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Methods in synthesis of flavonoids. Part 3: Molybdenum(IV)-catalyzed coupling of cinnamyl alcohols to phenol derivatives

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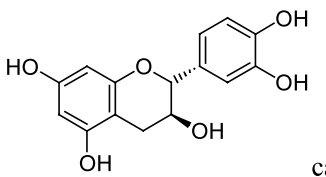
Abstract—This paper deals with the formal total synthesis of flavonoids bearing the hydroxylation pattern of the catechin series based on an access to the fully functionalized skeleton via the alkylation of phloroglucinol tribenzyl ether by 3,4-dibenzyloxycinnamyl alcohol. This reaction was revealed to be most successful when catalyzed by the $Mo(acac)_2(SbF_6)_2$ complex. In addition, the underlying concepts to the different ways that can be used in this C_6–C_3+C_6 strategy are discussed.

Among the two possible strategies of synthesis of the C_6–C_3–C_6 flavonoid skeleton, the C_6+C_3–C_6 biomimetic type has often been neglected for the benefit of the C_6–C_2+C_1–C_6 one. Indeed, it involves the difficult arylation step of a cinnamic moiety by a phenolic nucleophile. Some examples have been reported in the literature but they always stated side reactions or poor yields when using either a good nucleophilic synthon such as phloroglucinol ring or an electrophilic caffeic acid derivative,[1,2] and yet both could be turned to good account in an easy access to flavan-3-ol and flavan precursors that bear the hydroxylation pattern of catechin.



catechin

Therefore, we did not succeed to form either a chalcone by a Lewis acid (BF_3–OEt_2) catalyzed acylation[1] or a deoxychalcone by a Brønsted acid (CH_3CO_2H) catalyzed cinnamylation[2,3] (double substitution of the phloroglucinol ring occurred). Other methods have successfully described the coupling of cinnamyl chloride to aromatic nucleophiles; however, in all cases, they were just only simple ones, such as ArN_2 (in the presence of $Pd(PPh_3)_4$)[4] or ArONa,[5] thus precluding any of the adducts from bearing the hydroxylation pattern of the natural series.

As part of our program aiming at synthesizing bioactive flavonoids of the catechin series,[6–8] we explored the different ways to build the skeleton using the biomimetic strategy. This led us to consider three different cases according to the oxidation state of the cinnamic precursor compared to the built system (Scheme 1). Each oxidation state of this precursor (acid, aldehyde or alcohol) could be valuable in the specific synthesis of different classes of flavonoid intermediates (e.g. chalcones, 2-phenyl-2*H*-chromenes or cinnamylphenols, respectively).

In this way, tri-*O*-benzylphloroglucinol has been acylated (Scheme 1, way A) in 58% yield by di-*O*-benzylcaffeic acid, after activation by forming a mixed anhydride with trifluoroacetic anhydride, leading to a chalcone that was further transformed into the targeted ^{13}C-labeled catechin.[6] Furthermore, as the first example in this strategy, the cinnamaldehyde diacetyl acylal has been used to alkylate phloroglucinol in a palladium-catalyzed double allylic substitution (Tsuji–Trost reactions), yielding a 2-phenyl-2*H*-chromene heterocycle (way B).[9] However, difficulties were encountered due to the very low stability of the adducts.

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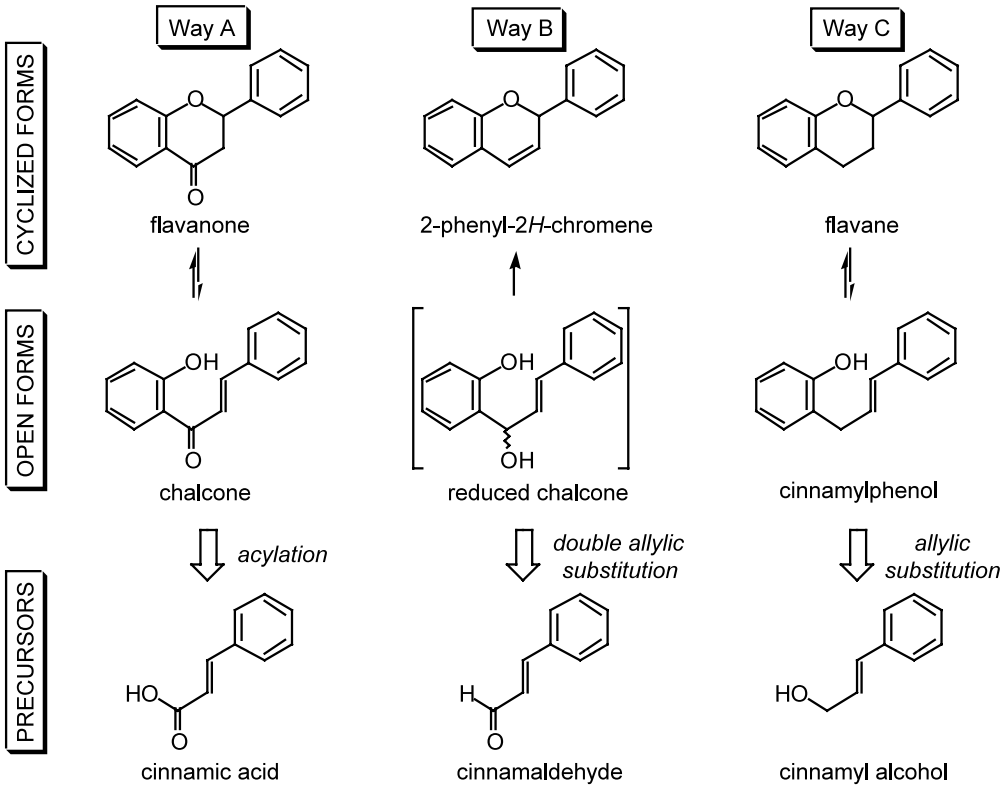


Scheme 1. The C_6+C_3–C_6 strategy: relation between different flavonoid skeletons and their cinnamic precursor according to their oxidation state.

Concerning the coupling of phloroglucinol and cinnamyl alcohol derivatives (way C), the palladium-catalyzed substitution of cinnamyl acetate by phloroglucinol has also been attempted but results were quite disappointing.[9]

Finally, we applied the same strategy as the one recently described by Malkov et al.,[10] that deals with a molybdenum(IV)-catalyzed C–C coupling of simple phenols with cinnamyl alcohol (way C). Results are described hereafter.

The Lewis acid catalyst [2% of $Mo(acac)_2(SbF_6)_2$] smoothly generates the allylic cation.[10] We used these mild conditions to couple protected phloroglucinol (that was expected to be more nucleophilic than monophenolic derivatives) to the 3,4-dialkyloxycinnamic alcohol (where the alkoxy group in *para* to the allylic moiety could influence the reaction by stabilizing the generated allylic cation).

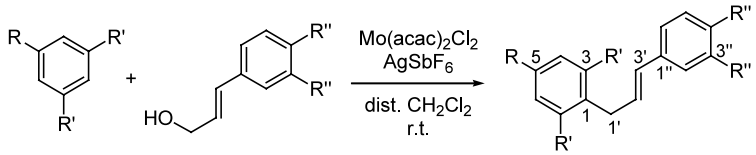
The catalyst precursor $Mo(acac)_2Cl_2$ was prepared in acetonitrile according to the literature procedure from $MoCl_5$, in the presence of 2,4-pentanedione.[10,11] The catalyst $Mo(acac)_2(SbF_6)_2$ was obtained in situ extemporaneously in each experiment by ionic exchange in the presence of $AgSbF_6$.[10]

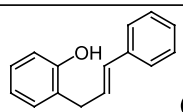
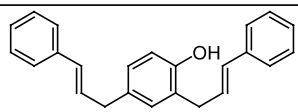
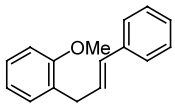
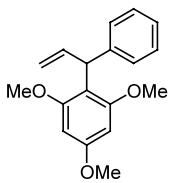
Substituted or free phenol and phloroglucinol were used as aromatic nucleophiles while cinnamyl alcohol and 3,4-dibenzyloxycinnamyl alcohol played the role of electrophiles.[12] Results are shown in Table 1. Using free phenol and cinnamyl alcohol (entry 1), we were not able to obtain as good results as those of Malkov (22% of the major product instead of 60%). Anisole gave similar yields (entry 2). As expected, phloroglucinol derivatives were more reactive. An unseparable mixture of many products was obtained using free or acetylated phloroglucinol (entries 3 and 4). Phloroglucinol trimethyl ether furnished 30% of an unexpected product resulting from the substitution of cinnamyl alcohol at position 3, thus building up the neoflavonoid-type skeleton (entry 5), while when opposed to 3,4-dibenzyloxycinnamyl alcohol (entry 6), the product of substitution at position 1 was isolated as the major adduct (21% yield), showing the influence of the substituting groups of the cinnamic part.

The use of phloroglucinol tribenzyl ether gave good yields of the expected product (52%, entry 7)[13] that features the substitution pattern of the catechin series. An elegant metathesis access to cinnamyl phenols using Grubbs catalyst described recently similar yields but, once again, none of the prepared compounds is bearing the required hydroxylation pattern.[14] Finally, tris[*t*-butyl-(dimethyl)silyl]phloroglucinol was tested and gave the best yields of product (70–80%, entry 8). However, this last coupling product could not be obtained in a pure form due to the difficulty to get rid of the starting silylated phloroglucinol (very close migration of both compounds on silica gel, CH_2Cl_2).

In conclusion, this work shows that there are at least three different ways that the C_6+C_3–C_6 strategy allows

Table 1. Results of molybdenum(IV)-catalyzed couplings of phenols to cinnamic alcohol derivatives



Entry	R	R'	R''	Yield (%)	Other products (yield %)
1	OH	H	H	22	 (7%)  (7%)
2	OCH_3	H	H	24	 (3%) + many other unidentified products
3	OH	OH	H	-	unseparable mixture
4	OAc	OAc	H	-	unseparable mixture
5	OCH_3	OCH_3	H	-	 (30%) + many other unidentified products
6	OCH_3	OCH_3	OBn	21	tars
7	**OBn**	**OBn**	**OBn**	**52**	-
8	**OTBS**	**OTBS**	**OBn**	**70-80**	-

us to reach specific open form intermediates en route to the synthesis of different types of flavonoids depending on the cinnamic precursor (C_3–C_6) used. After having studied various reactions in this way (acylation by a caffeic acid,[6] Tsuji–Trost reactions using an acylal from cinnamaldehyde or a cinnamyl acetate flavonoids), we found here that the molybdenum(IV)-catalyzed coupling of cinnamyl alcohols to phenols, initially proposed by Malkov et al., can also be applied in an efficient way to phloroglucinol rings when using benzyl or *t*-butyldimethylsilyl as hydroxyl protecting groups. The fully functionalized cinnamylphloroglucinols thus in our hands (entries 7 and 8), can be regarded as suitable precursors of natural flavonoids. For instance, bearing the hydroxylation pattern of the catechin series, these precursors can be seen as a starting material for a formal total synthesis of these natural compounds, if we consider the nice transformation of such intermediates as developed by Ferreira et al.[15,16] Moreover, this methodology is likely to be also applied to more complex natural polyphenols for their coupling to other allylic alcohols (e.g. cinnamyl and prenyl alcohols) or even to more complex terpenoids.

Acknowledgements

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12. *Typical procedure for Mo(IV)-catalyzed preparation of cinnamylphenols*: A solution of the cinnamic alcohol (1 mmol), the phenol (1.3 mmol), $Mo(acac)_2Cl_2$ (0.027 mmol, 10 mg) and $AgSbF_6$ (0.029 mmol, 10 mg) in distilled CH_2Cl_2 was stirred at room temperature under

nitrogen for 1–2 h. During the reaction, the color evolved from red to green. Then, the organic mixture was washed with 5% aq. Na_2CO_3, water and brine, before drying over Na_2SO_4 and concentration under vacuum. The product was purified by silica gel chromatography.

13. *Data for 1,3,5-tribenzyloxy-2-[3′-(3″,4″-dibenzyloxyphenyl)-allyl]benzene* (Table 1, entry 7): UV (MeOH) λ_{max} nm: 217, 263. IR (KBr) ν cm^{-1}: 3029, 2896, 1596, 1505, 1454, 1430, 1380, 1260, 1202, 1132, 1007, 737, 698. ^1H HRNMR ($CDCl_3$, 500 MHz), δ ppm: 3.60 (d, $J=6.5$ Hz, 1′-H), 5.03 (s, 5-$OC\underline{H}_2C_6H_5$), 5.07 (s, 1- and 3-$OC\underline{H}_2C_6H_5$), 5.12 (s, 3″-$OC\underline{H}_2C_6H_5$), 5.14 (s, 4″-$OC\underline{H}_2C_6H_5$), 6.19 (dt, $J=6.5$, 15.7 Hz, 2′-H), 6.29 (d, $J=15.7$ Hz, 3′-H), 6.33 (s, 4-H and 6-H), 6.80 (dd, $J=2.0$, 8.3 Hz, 6″-H), 6.86 (d, $J=8.3$ Hz, 5″-H), 6.95 (d, $J=2.0$ Hz, 2″-H), 7.29–7.48 (m, $OCH_2C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$, 125 MHz), δ ppm: 26.5 (C-1′), 70.3, 70.4 (1-, 3- and 5-$O\underline{C}H_2C_6H_5$), 71.5, 71.6 (3″- and 4″-$O\underline{C}H_2C_6H_5$), 93.4 (C-4 and C-6), 110.5 (C-2), 112.8 (C-2″), 115.5 (C-5″), 119.7 (C-6″), 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 128.4, 128.5, 128.6 ($OCH_2\underline{C}_6H_5$ *meta*- and *para*), 127.9 (C-2′), 129.2 (C-3′), 132.4 (C-1″), 137.0, 137.3, 137.5 ($OCH_2\underline{C}_6H_5$, *ipso*), 148.1 (C-4″), 149.2 (C-3″), 157.9 (C-1 and C-3), 158.6 (C-5). MS (FAB+, nitrobenzyl alcohol) m/z (intensity): 725 (40, MH^+, $M=C_{50}H_{44}O_5$), 462 (15), 409 (40), 330 (20), 308 (100).

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