Boron trifluoride–etherate mediated synthesis of 3-desoxyanthocyanidins including a total synthesis of tricetanidin from black tea

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Abstract—The synthesis of a series of 3-desoxyanthocyanidins via a $BF_3 \cdot Et_2O$-mediated aldol condensation between a substituted acetophenone and salicylaldehyde derivatives is described. Using this new synthetic methodology the synthesis of tricetanidin, a natural pigment isolated from black tea, was accomplished. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Black tea is, apart from water, the most highly consumed beverage in the world. Black tea contains substantial amounts of polyphenolic compounds, many of which are unique to this beverage, being formed when fresh leaves of *Camellia sinensis* are 'fermented'. Fresh leaves contain substantial amounts of flavonoids, particularly flavanols (up to 20% dry weight), and fermentation transforms these by enzymically-driven (polyphenol oxidase) and coupled chemical oxidations into at least one 'monomeric' product (tricetanidin **2**). Sanderson and co-workers have shown that (−)-epigallocatechin gallate **1** is transformed by PPO, presumably via a *para*-quinonemethide intermediate, into the 3-desoxyanthocyanidin tricetanidin **2**.[1] There have been no further reports on the role of tricetanidin in tea oxidation.

Furthermore, black tea contains several classes of 'dimeric' and 'oligomeric' flavonoids.[2] Some of these larger mass products, that form through transformation of the flavonoid B-rings, have been characterised.[3–6] However, the brownish thearubigins (TR), the major oligomeric group, accounting for some 10–20% of the dry weight of black tea and for 30–60% of the solids in liquors after infusion due to their hot-water solubility[2,7] remain structurally ill-defined. We suggest the hypothesis that reactive electrophiles such as tricetanidin **2** or related 3-desoxyanthocyanidins play a crucial role in the formation and biosynthesis of the TRs. We have previously observed that the addition of certain monomeric flavonoids to a crude preparation of TR generates an unexpected hyperchromic effect that is reminiscent of anthocyanin copigmentation,[8–10] and we wonder if this is indicative of disturbance of desoxyanthocyanidin equilibria in the oligomeric TR.

Epigallocatechin-gallate **1**   Polyphenoloxidase during black tea fermentation →   Tricetanidin **2**
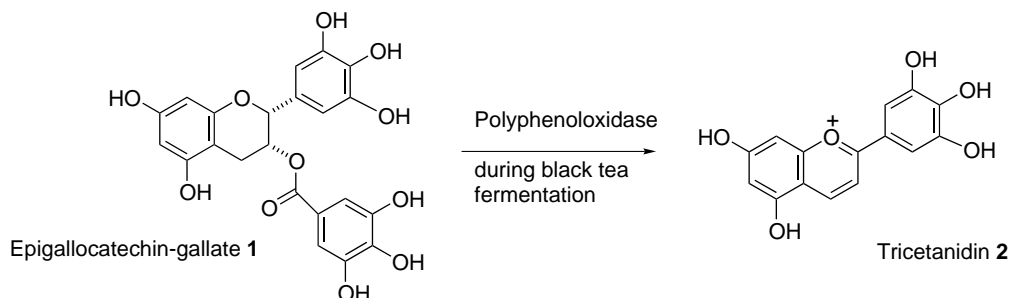
* Corresponding author.

In order to verify this hypothesis we needed to synthesise sufficient quantities of tricetanidin and related 3-desoxyanthocyanidins, which would act as chromatographic and spectroscopic standards and which we could use as monomers for the production of thearubigens in model tea systems.[8] It is worth noting that related 3-desoxyanthocyanidins have recently been isolated from *Arrabidaea chica*, which is used as a herbal remedy in Tropical America.[9]

2. Results and discussion

Synthetic approaches towards anthocyanidins have been reviewed in detail[10] and the synthesis of 3-desoxyanthocyanidins has been previously reported by Robinson.[11] Initially, we started out using Robinson's conditions for the synthesis of 3-desoxyanthocyanidins from a substituted acetophenone **4a** and a salicyl aldehyde derivative **3a,c** with HCl gas in diethyl ether. Unfortunately we found that these conditions, although perfectly reproducible as described, lead under optimised conditions to a conversion to the desired 3-desoxyanthocyanidin in only 10–15%. We considered the Robinson acid-mediated aldol reaction followed by elimination of water as still the most promising approach towards a successful synthesis. Hence, we considered alternative Lewis acid-mediated conditions resulting in an improved conversion and yield. Table 1 shows a selection of Lewis acids employed in the transformation (entries 1–5).

The best results were obtained using the neat BF$_3$·etherate complex. Using salicylaldehyde **3a** itself, the reaction could be performed under solvent-free conditions to give the anthocyanidins **5a,b** in good yields.[12] Similar solvent-free conditions have been reported for the synthesis of pyrylium salts.[13] Using *ortho*-vanillin **3b** or 3,5-dimethoxysalicylaldehyde **3c** the reaction had to be performed in dichloromethane as a solvent. Again the yields of **5c–e** were good. All 3-desoxyanthocyanidins **5a–e** were isolated as their tetrafluoroborate salts after recrystallisation from acetic acid as deep red to orange powders displaying a characteristic low field resonance for the H-3 and H-4 protons in their ^{1}H NMR spectra.[12] Furthermore, they showed a
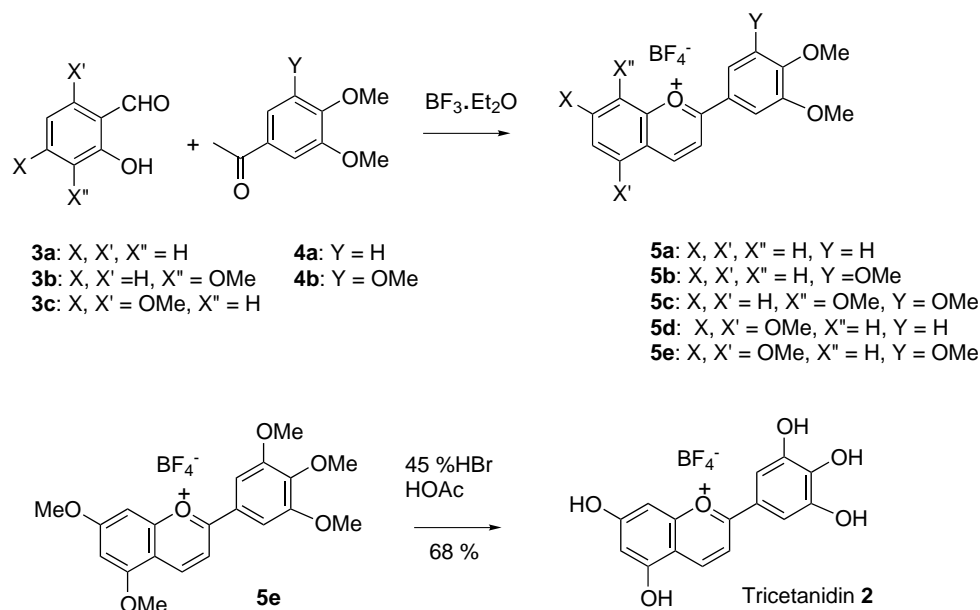

3a: X, X', X" = H
3b: X, X' = H, X" = OMe
3c: X, X' = OMe, X" = H

4a: Y = H
4b: Y = OMe

5a: X, X', X" = H, Y = H
5b: X, X', X" = H, Y = OMe
5c: X, X' = H, X" = OMe, Y = OMe
5d: X, X' = OMe, X" = H, Y = H
5e: X, X' = OMe, X" = H, Y = OMe

Table 1. Yields and conditions for the synthesis of 3-desoxyanthocyanidins **5a–e**

Entry no.	Aldehyde	Ketone	Product	Conditions	Yield (%)[a]
1	**3a**	**4a**	**5a**	HCl gas in Et$_2$O[b]	15
2	**3a**	**4a**	**5a**	TiCl$_4$ in CH$_2$Cl$_2$ at −78°C for 2 h	Decomposition[c]
3	**3a**	**4a**	**5a**	SnCl$_4$ in CH$_2$Cl$_2$ at −78°C for 2 h	20
4	**3a**	**4a**	**5a**	PPTS/(OMe)$_3$CH reflux in CH$_2$Cl$_2$	Decomposition
5	**3a**	**4a**	**5a**	Neat BF$_3$·Et$_2$O	76
6	**3a**	**4b**	**5b**	Neat BF$_3$·Et$_2$O	81
7	**3b**	**4b**	**5c**	BF$_3$·Et$_2$O in CH$_2$Cl$_2$ at rt	69
8	**3c**	**4a**	**5d**	BF$_3$·Et$_2$O in CH$_2$Cl$_2$ at rt	72
9	**3c**	**4b**	**5e**	HCl gas in Et$_2$O[b]	10
10	**3c**	**4b**	**5e**	BF$_3$·Et$_2$O in CH$_2$Cl$_2$ at rt	78

[a] Isolated yield after recrystallisation.
[b] Conditions from reference.
[c] No product could be observed by ^{1}H NMR.

characteristic absorption in the infrared around 1620 cm^{-1}, which we assign as the C=O stretching frequency. All compounds gave satisfactory elemental analysis. It is worth noting that the pure compounds decompose considerably in acetone after 1 h and in acetonitrile and DMSO after 5–6 h. They are however stable in acetic acid and as solids.

Tricetanidin **2** itself could be obtained after demethylation with HBr/HOAc using Cram's conditions[14] in a moderate yield. The compound displayed identical spectroscopic features as compared with an authentic sample.[15,16]

3. Conclusion

In conclusion, we have developed a facile and convenient synthesis of 3-desoxyanthocyanidins using a BF$_3$-mediated aldol condensation and have reported the first total synthesis of the monomeric black tea pigment tricetanidin. The compounds will serve us as analytical standards and as model compounds for further studies into the biosynthesis and structure of oligomeric polyphenols and the polymeric thearubigins. All compounds synthesised are useful intermediates in organic synthesis.

Acknowledgements

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13. Typical experimental procedure for the synthesis of (**5b**): To a mixture of salicylaldehyde **3a** (122 mg, 1 mmol) and 3,4,5-trimethoxyacetophenone **4b** (210 mg, 1 mmol) were added BF$_3$·etherate (0.15 ml, 1.4 mmol). The solution became immediately dark red. The solution was stirred at rt until it became completely solid. Diethyl ether (5 ml) was added to the solid and the mixture was heated under reflux for 1 h. The volatiles were removed in vacuum and the residue was recrystallised from hot acetic acid. The resulting red powder was washed twice with 5 ml diethyl ether and dried to give 307 mg (81%) of 3-desoxyanthocyanidin **5b** as a red powder. Mp 168°C (dec.). ^{1}H NMR 270 (acetone-d_6) $\delta = 9.61$ (d, $J = 8.7$ Hz, 1H, Ar); 9.12 (d, $J = 8.7$ Hz, 1H, Ar); 8.52 (m, 2H, Ar); 8.11 (m, 2H, Ar); 7.30 (s, 1H, Ar); 7.00 (s, 1H, Ar); 4.07 (s, 9H, CH$_3$O). C$_{18}$H$_{17}$O$_4$BF$_4$ (384.13) calcd: C, 56.28; H, 4.46; found: C, 57.08; H, 4.49%. IR (KBr) ν_{max}/cm^{-1} = 3415 (s, br, OH); 1638 (m, C=C); 1618; 1589; 1544; 1498; 1456; 1424; 1354; 1266; 1123; 1084; 948; 606.
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15. Tricetanidin (**2**): ^{1}H NMR (270 MHz) (D$_2$O/1% acetic acid-d_4): $\delta = 9.03$ (1H, d, J 8.8 Hz, 1H, H-4), 7.95 (1H, d, J 8.8 Hz, H-3), 7.45 (2H, s, H2'), 6.88 (1H, d, J 2 Hz), 6.65 (1H, d, J 2 Hz). ^{13}C NMR (90 MHz) (D$_2$O/1% HOAc): $\delta = 173.1$, 172.0, 160.0, 149.0, 148.4, 145.2, 120.5, 113.5, 110.8, 110.0, 103.2, 96.1 (after ^{1}H–^{13}C HMBC analysis at 500 MHz the signal at 160.0 ppm corresponds to two unresolved resonances of C-5 and C-8a).
16. Spectroscopic data for authentic tricetanidin were kindly provided by Unilever (UK).