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4-HYDROXYCOUMARIN AND RELATED SYSTEMS: SITOSELECTIVITY OF THE MITSUNOBU REACTION WITH PRENYL ALCOHOLS

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Abstract- The Mitsunobu reaction leads to the formation of new C-C bonds between prenyl alcohols and 1,3-dicarbonyl compounds like 4-hydroxycoumarin or its nitrogen isoster. Buchapine was obtained through a one-pot procedure from 4-hydroxy-2-quinolone and dimethylallyl alcohol.

The Mitsunobu reaction,[1] in spite of its wide scope in organic synthesis, has not been much exploited to form single C-C bonds.[2] Its regio- and stereochemistry has been widely reviewed.[3] Recently Ko[4] found complete regioselection for the β-hydroxyl group in Mitsunobu reactions carried on *syn*-2,3-dihydroxy esters. Normally the reaction proceeds with inversion of configuration at the hydroxyl center, and however, DeShong *et al.* [5] observed complete retention of configuration in the lactonization of a series of hindered alcohols. Some preliminary data of ours indicate that the Mitsunobu reaction affords an easy way to distinguish between alcoholic and phenolic hydroxyls in esterification.[6]

With 1,3-dicarbonyl compounds, because of the enolate charge delocalization, the reaction yields mixtures of *C*- and *O*-alkylation products.[3] Disulfones with reactive methylene groups that are not enolisable yielded *C*-alkylation products exclusively.[7] In all other instances *O*-alkylation has proven highly competitive *vs. C*-alkylation, if not prevalent. Literature data[8] indicate a poor regioselectivity in Mitsunobu reactions on 1,3-dicarbonyl compounds like Meldrum acid (**1**), its 5-substituted derivatives and other cyclic ß-dicarbonyl systems. All reported attempts to monoalkylate Meldrum acid have failed: when primary allyl or benzyl alcohols are employed as alkylating agents, *C*-dialkylation occurs, while simple alcohols like 2-propanol or 2-phenylethanol do not yield the desired products. Working with 5-

substituted derivatives of Meldrum acid, regioselectivity of *C- vs. O*-alkylation can be increased by adding a Pd(0) complex in catalytic amounts.[8] Pd(0) exerts this effect, in accordance with HSAB theory, by softening both the acidity of the allyl part and the basicity of the carbanion. The Pd-mediated Mitsunobu reaction, however, has been of no avail in attempts to *C*-monoalkylate Meldrum acid. On the other hand, ß-tetronic acid (**2**) and its derivatives can easily be *O*-alkylated with good yields by a great variety of alcohols using the Mitsunobu reaction.[7]

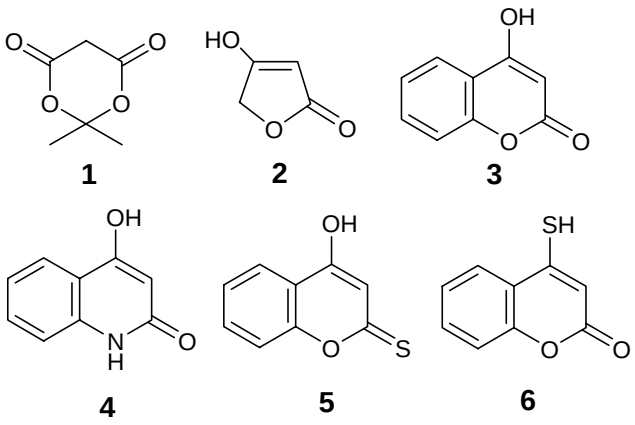


Figure 1

Likewise, as reported by Suzuki,[9] the dehydroalkylation with primary and secondary alcohols of 4-hydroxycoumarin (**3**) gives exclusively *O*-alkylation products in excellent yields (over 80%). In the same way Ito[10] prepared new 4-*O*-coumarinyl derivatives to serve as chiral derivatizing agents for NMR spectrometry.

Our interest in the synthesis of 3-alkylated 4-hydroxycoumarin derivatives and related systems led us to explore the applicative range of the Mitsunobu dehydroalkylation of 4-hydroxycoumarin[11] and its nitrogen- and sulfur-isosteres (**4** and **5, 6**) respectively. Our work focused on the sitoselectivity of the Mitsunobu reaction with prenyl alcohols. We were also spurred to the task by recently published screenings of natural products in search of new inhibitors of HIV-1-RT. Among quinoline alkaloids two compounds, buchapine (or buchapsine) (**8**) and its precursor (**7**), have been identified as interesting inhibitors (IC_{50} 12 and 8 µM, respectively).[12]

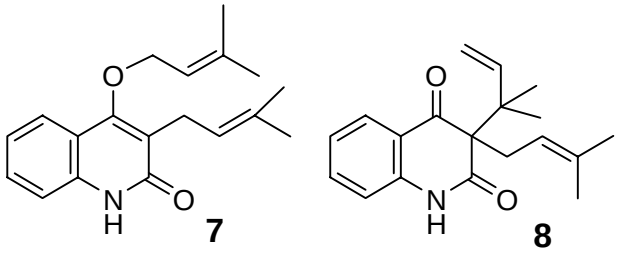
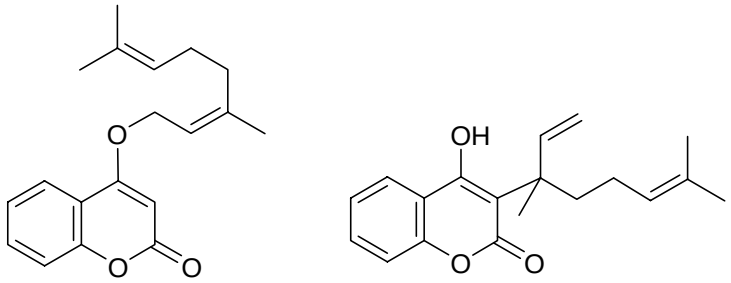


Figure 2

These unusual hemiterpenic quinoline alkaloids have been isolated from the plants of genus *Haplophyllum* and from *Euodia roxburghiana*,[13] a plant that is widely employed by traditional medicine in Australia and some parts of Asia.

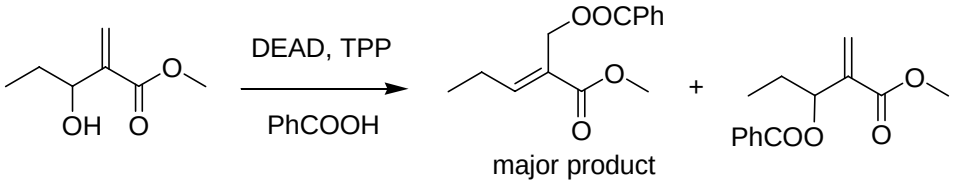
Starting from our previous findings that allyl alcohol gave the 4-*O*-allyloxycoumarin[14] exclusively (71%), we carried out the prenylation of 4-hydroxycoumarin in the conditions that have been used to prepare carboxylic esters.[3] With nerol the reaction was very fast, yielding 4-neryloxycoumarin (**9**) (46%) and the *C*-monoprenylated product (**10**) (38%). This is quite at variance with reported Mitsunobu dehydroalkylations on 4-hydroxycoumarin that yielded *O*-alkylated derivatives exclusively. Our findings of a transposed isoprenic chain from nerol may be explained by an allylic rearrangement taking place in the nucleophilic substitution on the oxyphosphonium salt (SN2').



9 **10**

Figure 3

Although the protocol for the Mitsunobu reaction has been extensively utilized for saturated alcohols and the mechanism has been well studied and defined, uncertainty lingers about the factors that govern its course when allylic or benzylic alcohols are employed. Mitsunobu displacements of allylic hydroxyl groups are generally considered to proceed with high SN2 regioselectivity. Although allylic alcohols react according to the normal SN2 mechanism, instances are found in the literature when an SN2' mechanism predominates. With an ester at the β-position, the Michael acceptor nature of the allylic alcohol promotes predominant SN2' attack.[3]



Scheme 1

To the best of our knowledge no occurrences of SN2' on primary allylic substrates (C=C-CH_2X) are described in the literature, while under bimolecular kinetic conditions compounds of the C=C-CR_2X type undergo SN2' exclusively.

The same reaction, when carried out with 3-methyl-2-butenol, gave four products in comparable yields. As reported for the Meldrum acid, 4-hydroxycoumarin also gave *C,C*-bisprenylated derivatives (Figure 4), confirming that the reaction shows no regioselectivity at all. The *C,C*-bisalkylated product with a transposed prenyl chain (**13**) is of particular interest because of its relationship to buchapine (**8**).

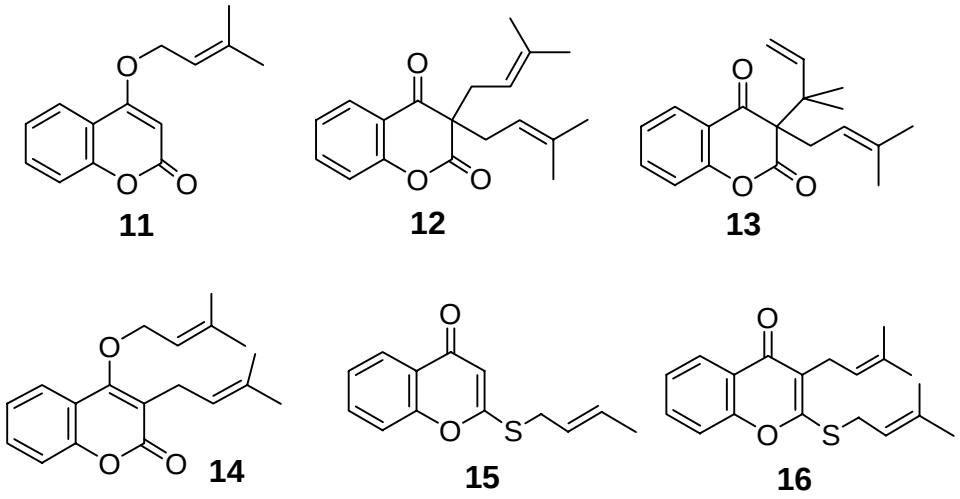
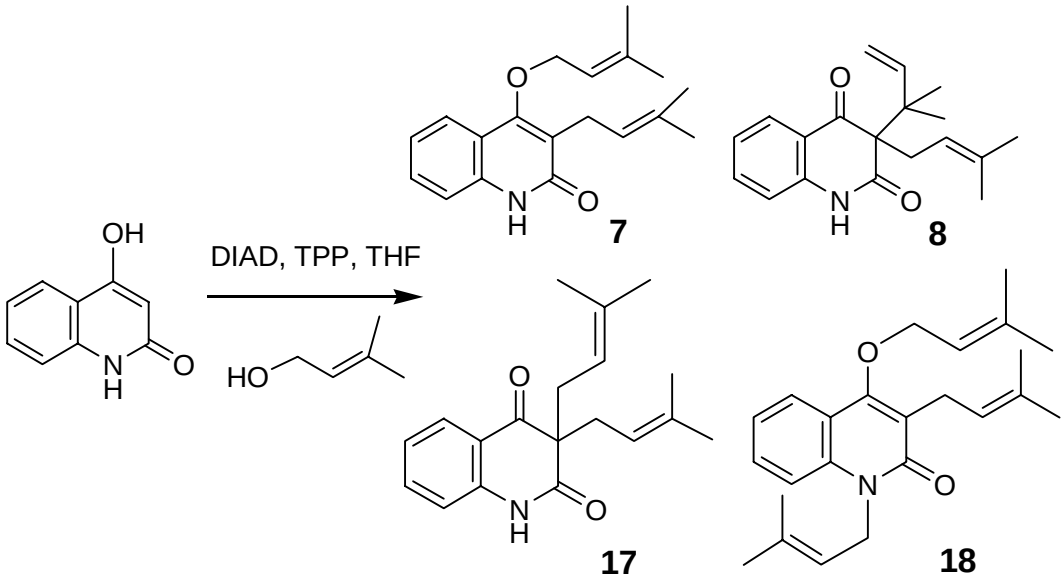


Figure 4

The synthesis of compounds (**11-14)** by direct allylation has been reported.[15] The same reaction carried on 4-hydroxy-2-quinolone[16] gave 10% of the *C,O*-alkylated compound (**7**); successively an abnormal Claisen transposition of the latter generated buchapine (**8**) with a yield of 40%.



Scheme 2

As expected under Mitsunobu conditions, 4-hydroxy-2-quinolone reacted with dimethylallyl alcohol like 4-hydroxycoumarin; consequently we isolated from the reaction mixture four products, namely buchapine

(38%), its likely biogenetic precursor (**7**) (32%) the *C,C*-bisprenylated product (26%) (**17**) and an *C,O,N*-trisprenylated product (**18**) (4%). With this synthetic approach we could very easily obtain one-pot the mentioned biologically active alkaloid buchapine in an acceptable yield.

When carried out on 4-hydroxy-2-thiocoumarin[17] the reaction failed to give the sulfur isoster of buchapine: a mixture of two products was obtained instead, with a prevalence of the *S*-prenylated derivative (**15**) over the *C,S*-bisalkylated product (**16**). The result can be explained on the grounds that the electrons of sulfur are highly polarizable.

Our results further demonstrated the potential of the Mitsunobu reaction in the formation of C-C bonds starting from 1,3-dicarbonyl substrates like 4-hydroxycoumarin or its nitrogen isoster. Buchapine was obtained through a one-pot procedure from 4-hydroxy-2-quinolone and dimethylallyl alcohol in acceptable yield.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General Methods.

Anhydrous conditions were achieved (when indicated) by flame-drying flasks and other equipment. Reactions were monitored by TLC on Alugram Sil - Macherey Nagel F254 (0.25 mm) plates, which were visualized by UV inspection and stained with a 5% $KMnO_4$ solution or 5% H_2SO_4 in ethanol followed by heating. A Waters microPorasil column 7.8-300 was used for semipreparative HPLC, with detection by a Gilson 133 refractive index refractometer. Melting points were obtained on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker 300 Advance spectrometer at 25°C. CIMS were performed on a Finnigan-MAT TSQ70 with isobutane as reactant gas. Commercially available reagents and solvents were used without further purification, unless otherwise noted. Immediately prior to use CH_2Cl_2 and THF were distilled under N_2 from P_4O_{10} and sodium-benzophenone ketyl respectively.

General conditions for the Mitsunobu reaction. A solution in anhydrous THF containing triphenylphosphine (1.5 mol), the alcohol (1.5 mol) and the enol compound (1.0 mol) was magnetically stirred at 0°C under nitrogen. Diisopropyl azodicarboxylate (DIAD) (1.5 mol) was added to it dropwise over a period of 5 min. The orange-red colour of DIAD immediately disappeared. The weakly exothermic reaction was allowed to proceed at rt under stirring. Its duration ranged from 1 to 24 h, depending on the nature of the enol. After completion, as indicated by TLC monitoring (eluent hexane-ethyl acetate), the

reaction mixture was evaporated. The residue was diluted with hexane-ether 3:1, filtered through a thin pad of Celite to remove the precipitate of triphenylphosphine oxide and concentrated under reduced pressure. Finally, the products were purified by flash silica gel column chromatography or by preparative HPLC.

4-Neryloxycoumarin (9)

White powder, mp 93,5°C; IR (KBr) cm^{-1}: 2926, 1722, 1626, 1250, 927, 752. ^{1}H-NMR ($CDCl_3$) δ: 7.83 (dd, 1H, *J* = 1.46, 7.92 Hz, H-5), 7.55 (td, 1H, *J* = 1.55, 8.57 Hz, H-7), 7.32 (d, 1H, *J* = 8.15 Hz, H-8), 7.24 (br t, 1H, *J* = 7.33 Hz, H-6), 5.68 (s, 1H, H-3), 5.55 (br t, 1H, *J* = 6.7 Hz, H-2'), 5.02 (br t, 1H, *J* = 6.89 Hz, H-6'), 4.66 (d, 2H, *J* = 6.83 Hz, H-1'a,b), 2.15 (m, 4H, H-5'a,b, H-4'a,b), 1.85 (s, 3H, H-10'), 1.67 (s, 3H, H-9'), 1.60 (s, 3H, H-8'); CIMS: 299 $(M+H)^+$; EIMS: 298 (M^+); 272; 257; 187; 121; R_f = 0.71 (hexane/EtOAc 4:1). Anal. Calcd for $C_{19}H_{22}O_3$ C, 76.48; H, 7.43. Found: C, 76.40; H, 7.45.

3-(3,7-Dimethylocta-1,6-dien-3-yl)-4-hydroxycoumarin (10)

Colorless oil; IR (liquid film) cm^{-1}: 2361, 1633, 1446, 1157, 754. ^{1}H-NMR ($CDCl_3$) δ: 7.77 (dd, 1H, *J* = 1.59, 8.09 Hz, H-5), 7.47 (td, 1H, *J* = 1.61, 7.23 Hz, H-7), 6.99 (dd, 1H, *J* = 1.03, 8.38 Hz, H-8), 6.89 (td, 1H, *J* = 1.74, 8.17 Hz, H-6), 5.89 (dd, 1H, *J* = 17.48, 10.82 Hz, H-2'), 5.10 (br t, 1H, *J* = 7.12 Hz, H-6'), 5.04 (dd, 1H, *J* = 0.87, 10.83 Hz, H-1'b), 4.99 (dd, 1H, *J* = 0.87, 17.53 Hz, H-1'a), 1.97 (m, 2H, H-5'a,b), 1.68 (br s, 3H, H-8'), 1.60 (br s, 3H, H-9), 1.55 (m, 2H, H-4'a,b), 1.20 (s, 3H, H-10'); CIMS: 299 $(M+H)^+$; EIMS: 298 (M^+); 229; 163; 81; 69; R_f = 0.34 (hexane/EtOAc 4:1). Anal. Calcd for $C_{19}H_{22}O_3$ C, 76.48; H, 7.43. Found: C, 76.45; H, 7.50.

2-(3',3'-Dimethylallyilthio)chromen-4-one (15)

Yellow oil; IR (liquid film) cm^{-1}: 2972, 1643, 1587, 1356, 1130, 922, ^{1}H-NMR ($CDCl_3$) δ: 8.12 (d, 1H, *J* = 7.52 Hz, H-5), 7,71 (s, 6H, H-4', H-5'), 7.59 (br t, 1H, *J* = 6.76 Hz, H-7), 7.37-7.24 (m, 2H, H-6, H-8), 6.23 (br s, 1H, H-3), 5.28 (d, 1H, *J* = 6.4 Hz, H-2), 3.67 (d, 2H, *J* = 7.68 Hz, H-1'a,b), CIMS: 247 $(M+H)^+$; R_f 0.34 (hexane/EtOAc 19:1). Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H. 5.73 Found: C, 68.18; H, 5.78.

2-(3',3'-Dimethylallylthio)-3-(3'',3''-dimethylallyl)chromen-4-one (16)

Yellow gum; IR (KBr) cm^{-1}: 2926, 1730, 1635, 1373, 1105, 758, ^{1}H-NMR ($CDCl_3$) δ: 8.18 (dd, 1H, *J* = 7.44, 3,2 Hz, H-5), 7.70 (td, 1H, *J* = 7.72, 3.0 Hz, H-7), 7.60-7.35 (m, 2H, H-6, H-8), 5.34 (br t, 1H, *J* = 7.72 Hz, H-2'), 5.13 (br t, 1H, *J* = 8.0 Hz, H-2'), 3.80 (d, 2H, *J* = 7.88 Hz, H-1'a,b), 3.28 (d, 2H, *J* = 6.96

Hz, H-1"a,b), 1.79 (s, 3H, H-4'*), 1.76 (s, 3H, H-5'*), 1.73 (s, 3H, H-4"*), 1.66 (s, 3H, H-5"*); CIMS: 315 $(M+H)^+$; R_f 0.28 (hexane/EtOAc 4:1). Anal. Calcd for $C_{19}H_{22}O_2S$: C, 67.22; H, 5.21. Found: C, 67.45; H, 5.20.

3-Bis(3,3-dimethylallyl)quinoline-2,4-dione (17)

Yellow gum; IR (KBr) cm^{-1}: 2293, 1693, 1657, 1385, 752. ^{1}H-NMR ($CDCl_3$) δ: 10.40 (s, 1H, NH), 7,90 (br d, 1H, H-5), 7.52 (br t, 1H, *J* = 6.76 Hz, H-7), 7.14-7.01 (m, 2H, H-6, H-8), 4.92 (br t, 2H, H-2', H-2"), 2.75 (d, 4H, *J* = 7.68 Hz, H-1'a,b, H-1"a,b), 1.58 (s, 6H, H-4', H-4"), 1.47 (s, 6H, H-5', H-5"); CIMS: 298 $(M+H)^+$; R_f 0.62 (hexane/EtOAc 1:1). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H. 7.80 Found: C, 76.80; H. 7.70.

1,3-Bis(3,3-dimethylallyl)-4-(3,3-dimethylallyloxy)-2-quinolin-2-one (18)

Pale pink oil; IR (liquid film) cm^{-1}: 2970, 1603, 1415, 1082, 762. ^{1}H-NMR ($CDCl_3$) δ: 7.91 (br dd, 1H, *J* = 8.24 Hz, H-5), 7,78 (d, 1H, *J* = 8.04 Hz, H-8), 7.53 (td, 1H, *J* = 1.48 Hz, *J* = 8.44 Hz, H-7), 7.32 (t, 1H, *J* = 7.16 Hz, H-6), 5.65 (br t, 1H, *J* = 7.16 Hz, H-2'), 5.55 (br t, 1H, *J* = 7.16 Hz, H-2'"), 5.21(br t, 1H, *J* = 7.16 Hz, H-2"), 4.98 (d, 2H, *J* = 6.76 Hz, H-1'a,b), 4.53 (d, 2H, *J* = 7.16 Hz, H-1'"a,b), 3.45 (d, 2H, *J* = 6.76 Hz, H-1"a,b), 1.81(s, 3H, H-4'*), 1.80 (s, 3H, H-5'*), 1.78 (s, 3H, H-4'"*), 1.77 (s, 3H, H-5'"*), 1.68 (s, 3H, H-4"*), 1.67 (s, 3H, H-5"*); CIMS: 366 $(M+H)^+$; R_f 0.68 (hexane/EtOAc 1:1). Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H. 8.55 Found: C, 78.81; H. 8.41.

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