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George A. Kraus
Iowa State University, gakraus@iastate.edu

Ivan M. Geraskin
Iowa State University

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Synthetic Anthocyanidins from Natural Benzopyrans

George A. Kraus* and Ivan M. Geraskin

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

gakraus@iastate.edu

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Dedicated to Prof. Dr. Wilhelm Fleischhacker on account of his 85th Birthday.

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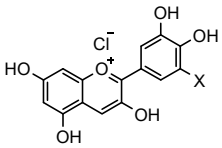
Anthocyanins are ionic polycyclic natural products. They are present in a variety of fruits and vegetables including blueberries, currants, cherries, grapes, raspberries, gooseberries and certain varieties of sweet potatoes. Anthocyanidins are aglycones of anthocyanins. Representative structures are shown in Figure 1. This class of compounds has been reported to exhibit a broad array of biological activities. Two reviews have described the antioxidant activity of anthocyanins [1, 2]. More recently, cabbage anthocyanins were reported to inhibit lipopolysaccharide-induced oxidative stress in blood platelets [3]. Blueberry extracts were reported to show chemoprevention of acrylamide toxicity [4]. Cherry anthocyanins inhibited polyphenol oxidase enzyme activity [5]. Anthocyanins have been suggested as a potential therapy for diabetic retinopathy [6]. Because of the strong interest in their biological activities, several methods have been developed to concentrate anthocyanins from plant extracts. Researchers have employed a number of techniques including mechanical shaking [7], countercurrent chromatography [8], and enrichment on macroporous resins [9].

The separation technologies permit the preparation of fractions enriched in anthocyanins, but other polar polyphenols still remain. Because of our interest in comparing the activity of synthetic anthocyanidins with natural anthocyanidins, we required pure materials. We evaluated literature syntheses of anthocyanidins [10]. The most commonly used method, dating back to the classic work of Robinson, involved the reaction of a substituted acetophenone with an aromatic aldehyde in the presence of a concentrated solution of gaseous hydrochloric acid [11]. While this method worked on a small scale, we sought a more convenient procedure, not requiring the specific preparation of the aforementioned aromatic precursors. There are many benzopyran-containing natural products that could be oxidized to generate anthocyanins, but few transformations have been reported. Bruillard and coworkers reduced flavonols using zinc amalgam [12]. Kondo and coworkers oxidized a dihydro anthocyanin [13]. Oxidation of hexahydro-precursors to anthocyanidins appears to have no precedent.

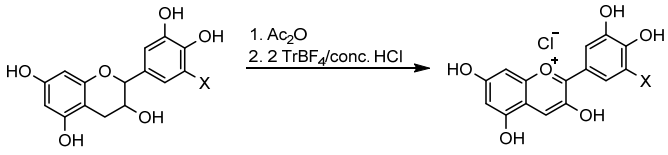
The optimal oxidant would convert benzopyrans cleanly into anthocyanidins without traces of the oxidant contaminating the product. To be sustainable, the oxidants should be used in catalytic amount and must be capable to be regenerated by environmental friendly oxidants. Although air can be employed to oxidize dihydroanthocyanidins, there are no reports of its use to oxidize more reduced precursors. Chloranil has been employed by Sweeny and Iacobucci to convert a dihydroanthocyanidin into an anthocyanidin [14]. Because of our concerns about separations, we explored the trityl tetrafluoroborate, another well-known hydride abstractor. This reagent had not been used to produce anthocyanidins. The byproduct of the oxidation, triphenylmethane, is a hydrocarbon that is readily separated from the highly polar products. Moreover, it can be re-oxidized.



1: X = H
2: X = OH

Figure 1: Structures of cyanidin chloride (**1**) and delphinidin chloride (**2**).

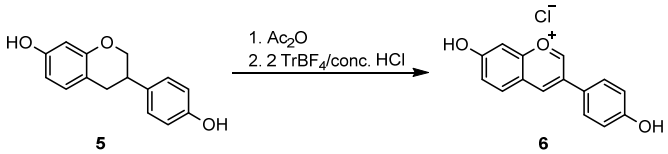
Reaction of epicatechin directly with trityl tetrafluoroborate afforded mostly trityl aryl ether formation plus small amounts of product. This could be averted by acetylation prior to hydride abstraction. Thus, the reaction of the penta-acetate of **3** afforded a 93% yield of **1** as its chloride, as shown in Scheme 1. The proton NMR and high-resolution mass spectrum of synthetic **1** matched the literature spectra. Similarly, the hexaacetate of **4** was converted into **2** in 65% yield.



3: X = H
4: X = OH

1: X = H
2: X = OH

Scheme 1: Synthesis of **1** and **2**.



5 **6**

Scheme 2: Synthesis of **6**.

This process could be extended to the preparation of isoflavylium salts. The diacetate of commercially available equol **5** was heated with trityl tetrafluoroborate to produce **6** in 69% yield, as shown in Scheme 2. The NMR and mass spectrum matched the literature spectra [15].

In summary, hydride abstraction can be used to make anthocyanidins and isoflavylium salts in good yields. This process is operationally convenient and can be used to prepare anthocyanidins in gram quantities for biological evaluation.

Experimental

Cyanidin chloride: To a solution of (-)-epicatechin pentaacetate (0.1000 g, 0.2 mmol) in DCE (2 mL) was added a solution of $TrBF_4$ (0.1319 g, 0.4 mmol) in DCE (5 mL). The reaction was refluxed overnight, and the DCE was evaporated. The residue was dissolved in ethanol (7 mL) and concentrated HCl (2 mL) was added. The reaction was refluxed overnight. Volatiles were evaporated. Crude product was triturated with diethyl ether to yield 0.0603 g of cyanidin chloride in 93% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 6.61 (1H, s, ArH), 6.85 (1H, s, ArH), 7.01 (1H, d, J = 8.8 Hz, ArH), 8.10 (1H, s, ArH), 8.22 (1H, dd, J = 8.8 Hz, ArH), 8.55 (1H, s, ArH).
^{13}C NMR (100 MHz, CD_3OD): δ 144.0, 137.2, 135.7, 134.7, 132.7 130.8, 129.8, 129.0, 127.8, 127.5, 127.2, 126.3, 125.9, 124.4, 99.8.
HRMS ESI (*m/z*): calcd. for $C_{15}H_{11}O_6^+$ $[M]^+$, 287.0550; found 287.0550.

Delphinidin chloride: To a solution of EGCG peracetate (0.0466 g, 0.059 mmol) in DCE (1 mL) was added a solution of $TrBF_4$ (0.0388 g, 0.118 mmol) in DCE (3 mL). The reaction was boiled overnight. DCE was evaporated; the residue was dissolved in ethanol (5 mL) and concentrated HCl (1 mL) was added. The reaction was refluxed overnight. Volatiles were evaporated. Crude product was triturated with diethyl ether to yield 0.0129 g of delphinidin chloride in 65% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 5.80 (1H, s, ArH), 5.99 (1H, s, ArH), 6.60 (1H, s, ArH), 6.83 (2H, s, ArH).
HRMS ESI (*m/z*): calcd. for $C_{15}H_{11}O_7^+$ $[M]^+$, 303.0499; found 303.0500.

7-Hydroxy-3-(4-hydroxyphenyl)chromenylium chloride*:* To a solution of (±)-equol diacetate (0.0416 g, 0.127 mmol) in DCE (2 mL) was added a solution of $TrBF_4$ (0.0842 g, 0.255 mmol) in DCE (5 mL). The reaction was refluxed overnight. DCE was evaporated. The residue was dissolved in ethanol (7 mL) and concentrated HCl (1.5 mL) was added. The reaction was refluxed overnight. Volatiles were evaporated. Crude product was triturated with diethyl ether to yield 0.0242 g of 7-hydroxy-3-(4-hydroxyphenyl)chromenylium chloride in 69% yield.

^{1}H NMR (400 MHz, CD_3OD): δ 7.08-7.2 (3H, m, ArH), 7.16-7.21 (3H, m, ArH), 7.24-7.29 (3H, m, ArH).
HRMS ESI (*m/z*): calcd. for $C_{17}H_{16}NaO_4^+$ $[M^+ - H^+ + Na^+ + C_2H_5OH]^+$, 307.0934; found 307.1332.

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