Tetrahedron Letters 49 (2008) 6999–7004

Contents lists available at ScienceDirect

Tetrahedron Letters

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

En route to color-stable pyranoflavylium pigments—a systematic study of the reaction between 5-hydroxy-4-methylflavylium salts and aldehydes

Stefan Chassaing *, Géraldine Isorez, Marie Kueny-Stotz, Raymond Brouillard

Laboratoire de Chimie des Polyphénols, Université L. Pasteur-Strasbourg I, associé au CNRS (UMR 7177), 4, rue Blaise Pascal, 67008 Strasbourg, France

ARTICLE INFO

Article history:
Received 6 July 2008
Revised 16 September 2008
Accepted 19 September 2008
Available online 27 September 2008

Keywords:
Pigments
Flavylium
Heterocyclic chemistry
Condensation
Charge-transfer complex
Pyranoanthocyanins

ABSTRACT

The reaction of 5-hydroxy-4-methylflavylium salts with aldehydes, furnishing color-stable pyranoflavylium pigments, has been investigated in terms of scope and limitations. An unexpected chemical reactivity was observed and the origin of this reactivity is discussed.

1. Introduction

The flavylium chromophore **1** is widely present in plants (Fig. 1) with more than 580 natural pigments exhibiting this motif so far reported.[1] Compared to other plant pigments, flavylium pigments, the so-called anthocyanins, present unique behavior in aqueous media. Indeed, depending on diverse parameters (such as their structural features, the pH/redox state of the medium, and the presence of either aromatic compounds or metal ions), the color printed by such pigments can be modulated to the point of fully disappearing.[2]

Due to the inherent chemical reactivity of flavylium, Nature developed efficient color-protective mechanisms, the more common being inter-/intramolecular copigmentation, metal-complex formation, and acylation of key sugar moieties.[3] Red wine ageing offers another alternative. The ageing chemistry leads to covalent modifications of flavyliums, yielding new pigments less sensitive to hydration and redox processes than the parent motif.[4] Among the different classes of aged red wine pigments, pyranoanthocyanins **2** (Fig. 1) have been characterized and their color stability toward water or sulphur dioxide was established.[5,6] The increased stability of **2** is clearly due to the extended conjugation offered by the presence of a new oxygenated cyclic unit α in the pigment structure (Fig. 1). It is worth noting that pyranoflavylium-derived pigments appear as attractive candidates as food colorants or hair dyes.

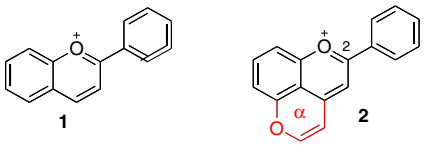


Figure 1. Flavylium (**1**) and pyranoflavylium (**2**) skeletons.

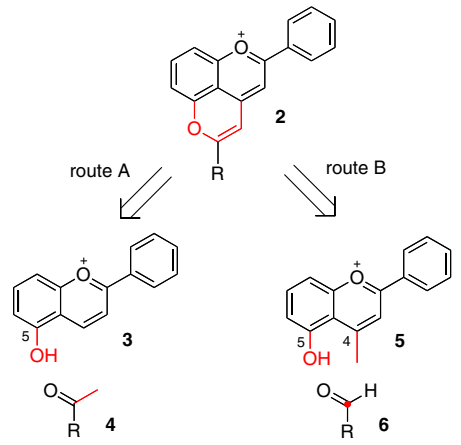
It is assumed that pyranoflavylium pigments naturally occurred by direct condensation of a 5-hydroxyflavylium cation **3** with biogenic acetyl units **4** (i.e., pyruvic acid (R = CO_2H) and acetaldehyde (R = H)).[4,7] However, we recently demonstrated that pyranoflavylium skeletons **2** could be obtained by condensation between 5-hydroxy-4-methylflavylium cations **5** and aldehydes **6** (Scheme 1).[8] Extending these preliminary results, we wish to report herein a more systematic study highlighting the scope of this methodology and revealing an unexpected substrate dependence.

2. Results and discussion

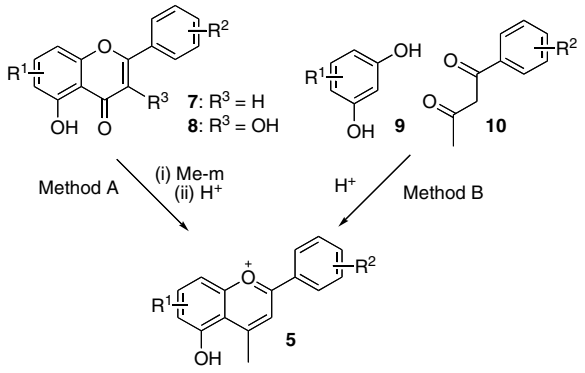
The required precursors **5** were easily obtained using two simple routes avoiding protective group chemistry (Scheme 2): (i) nucleophilic addition of MeMgBr or MeLi to 5-hydroxy-flavone **7** or -flavonol **8** when commercially available followed by dehydration (Method A),[8] (ii) a one-pot acid-mediated condensation between a phenolic derivative **9** and aroylacetones **10** (Method B).

* Corresponding author. Tel.: +33 390241340; fax: +33 670899695.
E-mail address: stefanchassaing@mac.com (S. Chassaing).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.139



Scheme 1. Routes to the pyranoflavylium skeleton: A = proposed biosynthetic route, B = our chemical route (R = alkyl and aryl).



Scheme 2. Protective-group free methods for accessing to precursors **5** (R^1, R^2 = H, OH, *O*-alkyl; m = MgBr, Li).

With various 4-methylflavylium cations **5** in hand, we first screened the condensation efficiency of the model cation **5a** with different aldehydes **6** (Table 1, entries 1–12). Electron-enriched benzaldehydes **6a–d** led to the formation of the expected adducts **2a–d** in good to excellent yields (entries 1–4).[9] Interestingly, phloroglucinol-type aldehyde **6e** did not give any product and both starting materials were recovered (entry 5). Steric hindrance could probably be responsible for the lack of reactivity. Surprisingly, benzaldehyde **6f** was also not reactive (entry 6). In sharp contrast to electron-rich aldehydes **6a–d**, benzaldehydes **6g–h** carrying electron-withdrawing groups were not converted either when submitted to condensation conditions (entries 7 and 8).

These surprising results suggested that nucleophilic addition to the aldehyde moiety might not be responsible for this condensation, as suggested before (cf Scheme 3).[8] If so, the reverse order of reactivity would have been observed; the more electron-poor benzaldehydes being more electrophilic, they should have given better results than electron-rich benzaldehydes.

Moreover, aliphatic aldehydes seem to follow the same reactivity trend. Acetaldehyde **6i** was indeed able to react with **5a** although much more slowly than aromatic electron-rich aldehydes (entry 9 vs 1–4). The electron-poor glyoxylic acid **6j** was unable to react with **5a** (entry 10). To look for possible nucleophilic species derived from 5-hydroxy-4-methyl-flavylium **5** and trap it, we also ran the same reaction in the presence of electrophilic organic halides such as methyl iodide and benzyl bromide. For both, no reaction occurred (entries 11 and 12), highlighting the importance of the electrophilic aldehyde function for the effectiveness of the interaction.

In a second series of experiments, we examined the influence of the cation structure on the reaction (Table 2). Analog **5b** lacking a hydroxyl group at the 5 position showed the same reactivity as **5a**, underlining that the 5-hydroxylic substituent does not play a crucial role in the condensation itself (entries 1–4). However, only the open-form products **11a–g** were obtained. Obviously, no further cyclization can take place without a nucleophilic substituent at the 5 position. Interestingly, the 5-methoxy derivative **5c** reacted in a similar way leading to the open products **11e–f** in high yields (entries 5 and 6). These results showed that (i) demethylation could not occur after nucleophilic addition; (ii) this reaction between 4-methylflavylium cations and aldehydes is a step-wise process, starting by condensation of the two partners and ending with ring closure whenever it is possible.

Table 1
Influence of the aldehyde structure on the condensation[a]

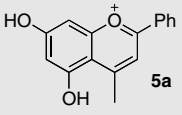
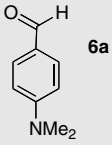
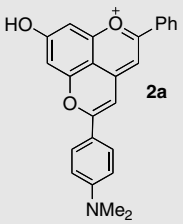
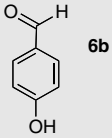
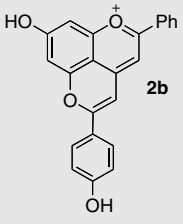
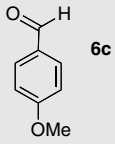
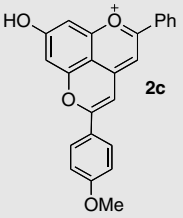
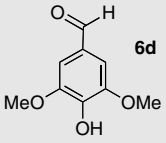
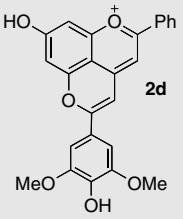
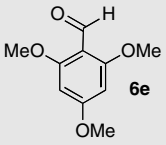
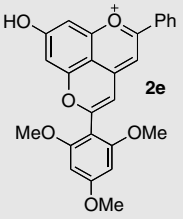
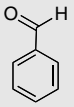
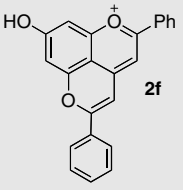
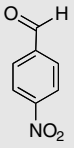
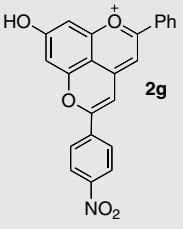
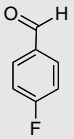
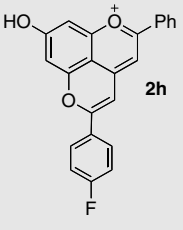
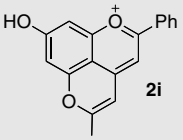
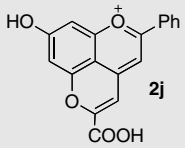
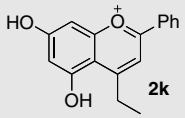
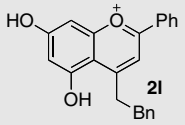
Entry	Cation	Electrophilic partner **6**	Expected product **2**	Yield[b]
1	 **5a**	 **6a**	 **2a**	70
2	**5a**	 **6b**	 **2b**	75

Table 1 (*continued*)

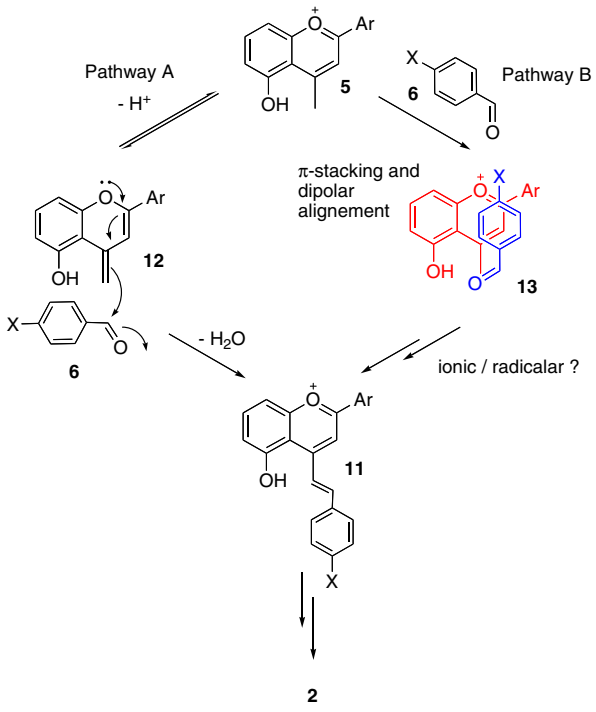
Entry	Cation	Electrophilic partner **6**	Expected product **2**	Yield[b]
3	**5a**	 **6c**	 **2c**	80
4	**5a**	 **6d**	 **2d**	72
5	**5a**	 **6e**	 **2e**	—[c]
6	**5a**	 **6f**	 **2f**	—[c]
7	**5a**	 **6g**	 **2g**	—[c]
8	**5a**	 **6h**	 **2h**	—[c]
9	**5a**	CH_3CHO **6i**	 **2i**	20[d]

(*continued on next page*)

Table 1 (*continued*)

Entry	Cation	Electrophilic partner **6**	Expected product **2**	Yield[b]
10	**5a**	HOOCCHO **6j**	 **2j**	–[c]
11	**5a**	MeI	 **2k**	–[c]
12	**5a**	BnBr	 **2l**	–[c]

[a] Reaction conditions: **5a** (1.0 equiv), **6** (1.3 equiv), EtOH, Δ (until complete conversion).
[b] Isolated yield of pure product obtained, when necessary, after recrystallization.
[c] No conversion observed (recovery of starting material).
[d] Conversion observed after 96 h reflux.



Scheme 3. A: previously suggested mechanism; B: newly suggested pathway (X: electron-donating group).

3-Oxygenated flavylium derivatives such as **5d–e** were also successfully submitted to this condensation. With 4-dimethylaminobenzaldehyde **6a**, the product **11g** was obtained in excellent yields from the permethylated oxonium **5d** (entry 7). Interestingly, the corresponding flavylium **5e** carrying a free hydroxyl group at the 5 position also reacted, although in lower yield (entry 8). However, this example showed that highly substituted pyranoflavylium such as **2m** could easily be obtained through this strategy.[10]

From a mechanistic point of view, our previous proposition relied on a nucleophilic attack of aldehyde **6** by the vinylogous enol ether **12** supposedly issued from **5** under reaction conditions (Scheme 3). As already pointed out above, the results described here were in contradiction with such a view. Since the success of the reaction was largely dependent on the electron density of the aldehyde and less on the flavylium cation, it seems that charge-transfer might be responsible for initiating the condensation between these two entities. Indeed, the higher the electron density of the aldehyde, the better would be interactions with the electrophilic flavylium. Aromatic substituents on the aldehyde moiety would strengthen π-interactions with the aromatic part of the flavylium. Moreover, with electron-donating substituent(s) on aromatic aldehydes, dipole-dipole interactions would place both partners in the right orientation for reaction (see **13** in Scheme 3). However, the way this charge-transfer complex evolves remains unknown.

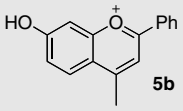
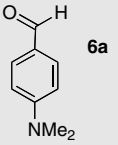
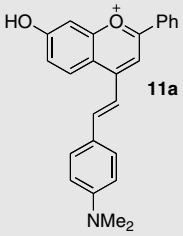
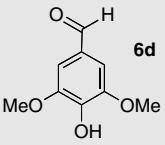
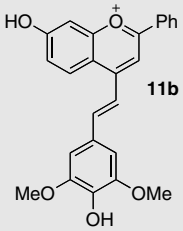
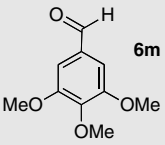
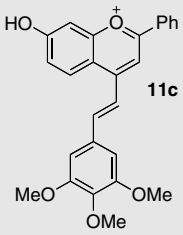
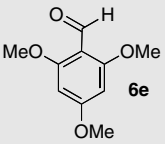
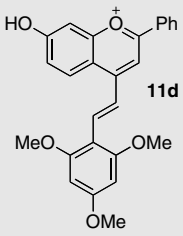
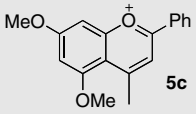
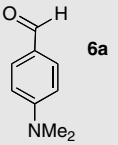
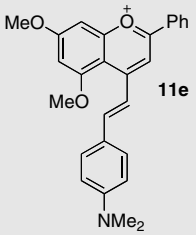
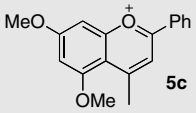
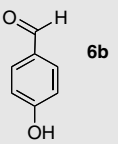
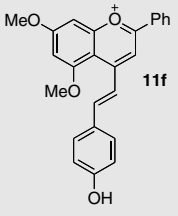
3. Conclusion

In summary, the influence of each partner in the condensation between 4-methylflavylium salts **5** and aldehydes was examined and proved to be highly dependent on the aldehyde nature. Only aromatic and electronic-rich aldehydes reacted leading to pyranoflavylium derivatives in high to almost quantitative yields. Charge transfer complexes were proposed as initiator for this transformation.

Further works are underway to detect such charge transfer complexes and to understand their evolution.

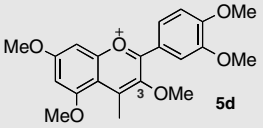
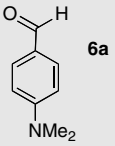
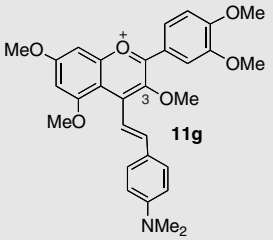
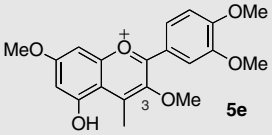
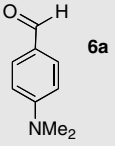
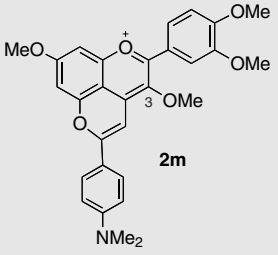
Typical experimental procedure: To a solution of 5-hydroxy-4-methylflavylium hexafluorophosphate **5** (0.25 mmol, 1.0 equiv) in 10 mL of ethanol is added aldehyde **6** (0.33 mmol, 1.3 equiv). The solution is then refluxed under air and after stirring overnight, the solvent is evaporated under reduced pressure. The resulting residue is washed with diethyl ether or ethyl acetate to give the expected pyranoflavylium hexafluorophosphate **2** in pure form. Recrystallization from acetic acid could be performed when necessary.

Table 2
Influence of the cation structure on the condensation process[a]

Entry	Cation	Electrophilic partner **6**	Expected product **2**/**11**	Yield[b]
1	 **5b**	 **6a**	 **11a**	89
2	**5b**	 **6d**	 **11b**	72
3	**5b**	 **6m**	 **11c**	90
4	**5b**	 **6e**	 **11d**	—[c]
5	 **5c**	 **6a**	 **11e**	84
6	 **5c**	 **6b**	 **11f**	81

(*continued on next page*)

Table 2 (*continued*)

Entry	Cation	Electrophilic partner **6**	Expected product **2**/**11**	Yield[b]
7	 **5d**	 **6a**	 **11g**	95
8	 **5e**	 **6a**	 **2m**	50

[a] Reaction conditions: **5a** (1.0 equiv), **6** (1.3 equiv), EtOH, Δ (until complete conversion).
[b] Isolated yield of pure product obtained, when necessary, after recrystallization.
[c] No conversion observed (recovery of starting material).

Acknowledgments

The authors thank the CNRS and the MNERT for funding. S.C., M.K. and G.I. thank the MNERT for PhD fellowships.

References and notes

1. (a) Williams, C. A.; Grayer, R. J. *Nat. Prod. Rep.* **2004**, *21*, 539–573; (b) Andersen, O. M.; Jordheim, M. In *Flavonoids: Chemistry, Biochemistry and Applications*; CRC Press: Boca Raton, 2006. pp 471–551 and references cited therein.
2. (a) Brouillard, R.; Dubois, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 1359–1364; (b) Brouillard, R.; Delaporte, B. *J. Am. Chem. Soc.* **1977**, *99*, 8461–8468.
3. For color stabilization through copigmentation, see: (a) Brouillard, R.; Mazza, G.; Saad, Z.; Albrecht-Gary, A.-M.; Cheminat, A. *J. Am. Chem. Soc.* **1989**, *111*, 2604–2611; (b) Dangles, O.; Saito, N.; Brouillard, R. *Phytochemistry* **1993**, *34*, 119–124. For color stabilization through metal complexation, see: (c) Shiono, M.; Matsugaki, N.; Takeda, K. *Nature* **2005**, *436*, 791. For color stabilization through acylation, see: (d) Redus, M.; Baker, D. C.; Dougall, D. K. *J. Agric. Food Chem.* **1999**, *47*, 3449–3454; (e) Whittemore, N. A.; Welch, K. T.; Cox, J. R.; Dougall, D. K.; Baker, D. C. *J. Org. Chem.* **2004**, *69*, 1663–1669.
4. (a) Brouillard, R.; Chassaing, S.; Fougerousse, A. *Phytochemistry* **2003**, *64*, 1179–1186; (b) Fulcrand, H.; Atanasova, V.; Salas, E.; Cheynier, V. In *Red Wine* . In Waterhouse, A. L., Kennedy, J., Eds.; ACS: Washington, DC, 2004; Chapter 6, pp 68–88 and references cited therein.
5. (a) Bakker, J.; Timberlake, C. F. *J. Agric. Food Chem.* **1997**, *45*, 35–43; (b) Hakansson, A. E.; Pardon, K.; Hayasaka, Y.; de Sa, M.; Herderich, M. *Tetrahedron Lett.* **2003**, *44*, 4887–4891.
6. Some natural pyranoanthocyanins have also been isolated from vegetal sources, see: (a) Lu, Y.; Foo, Y.; Sun, Y. *Tetrahedron Lett.* **2002**, *43*, 7341–7344; (b) Andersen, O. M.; Fossen, T.; Torskangerpoll, K.; Fossen, A.; Hauge, U. *Phytochemistry* **2004**, *65*, 405–410.
7. Cheynier, V. In *Flavonoids: Chemistry, Biochemistry and Applications*; CRC Press: Boca Raton, 2006; pp 289–301 pp 289–301 and references cited therein.
8. Roehri-Stoeckel, C.; Gonzalez, E.; Fougerousse, A.; Brouillard, R. *Can. J. Chem.* **2001**, *79*, 1173–1178.
9. *Analytical data of* **2b**: Purple powder. UV/vis (MeOH/5% 1 N HCl): $\lambda_{max}(\varepsilon)$ = 260, 374 (8300), 452 (10500) nm (M^{-1} cm^{-1}). ^{1}H NMR (300 MHz) (CD_3CN/1% TFA-d_1): δ 7.07–7.11 (2H, m), 7.23 (2H, s), 7.67 (1H, s), 7.65–7.70 (2H, m), 7.70 (1H, s), 7.72–7.78 (1H, m), 8.11–8.14 (2H, m), 8.15–8.19 (2H, m). MS (ESI, positive mode): 355 (100) [M^+]. HRMS (ESI): calculated 355.0965, found 355.0968.
10. *Analytical data of* **2m**: Purple powder. UV/vis (MeOH/5% 1 N HCl): $\lambda_{max}(\varepsilon)$ = 202, 270 (28800), 568 (18000) nm (M^{-1} cm^{-1}). ^{1}H NMR (300 MHz) (CD_3CN/1% TFA-d_1): δ 3.20 (6H, s, –NCH_3), 3.81 (3H, s, –OCH_3), 3.94 (3H, s, –OCH_3), 3.95 (3H, s, –OCH_3), 4.05 (3H, s, –OCH_3), 6.91–6.94 (2H, m), 7.16 (1H, d, J = 8.8 Hz), 7.24 (1H, d, J = 2.2 Hz), 7.26 (1H, d, J = 2.2 Hz), 7.35 (1H, s), 7.80 (1H, d, J = 1.8 Hz), 7.95 (1H, dd, J = 1.8 and J = 8.8 Hz), 8.11–8.14 (2H, m). MS (ESI, positive mode): 486 (100) [M^+]. HRMS (ESI): calculated 486.1911, found 486.1906.