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Monoalkylation of dihydroxycoumarins via Mitsunobu dehydroalkylation under high intensity ultrasound. The synthesis of ferujol

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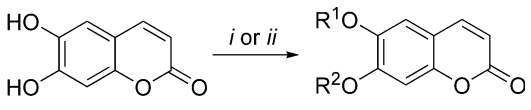
Abstract—Monoalkylation of natural dihydroxycoumarins was carried out by Mitsunobu dehydroalkylation under sonochemical conditions. Aesculetin (6,7-dihydroxycoumarin) was selectively alkylated in good yield with prenyl alcohols at position 7, as clearly shown by NOESY experiments; though less selectively, position 7 was also the most reactive in daphnetin (7,8-dihydroxycoumarin). The synthesis of the phytoestrogen ferujol is also reported for the first time.

1. Introduction

The Mitsunobu reaction[1] has been exploited in the chemistry of a wide range of naturally occurring compounds like carbohydrates,[2] peptides,[3] terpenes[4] and others with formation of ethers, esters and new C–C bonds.[5] The nucleophilic substitution of an alcohol group mediated by the triaryl- or trialkyl-phosphine/dialkyl azodicarboxylate redox system is widely used to prepare biologically active compounds with interesting applications in solid phase synthesis[6] and combinatorial chemistry.[7] The regio- and stereoselectivity of the reaction have been thoroughly reviewed.[5] Although its reaction mechanism with saturated alcohols is well known, uncertainty lingers on the factors that govern its course when allyl or prenyl alcohols are employed. Although allylic alcohols react according to the normal S_N2 mechanism, some instances are found in the literature of an S_N2' mechanism.[5] The reaction normally proceeds with inversion of configuration at the carbon atom bearing the hydroxy group, yet complete retention of configuration has been observed in the lactonization of hindered alcohols.[8] As regards regioselectivity, Ko[9] found that with *syn*-2,3-dihydroxy esters only the β-hydroxy group reacted. On the other hand, with 1,3-dicarbonyl compounds, the reaction yields mixtures of *C*- and *O*-alkylation products because the enolate charge is delocalized.[10] It is well known that 4-hydroxycoumarin usually gives *O*-alkylation products.[11] In a recent paper[12] we compared the outcomes of the reaction under conventional and sonochemical conditions, showing that high intensity ultrasound influences only slightly the regioselectivity, while markedly increasing reaction rates and yields. Our preliminary data,[13] further developed by Appendino,[14] indicate that the Mitsunobu reaction affords an easy way to perform a differential esterification of alcoholic and phenolic hydroxy groups.

We have now found that the Mitsunobu reaction allows a differential etherification of the phenolic groups in dihydroxycoumarins. Although phenol etherification has been widely exploited,[15] to the best of our knowledge, this result has never been published.



1 3-9

Scheme 1. *Reagents and conditions*: (*i*) ROH, PPh_3, DIAD, THF,)))) 45 min or stirring at 20°C for 5–8 h; (*ii*) Ac_2O, pyridine.

Keywords: dihydroxycoumarins monoalkylation; high intensity ultrasound; Mitsunobu dehydroalkylation; ferujol synthesis.
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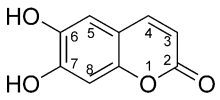
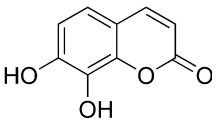
We wish to present here the first results obtained with several prenyl alcohols reacting with two, commercially available, differently substituted coumarins, namely the 6,7-dihydroxycoumarin (aesculetin) **1** and 7,8-dihydroxycoumarin (daphnetin) **2**.



1

Aesculetin



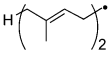
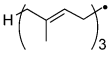
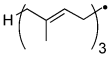
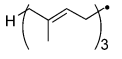
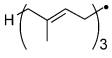
2

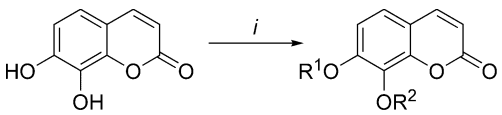
Daphnetin

2. Results and discussion

Using a novel prototype sonochemical reactor,[16] the reactions were carried out in anhydrous tetrahydrofuran employing several biologically significant alcohols like prenyl, geranyl, dihydrogeranyl and farnesyl alcohol.[17] The 400 MHz ^{1}H NMR spectral patterns of compounds **3–14** confirmed that all reaction products were *O*-alkylated coumarin derivatives and that no Claisen rearrangement had occurred.[10] Thus, aesculetin **1** (Scheme 1) exclusively afforded in yields better than those obtained employing magnetic stirring and with shorter reaction times, the 7-alkylated derivatives prenyletin **4**,[18] 7-geranyl **6** and 7-farnesylesculetine **7** (Table 1) with no significant influence on the regioselectivity which seems to be related to the acidity of the OH groups.

Table 1.

Compd	R^1	R^2	Yield % / React. Time))))	Stirring
3	H	CH_3	89 / 45 min	65 / 5 h
4	H		78 / 45 min	52 / 6 h
ii → **5**	Ac		-	65
6	H		72 / 45 min	37 / 8 h
7	H		65 / 45 min	36 / 8 h
ii → **8**	Ac		-	78
9			11 / 45 min	16



2 **10-14**

Scheme 2. *Reagents and conditions*: (*i*) ROH, PPh_3, DIAD, THF,)))) 45 min.

It should be noted that complete regioselectivity is not limited to prenyl alcohols: methanol gave isoscopoletin **3** in good yield. With farnesyl alcohol we also isolated the disubstituted derivative **9** as a by-product (11%).

When the same experimental conditions were used with daphnetin **2** (Scheme 2), the regioselectivity was low, resulting in a mixture of 7-*O*- and 8-*O*-monoalkylated derivatives together with small quantities of the 7,8-disubstituted compounds, relative yields depending on the molecular size of the alcohol. While methyl alcohol only gave the 7-substituted derivative **10a** (52%) besides 10% of the disubstituted compound **10b**, heavier alcohols led to a mixture of 7- and 8-substituted derivatives with the former always predominating (Table 2).

The structural assignment for monoalkylated polyphenols (e.g. distinction between 6- or 7-, and 7- or 8-substituted coumarins) has always been problematic, as shown by the numerous corrections that from time to time have appeared in the literature.[19] For aesculetin derivatives a first approach to the problem was to acetylate the reaction product and subsequently ratio-

Table 2.

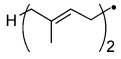
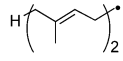
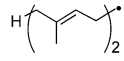
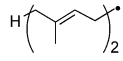
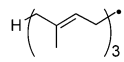
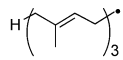
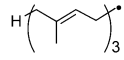
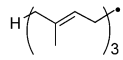
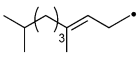
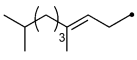
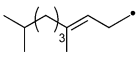
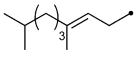
Compd	R^1	R^2	Yield %))))
10a	CH_3	H	52
10b	CH_3	CH_3	10
11a		H	25
11b	H		18
11c			7
12a		H	30
12b	H		23
12c			12
13a		H	20
13b	H		15
13c			14
14a		H	61
14b	H		30 (ferujol)
14c			4

Table 3. Chemical shift (ppm) of aromatic protons in compounds **A** and **B** (see text) and their acetyl derivatives[a]

Compd	H-3	$\delta\Delta$	H-4	$\delta\Delta$	H-5	$\delta\Delta$	H-8	$\delta\Delta$
A	7.60	–	6.28	–	6.96	–	6.82	–
Acetyl deriv.	7.72	0.12	6.41	0.13	7.40	0.44	7.00	0.18
B	7.60	–	6.27	–	6.96	–	6.82	–
Acetyl deriv.	7.59	0.01	6.29	0.02	7.15	0.19	6.88	0.06

[a] $CDCl_3$, 400 MHz.

nalize chemical shift variations of the aromatic protons. Thus, we acetylated the compounds obtained from the reaction of **1** with prenyl- (**A**) and farnesyl alcohol (**B**), then we analyzed the ^1H NMR spectra of the acetyl derivatives (Table 3).

From chemical shift data for both acetyl compounds, in particular from the larger high-frequency shift of H-5 relative to H-8, it was reasonable to attribute structures **4** and **7** to products **A** and **B**, respectively. This attribution depended however, on the correct assignment of the H-5 and H-8 resonances. To solve the problem unambiguously it sufficed to attribute the resonance of H-5; then, as H-3 and H-4 on the basis of chemical shift considerations were easily assigned to the doublets at the lowest and highest C(sp^2)-H frequencies, respectively, a simple NOEDIF experiment led to the required distinction between H-5 and H-8, because only the former gave a strong, positive NOE effect by irradiation of H-4 (see Fig. 1 for a general example).

We wish to point out that the same technique may also give the answer to the regiochemical problem: in fact, irradiation of H-5 gives a positive NOE on the protons of R only if the substituent is at position 6. If no NOE is observed, irradiation of H-8 may solve the problem. Finally, it is obvious that a NOESY experiment (τ_{mix} = 600 ms) is the most convenient way to solve the regiochemistry in just one step.

As for daphnetin derivatives, the ambiguity was between the 7- or 8-derivative. Once again the NOESY spectrum gave the answer: firstly the distinction between the H-5 and H-6 resonances (both being doublets with similar chemical shifts) was made on the basis of a crosspeak between H-4 and one of the doublets; this one therefore must be attributed to H-5. Moreover, a close contact between H-6 and the substituent was revealed (when present) by the existence of the corresponding crosspeak (Fig. 2).

In the wake of these results we carried out the first synthesis of the natural phytoestrogen ferujol **14b**,[20] employing 6,7-dihydrogeranyl alcohol[21] and daphnetin in the Mitsunobu reaction. The reaction yielded, besides a very small quantity of the dialkylated product (4%), both the regioisomers **14a** and **14b** (61 and 30%, respectively).[22] These were separated by HPLC and identified in the usual manner (NOEDIF).

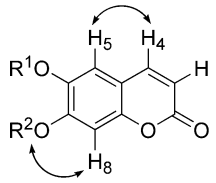


Figure 1.

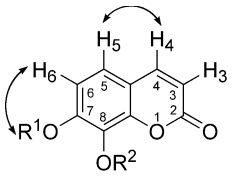


Figure 2.

3. Conclusions

In conclusion, our method led to several compounds endowed with biological activities or precursors thereof, e.g. the phytoestrogen ferujol **14b** first isolated from *Ferula jaeschkeana*.[20a] On the other hand a simple methylation of compound **12a** could yield the antiviral and antiplatelet aggregation agent collinine (from *Zanthoxylum schinifolium*)[23] and selective epoxidation of 7-farnesylesculetin **7** could yield some new hopene squalene cyclase inhibitors.[13b]

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16. Cravotto, G.; Omiccioli, G.; Vazzoler, E. Patent PN 2003-A000032. Our sonochemical apparatus, developed in collaboration with TEKIMP srl (Castelfranco Veneto, TV, Italy) and designed for stringent reaction conditions, consists of a transducer built with pre-pressed piezoelectric ceramic rings that can be tuned between the frequencies of 18 and 45 kHz. It is equipped with a dynamic probe that, when in operation, can be made to move alternatively up and down at a chosen speed. The probe system (comprising the transducer, the booster and an immersion horn) can work in continuous mode for many hours thanks to an efficient cooling system. The probe is refrigerated by an oil forced-circulation circuit that conveys heat to an oil-freon heat exchanger; this in turn is cooled by a chiller. A regulation console monitors all relevant parameters. To achieve optimal acoustic efficiency all reactions are carried out in Teflon tubes (1 mm thick). For a rapid and efficient cooling the reactor is thermostatted using four Peltier modules.
17. *General conditions for the Mitsunobu reaction*. A solution in anhydrous THF containing triphenylphosphine (1 equiv.), the alcohol (1 equiv.) and the dihydroxycoumarin was sonicated at 10°C under an argon atmosphere (18.0 kHz, 380 W). Diisopropyl azodicarboxylate (DIAD) (1 equiv.) was added dropwise over 5 min. The orange-red colour of DIAD immediately disappeared and a weakly exothermic reaction occurred. The mixture was sonicated for 35–55 min at 20°C. When the reaction was complete, as indicated by TLC (eluant: *n*-hexane–ethyl acetate), the mixture was evaporated. The residue was diluted with hexane–ether 3:1, v/v, 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. All the reactions were carried out under nitrogen in a Teflon tube (thickness 1 mm, diameter 35 mm, volume 40 mL) inserted in the thermostatted reactor.
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22. **Isoferujol**: 7-[(3,7-dimethyl-2-octenyl)oxy]-8-hydroxy-2*H*-1-benzopyran-2-one (**14a**): white powder; mp 56–58°C; IR (KBr) 3255, 1738, 1713, 1692, 1607 and 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H, $^3J=9.5$ Hz, H-4), 6.97 (d, 1H, $^3J=8.6$ Hz, H-5), 6.85 (d, 1H, $^3J=8.6$ Hz, H-6), 6.39 (br s, 1H, OH), 6.25 (d, 1H, $^3J=9.5$ Hz, H-3), 5.47 (tq, 1H, $^3J=6.7$ and $^4J=1.3$ Hz, H-2′), 4.70 (d, 2H, $^3J=6.7$ Hz, H-1′), 2.04 (t, 2H, $^3J=7.6$ Hz, H-4′), 1.73 (d, 3H, $^4J=1.3$ Hz, 3′-Me), 1.52 (nonuplet, 1H, $^3J=6.6$ Hz, H-7′), 1.46–1.37 (m, 2H, H-6′), 1.19–1.09 (m, 2H, H-5′), 0.86 (d, 6H, $^3J=6.6$ Hz, 2×7′-Me); CIMS: 317 $(M+H)^+$. Anal. calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.16; H, 7.62.
Ferujol: 8-[(3,7-dimethyl-2-octenyl)oxy]-7-hydroxy-2*H*-1-benzopyran-2-one (**14b**): white powder; mp 68–70°C [lit.[20a] 68–70°C]; IR (KBr) 3410, 1735, 1705, 1601 and 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H, $^3J=9.6$ Hz, H-4), 7.09 (d, 1H, $^3J=8.5$ Hz, H-5), 6.87 (d, 1H, $^3J=8.5$ Hz, H-6), 6.34 (br s, 1H, OH), 6.23 (d, 1H, $^3J=9.6$ Hz, H-3), 5.47 (tq, 1H, $^3J=7.6$ and $^4J=1.0$ Hz, H-2′), 4.84 (d, 2H, $^3J=7.6$ Hz, H-1′), 1.97 (t, 2H, $^3J=7.6$ Hz, H-4′), 1.64 (d, 3H, $^4J=1.3$ Hz, 3′-Me), 1.49 (nonuplet, 1H, $^3J=6.6$ Hz, H-7′), 1.40–1.24 (m, 2H, H-6′), 1.12–1.00 (m, 2H, H-5′), 0.84 (d, 6H, $^3J=6.6$ Hz, 2×7′-Me); CIMS: 317 $(M+H)^+$. Anal. calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.15; H, 7.63.
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