Straightforward Synthesis of Highly Hydroxylated Phloroglucinol-Type 3-Deoxyanthocyanidins

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Abstract: Phloroglucinol-type 3-deoxyanthocyanidins were synthesized through the interaction between phloroglucinol derivatives and arylethynylketones in acetic acid in the presence of aqueous hexafluorophosphoric acid. This methodology was applied to achieve the synthesis of natural apigeninidin, luteolinidin and tricetanidin with high yields.

Key words: acid-mediated condensation, heterocycles, ketones, phenols, 3-deoxyanthocyanidins

Flavylium-derived salts (anthocyanins) represent an important family of natural pigments, being responsible for the color of most flowers, fruits, and leaves of angiosperms. Such pigments are also found in other plant tissues (roots, tubers, stems, bulbs) and in various gymnosperms, ferns, and some bryophytes.[1] Structurally, this family of pigments is characterized by the presence of the flavylium chromophore **1** diversely substituted with hydroxyl, alkyloxy, acyl or glycosyloxy groups (Figure 1). Most of the natural flavylium pigments possess a phloroglucinol-type cycle A ($R^5 = R^7 = OH$). The 3-oxygenated derivatives (anthocyanidins), are red-colored pigments that are color-unstable and therefore seldom found naturally in their free form. In contrary, the 3-deoxyanalogues (3-deoxyanthocyanidins) are yellow-orange pigments quite stable in acidic media. Apigeninidin (**2**), luteolinidin (**3**) and tricetanidin (**4**) are major representatives of this group of pigments, as they were isolated from various food plants like corn, sorghum and black tea leaves (Figure 1).[2]

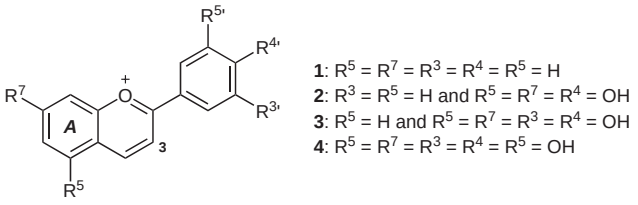
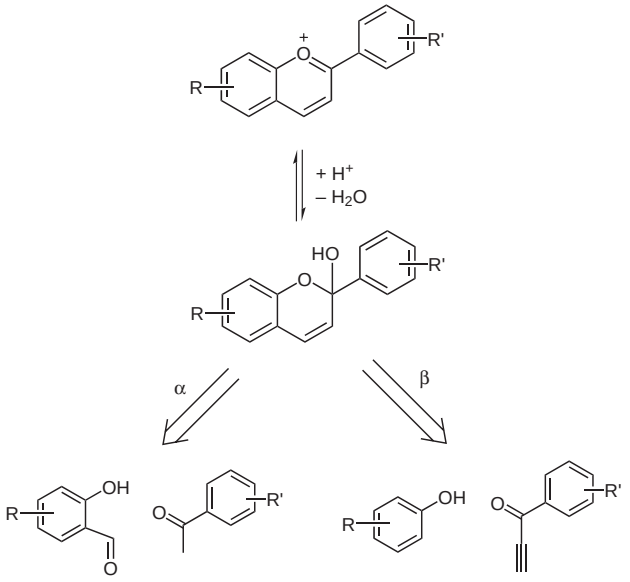


Figure 1 The flavylium chromophore **1** and the major representatives of natural 3-deoxyanthocyanidins

Although being suggested for long as food colorants,[3] 3-deoxyanthocyanidins recently attracted an increasing interest in many other areas due to the discovery of their potential use as hair dyes,[4] laser dyes,[5] molecular-level memory systems,[6] and also as nutraceuticals for humans.[7]

From a synthetic point of view, some attractive approaches towards anthocyanidins have already been reported in the literature.[8] However, it is worth noting that the preparation of 3-deoxyanthocyanidins possessing such a phloroglucinol-type cycle A still constitutes a real synthetic challenge. Until now, only a few methods are known and they all exhibit inherent limitations. Pratt and Robinson described, in the early twenties, a method consisting in an acid-mediated aldol condensation between a salicylaldehyde derivative and an acetophenone (Scheme 1: disconnection α).[9] In this case, it is well established that, if unprotected phloroglucinaldehyde is involved, these conditions lead to a hard-to-purify mixture of organic salts where the targeted flavylium cation is at best present in small amounts (5–20% yield). Nevertheless, two successful alternatives were recently published.[10,11]



Scheme 1 Retrosynthetic analyses of the 3-deoxyanthocyanidin skeleton: α = classical disconnection[10] and β = investigated disconnection

In the present work, we report an efficient and straightforward procedure for the preparation of phloroglucinol-type 3-deoxyanthocyanidins via an acid-mediated condensation between phenolic derivatives and arylethynylketones (Scheme 1: disconnection β).

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Since phloroglucinol derivatives can easily react as C- and/or O-nucleophile, we reasoned that under acidic conditions they could add on ynones and then cyclize to the 3-deoxyanthocyanidin salts.[12] Therefore, in order to check the potential of this synthetic tool, we initially prepared different arylethynylketone patterns **6a**–**g** via a nucleophilic addition–oxidation sequence starting from the corresponding benzaldehydes **5a**–**g** (Scheme 2). We then investigated the acid-mediated interaction of **6a**–**g** with phloroglucinol derivatives and after optimization of the reaction conditions, we found that aqueous HPF_6 nicely promotes the expected condensation process (providing flavylium hexafluorophosphates in high yields, Table 1). This reaction is probably driven by the precipitation of the flavylium salt in the medium. We actually noticed upon a counteranion screening that flavylium hexafluorophosphates exhibit the lowest solubility in acetic acid among Cl^-, Br^-, HSO_4^-, and BF_4^-, highlighting probably the formation of the most intimate ion pair in the case of the interaction between a flavylium cation and a hexafluorophosphate anion.[13] Moreover, it should be noted that whereas flavylium chlorides,[11] tetrafluoroborates,[10,14] or triflates[14] have been already described, no report of flavylium hexafluorophosphates was so far mentioned.

Table 1 Scope of the Acid-Mediated Condensation Between an Arylethynylketone and a Phloroglucinol Derivative[a]

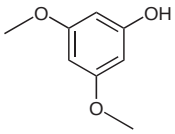
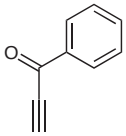
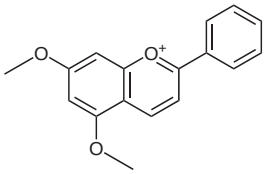
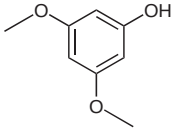
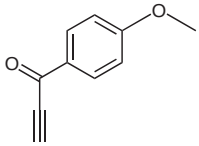
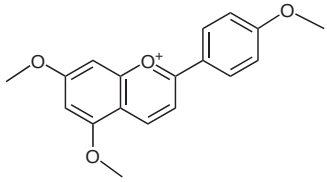
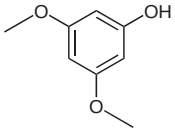
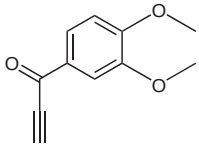
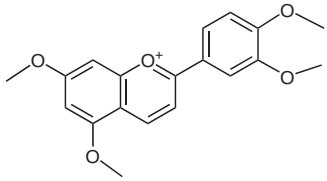
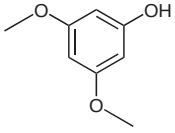
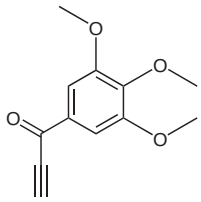
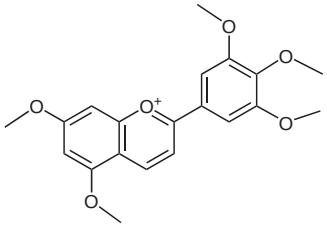
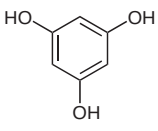
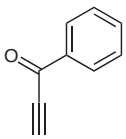
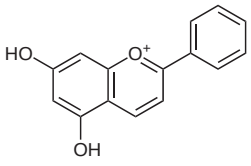
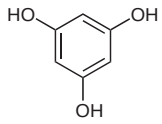
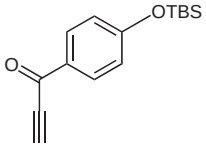
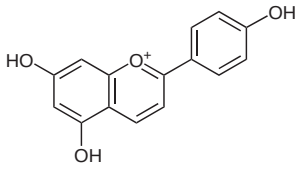
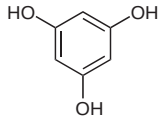
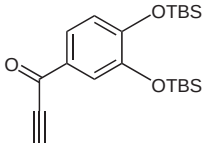
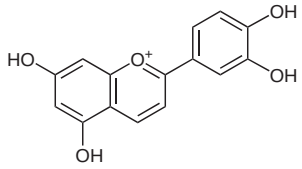
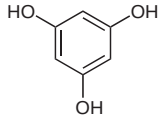
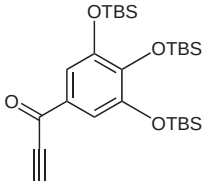
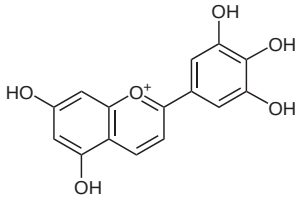
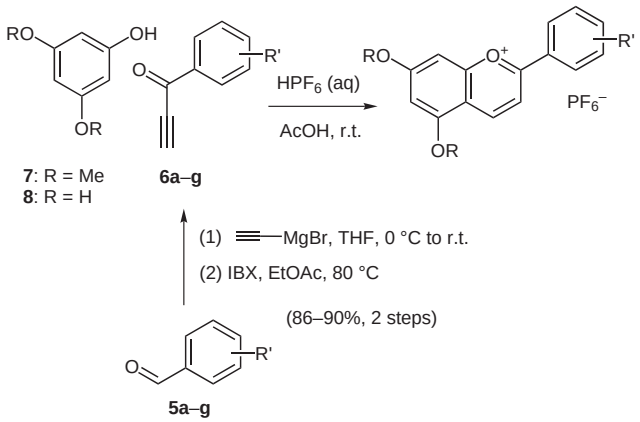
Entry	Phloroglucinol derivative	Arylethynylketone	Product	Yield (%)[b]
1	 **7**	 **6a**	 **9**	99
2	 **7**	 **6b**	 **10**	93
3	 **7**	 **6c**	 **11**	94
4	 **7**	 **6d**	 **12**	95
5	 **8**	 **6a**	 **13**	91

Table 1 Scope of the Acid-Mediated Condensation Between an Arylethynylketone and a Phloroglucinol Derivative[a] (continued)

Entry	Phloroglucinol derivative	Arylethynylketone	Product	Yield (%)[b]
6	 **8**	 **6e**	 **2**	82
7	 **8**	 **6f**	 **3**	84
8	 **8**	 **6g**	 **4**	82

[a] Reaction conditions: HPF_6 (50% in H_2O), AcOH, r.t., 48 h.
[b] Isolated yield of pure product obtained, when necessary, after recrystallization.



Scheme 2 Synthetic route to phloroglucinol-type 3-deoxyanthocyanidins

At first, since permethylated 3-deoxyanthocyanidins are generally regarded as the more convenient synthetic precursors of their phenolic analogues, we precisely checked our conditions for the access to such permethylated salts.[10,15] We thus considered the interaction between phloroglucinol dimethylether **7** and the arylethynylketones **6a**–**d** (Scheme 2). It clearly appeared that the use of aqueous HPF_6 significantly facilitated the condensation–cyclization process, chrysinidin dimethylether (**9**), apigeninidin trimethylether (**10**),[16] luteolinidin tetramethylether (**11**), and tricetanidin pentamethylether (**12**) being prepared with excellent yields (entries 1–4).

Nevertheless, as the deprotection of permethylated 3-deoxyanthocyanidins is generally effective in only moderate yields,[10,14] we envisaged the access to polyhydroxylated structures by directly involving phloroglucinol (**8**) in the condensation process (Scheme 2). Fortunately, when first involving **8** and **6a** in the condensation–cyclization process, our conditions proved to be very effective for the condensation, with **13** being prepared with an excellent yield of 91% (entry 5).[17] In order to check the compatibility of our conditions with different protective groups, we submitted the arylethynylketones **6e**–**g** bearing acid-labile *tert*-butyldimethylsilyl groups to the condensation process. Interestingly enough, an efficient synthesis of natural apigeninidin (**2**), luteolinidin (**3**), and tricetanidin (**4**) was achieved without any further deprotection step (entries 6–8).[18]

In summary, the interaction of phloroglucinol derivatives with arylethynylketones in the presence of HPF_6 appears indeed as a simple and efficient synthetic method for the preparation of polymethylated and, above all, polyhydroxylated 3-deoxyanthocyanidins. We also developed an orthogonal protective-group strategy allowing a direct and efficient access to highly hydroxylated derivatives. Moreover, the total syntheses of natural **2**–**4** have been achieved in only four steps with high overall yields starting from commercially available unprotected benzaldehydes (69%, 72%, and 61%, respectively).

Further work is now underway to expand the scope of this synthetic tool for the preparation of more sophisticated flavylium derivatives such as flavylium-benzopyrilium and oligoflavylium skeletons.

Typical Procedure for the Acid-Mediated Condensation of Phloroglucinol Derivatives with Arylethynylketones

To a solution of arylethynylketone **6** (5 mmol, 1.0 equiv) and phloroglucinol derivative **7** or **8** (5 mmol, 1.0 equiv) in 10 mL of AcOH were added 2 mL of HPF_6 (50% in H_2O). The solution, becoming immediately dark red, was stirred during 48 h at r.t. The resulting mixture is then plunged in 100 mL of Et_2O where the flavylium salt precipitated. The orange to red solid is recovered by filtration, washed with Et_2O and finally dried under vacuum to give the expected 3-deoxyanthocyanidin. Recrystallization from AcOH was performed when necessary.

Acknowledgment

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(16) **Apigeninidin Trimethylether Hexafluorophosphate (10)** Purple powder; yield 93%; mp 201 °C. IR (KBr): 1652, 1640 (s, C=O), 1600, 1569, 1506, 1456, 1436, 1378, 1339, 1241, 1124, 1052, 834 (m, P–F) cm^{-1}. UV/Vis [MeOH–HCl (5%, 1 N)]: λ_{max} (ε) = 266 (24900), 394 (18000), 460 nm (13600 $M^{-1}\cdot cm^{-1}$). ^1H NMR [300 MHz, CD_3CN–TFA-d_1 (1%)]: δ = 3.96 (3 H, s, OCH_3), 4.07 (3 H, s, OCH_3), 4.09 (3 H, s, OCH_3), 6.80 (1 H, d, *J* = 2.2 Hz), 7.19 (2 H, m), 7.23 (1 H, dd, *J* = 2.2, 0.7 Hz), 8.05 (1 H, d, *J* = 8.5 Hz), 8.32 (2 H, m), 9.07 (1 H, dd, *J* = 8.5 Hz, ^5J = 0.7 Hz). ^{13}C NMR [75 MHz, CD_3CN–TFA-d_1 (1%)]: δ = 55.9/57.0/57.2 (OCH_3), 93.4, 99.8, 111.3, 113.4, 115.8, 120.8, 131.9, 148.7, 158.8, 159.0, 167.0, 171.4, 171.7. MS (ESI, positive mode): 297 (100) [M^+]. HRMS (ESI): *m/z* calcd: 297.1121; found: 297.1109.

(17) **Chrysinidin Hexafluorophosphate (13)** Orange powder; yield 91%. IR (KBr): 3412 (s, br, OH), 1642 (s, C=O), 1580, 1563, 1541, 1381, 1340, 1269, 1239, 1203, 1193, 835 (m, P–F) cm^{-1}. UV/Vis [MeOH–HCl (5%, 1 N)]: λ_{max} (ε) = 274 (35400), 474 nm (36200 $M^{-1}\cdot cm^{-1}$). ^1H NMR [300 MHz, CD_3CN–TFA-d_1 (1%)]: δ = 6.81 (1 H, d, *J* = 2.2 Hz), 7.11 (1 H, dd, *J* = 2.2, 0.7 Hz), 7.72 (2 H, m), 7.84 (1 H, m), 8.13 (1 H, d, *J* = 8.4 Hz), 8.35 (2 H, m), 9.25 (1 H, dd, *J* = 8.4, 0.7 Hz). ^{13}C NMR [75 MHz, CD_3CN–TFA-d_1 (1%)]: δ = 95.7, 102.9, 111.2, 114.4, 128.9, 129.1, 130.0, 135.8, 150.5, 158.4, 159.4, 171.1, 171.4. MS (ESI, positive mode): 239 (100) [M^+]. HRMS (ESI): *m/z* calcd: 239.0703; found: 239.0696.

(18) All synthesized compounds exhibit NMR spectroscopic data identical to previously reported ones in the literature.[10–12]