; HRMS (ESI): calcd for $C_{25}H_{20}O_2Na$: 375.1360 $(M+Na)^+$, found: 375.1356.

4.7. 3-Benzhydryl-4-(phenylethynyl)-2*H*-chromen-2-one (5d)

To a solution of **4a** (0.2 g, 0.43 mmol) in DMF (6 mL) under nitrogen was added $Pd(PPh_3)_4$ (25 mg, 0.02 mmol). After stirring for 15 min at room temperature, the following reagents were added sequentially: phenyl acetylene (48 mg, 0.48 mmol), CuI (8 mg, 0.04 mmol), and Et_3N (0.3 mL, 2.17 mmol). The mixture was stirred at 70 °C for 12 h until no triflate remained. The reaction mixture was concentrated in vacuo, the residue was dissolved in EtOAc (30 mL), and washed with water (20 mL). The organic layer was washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography affords the desired product **5d** (138 mg, 77% yield). Viscous liquid; R_f (20% EtOAc/hexanes) 0.6; IR (neat): ν_{max} 3436, 2925, 1604, 1384, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.00 (1H, dd, J=1.4, 8.0 Hz, Ar–H), 7.50–7.22 (18H, m, Ar–H), 6.21 (1H, s, CH–Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 152.9, 140.9, 139.2, 133.4, 132.9, 132.3, 131.7, 130.2, 129.2, 128.6, 127.4, 127.1, 125.2, 124.5, 123.8, 119.2, 117.0, 116.7, 87.3, 83.2, 52.0; HRMS (ESI): calcd for $C_{30}H_{20}O_2Na$: 435.1355 $(M+Na)^+$, found: 435.1355.

4.8. 4-(Benzylamino)-3-(1,3-diphenylprop-2-ynyl)-2*H*-chromen-2-one (6a)

To a solution of **3d** (100 mg, 0.28 mmol) and Et_3N (0.06 mL, 0.42 mmol) in dichloromethane (10 mL), was added *N*-phenyltriflimide (70.2 mg, 0.31 mmol). The reaction mixture was stirred for 3 h at room temperature and evaporated in vacuo to get crude product. The above triflate was dissolved in 1,4-dioxane (4 mL) and was added pyridine (0.045 mL, 0.56 mmol) followed by benzylamine (0.046 mL, 0.42 mmol). Then, the reaction mixture was stirred at room temperature for 2.5 h. After completion of reaction (monitored by TLC), the reaction mixture was evaporated in vacuo, and the residue was purified by column chromatography to afford the desired product **6a** (70 mg, 56% yield). Pale brown solid, mp: 136–138 °C; R_f (30% EtOAc/hexanes) 0.5; IR (neat): ν_{max} 3246, 2923, 1663, 1542, 1026, 1001, 757, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (1H, d, J=7.8 Hz, Ar–H), 7.91 (1H, t, J=6.6 Hz, Ar–H), 7.66 (1H, t, J=7.5 Hz, Ar–H), 7.27 (17H, m, Ar–H, CH), 5.47 (1H, s, NH), 4.70 (1H, dd, J=6.9, 16.8 Hz, CH_2Ph), 4.53 (1H, dd, J=6.3, 16.8 Hz, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5, 152.0, 150.2, 139.5, 135.9, 133.2, 131.9, 128.8, 128.6, 128.3, 127.2, 127.1, 126.8, 125.8, 125.6, 123.7, 122.8, 116.9, 115.5, 104.9, 96.1, 90.7, 46.5, 30.6; HRMS (ESI): calcd for $C_{31}H_{24}NO_2$: 442.1802 $(M+H)^+$, found: 442.1806.

4.9. 3-(1,3-Diphenylprop-2-ynyl)-4-morpholino-2*H*-chromen-2-one (6b)

To a solution of **3d** (100 mg, 0.28 mmol) and Et_3N (0.06 mL, 0.42 mmol) in dichloromethane (10 mL), was added *N*-phenyltriflimide (70.2 mg, 0.31 mmol). The reaction mixture was stirred for 3 h at room temperature and evaporated in vacuo to get crude product. The above triflate was dissolved in 1,4-dioxane (5 mL) and was added pyridine (0.04 mL, 0.56 mmol) followed by morpholine (0.04 mL, 0.42 mmol). Then, the reaction mixture was heated to 80 °C and stirred for 2 h. After completion of reaction (monitored by TLC), the reaction mixture was evaporated in vacuo and the residue was purified by column chromatography to afford the desired product **6b** (66 mg, 55% yield). Brown crystalline solid, mp: 193–195 °C; R_f (20% EtOAc/hexanes) 0.3; IR (neat): ν_{max} 3385, 3029, 2962, 2851, 2120, 1698, 1597, 1448, 1282, 1110, 914, 762, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07(1H, dd, J=1.5, 8.3 Hz, Ar–H), 7.56–7.19 (13H, m, Ar–H), 6.71(1H, s, CH–Ar), 3.88–3.76 (4H, m, CH_2OCH_2), 3.58–3.37 (2H, br m, CH_2N), 3.25–3.14 (2H, br m, CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 157.5, 153.4, 127.7, 127.6, 127.6, 126.2, 125.1, 123.7, 117.4, 98.4, 81.5, 67.1, 51.1; HRMS (ESI): calcd for $C_{28}H_{24}NO_3$: 422.1756 $(M+H)^+$, found: 422.1755.

Acknowledgements

B.S. and N.N.R. thank the CSIR, New Delhi for financial assistance. C.R.R. is grateful to Dr. J. S. Yadav and Dr. S. Chandrasekhar, Indian Institute of Chemical Technology, Hyderabad for their support and encouragement. The authors are also thankful to the referees for their valuable suggestions.

References and notes

1. Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry, and Biochemistry*; Wiley: New York, NY, 1982.
2. Naser-Hijazi, B.; Stolze, B.; Zanker, K. S. *Second Proceedings of the International Society of Coumarin Investigators*; Springer: Berlin, 1994.
3. Spino, C.; Dodier, M.; Sotheeswaran, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3475.

4. Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59.
5. Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932.
6. Itoigawa, M.; Ito, C.; Tan, H. T.-W.; Kuchide, M.; Tokuda, H.; Nishino, H.; Furukawa, H. *Cancer Lett.* **2001**, *169*, 15.
7. Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755.
8. Yamamoto, Y.; Kurazono, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1626.
9. Raj, G.; Kumar, R.; McKinney, W. P. *Am. J. Med. Sci.* **1994**, *307*, 128.
10. Hadler, M. R.; Shadbolt, R. S. *Nature* **1975**, *253*, 275.
11. Estevez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Rep.* **1997**, *14*, 465.
12. Clerici, A.; Porta, O. *Synthesis* **1993**, 99.
13. Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Ogawa, A.; Kambe, N.; Sonoda, N. *Synthesis* **1988**, 257.
14. Wang, S.; Milne, G. W. A.; Yan, X.; Posey, I. J.; Nicklaus, M. C.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1996**, *39*, 2047.
15. Dittmer, D. C.; Li, Q.; Avilov, D. V. *J. Org. Chem.* **2005**, *70*, 4682.
16. Kalinin, A. V.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4999.
17. Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995.
18. Davis, S. E.; Church, A. C.; Tummns, R. C.; Beam, C. F. *J. Heterocycl. Chem.* **1997**, *34*, 1159.
19. Chen, D. U.; Kuo, P. Y.; Yang, D. Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2665.
20. Kischel, J.; Michalic, D.; Zapf, A.; Beller, M. *Chem. Asian J.* **2007**, *2*, 909.
21. Majumdar, K. C.; Sarkar, S. *Tetrahedron* **2002**, *58*, 8501.
22. Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Synthesis* **2003**, 1286.
23. Grigg, R.; Nurnabi, M.; Rahul, M.; Sarkar, A. *Tetrahedron* **2004**, *59*, 3359.
24. Wuxie, J.; Yue, L.; Chen, W.; Du, W.; Zhu, J. *Org. Lett.* **2007**, *9*, 413.
25. Naumov, M. I.; Sutirin, S. A.; Shavyrin, A. S.; Ganina, O. G.; Beletskaya, I. P.; Rey, V. B.; Combes, S.; Finet, J. P.; Fedorov, A. Y. *J. Org. Chem.* **2007**, *72*, 3293.
26. Toth, G.; Moinar, S.; Tamas, T.; Borbely, I. *Org. Prep. Proced. Int.* **1999**, *31*, 222.
27. Tabakovic, I.; Tabakovic, K.; Gaon, I. *Org. Prep. Proced. Int.* **1997**, *29*, 223.
28. Zhang, L.; Meng, T.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 7279 and references cited therein.
29. Enders, A. *Angew. Chem.* **1957**, *69*, 481.
30. Ziegler, R. *Monatsh. Chem.* **1957**, *88*, 25.
31. Ahluvalia, V. K.; Arora, K. K.; Mukherjee, I. *Indian J. Chem., Sect. B* **1985**, 298.
32. Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron* **2007**, *63*, 11636.
33. Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791 and references cited therein.
34. Reddy, Ch. R.; Rajesh, G.; Balaji, S. V.; Chethan, N. *Tetrahedron Lett.* **2008**, *49*, 970.
35. Reddy, Ch. R.; Mahipal, B.; Rao, Y. S. *ARKIVOC* **2008**, 250 and references cited therein.
36. It was also noted that the benzylation was successful only with the propargyl alcohols generated from aromatic aldehydes (entries 5, 6 and 8, Table 2), and not with the propargyl alcohol generated from aliphatic aldehyde (entry 10, Table 2). This may be due to the benzylic nature of the former alcohols.
37. There is only one report in the literature for the synthesis of coumatetralyl from 4-hydorxycoumarin under $AcOH/H_2SO_4$ medium. See reference: Bayer, F. *Chem. Abstr.* **1960**, 579.
38. The filtered catalyst was used for another reaction, after washing with 0.5 N HCl followed by water and dried.
39. Tsuji, J. *Perspectives in Organopalladium Chemistry for the 21st Century*; Elsevier: Amsterdam, 1999.
40. Bailly, C.; Bal, C.; Barbier, P.; Combes, S.; Finet, J.-P.; Hildebrand, M.-P.; Peyrot, V.; Wattez, N. *J. Med. Chem.* **2003**, *46*, 5437.
41. Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642.
42. Yao, M.-L.; Deng, M.-Z. *Heteroat. Chem.* **2000**, *11*, 380.
43. The substrate **3d** may undergo cyclization under the reaction conditions to give furocoumarin compound[32] along with the expected coupling product (observed in MS of reaction mixture) and other unidentified compounds as complex mixture.