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SHORT & EXPEDIENT SYNTHESIS OF PYRIDINE CONTAINING DIHYDROCHALCONE 1-(2-HYDROXYPHENYL)-3-(PYRIDIN-4-YL)PROPAN-1-ONE: A NON-NUTRITIVE ARTIFICIAL SWEETENER

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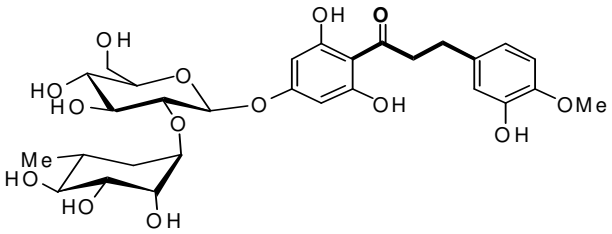
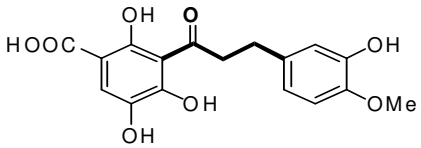
An efficient synthesis of the artificial sweetener 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one employing Fries Rearrangement as a key step in the construction of pyridine containing dihydrochalcone is reported. A novel approach for the synthesis of heteroaryl containing dihydrochalcones via Fries Rearrangement method is reported, and can serve as a general method for the preparation of a wide range of heteroaryl containing dihydrochalcones.

In the past 20 years, there have been many attempts to produce dihydrochalcone (DHC) analogues with taste qualities as good as that of sucrose. Among known artificial sweeteners, 3′-carboxyhesperetin dihydrochalcone **1** (NHDC) was shown to be 3400 times more potent than (6.5% w/v) sucrose and also in comparison to other best-known artificial sweeteners such as saccharin, aspartame and acesulfame potassium[1]. Artificial sweeteners are found in some commonly consumed foods such as diet sodas, cereals, sugar-free desserts such as ice cream and also found in many products due to their low or non-caloric characteristics. Artificial sweeteners have greatly benefited diabetic patients to control their blood sugar levels[1].

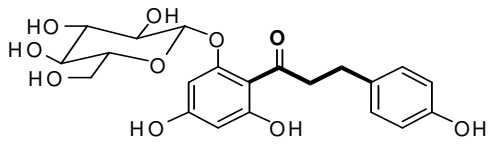
Dihydrochalcone **2** was first identified as a sweetener by Whitelaw and Daniel in 1991 (Figure



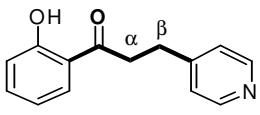
Neohesperidin dihydrochalcone (NHDC) **1**



2,4,6-trihydroxy-3-[3-(3-hydroxy-4-methoxy phenyl)-1-oxopropyl]-benzoic acid **2**



Phloridzin **3**



1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one **4**

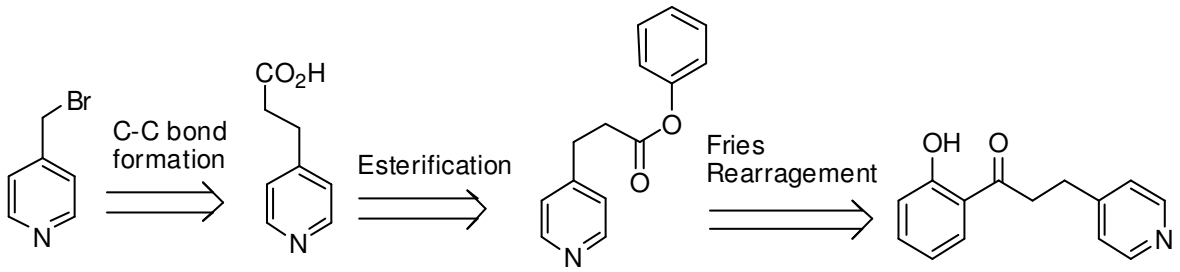
Examples for dihydrochalcone based sweeteners

Figure-1

1)[2]. Since then, some analogues of DHC with electron donor or electron withdrawing substituent have been described as sweetener as compared to sucrose. Another example for DHC motif is Phloridzin **3**, a specific and unique polyphenol belonging to apple tree family (Rosaceae). Phloridzin inhibits the glucose transport and has been widely used at high concentrations to induce glycosuria (elimination of the glucose through the urinary tract)[2]. Despite the simple structure of DHC and its physicochemical features, such as a good solubility in water, which could make it attractive for further development, there are a few reports on the synthesis of DHC derivatives[4].

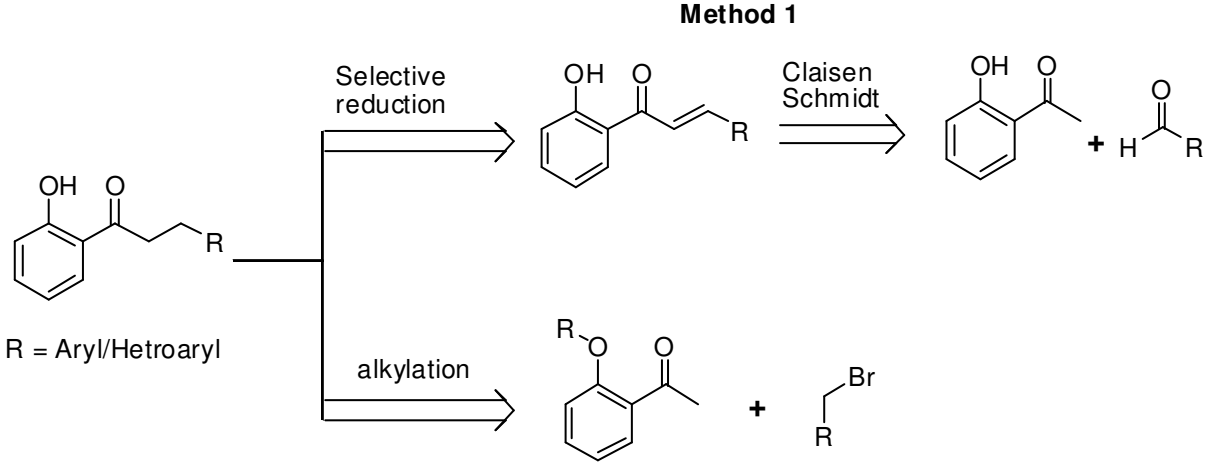
Recently, pyridine ring containing dihydrochalcone (PDHC) 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one **4** and other hetero-aryl DHC were identified as new artificial sweeteners by Givaudan SA, and these new hetero aryl DHC, offered more potency as compared to NHDC[5]. We were therefore interested in a practical synthesis of **4**, which could be potentially employed for a large-scale synthesis. In this article, we herein describe an expedient short synthesis for **4** from commercially and inexpensive chemicals such as 4-bromomethyl pyridine hydro bromide and phenol (Figure-2).

One of the classical methods employed for the synthesis of dihydrochalcone is Claisen-Schmidt condensation of an aromatic aldehyde with acetophenone in the presence of a base[6], followed by hydrogenation of the double bond (Figure-3, method 1). In the case of hydroxy group containing aromatic



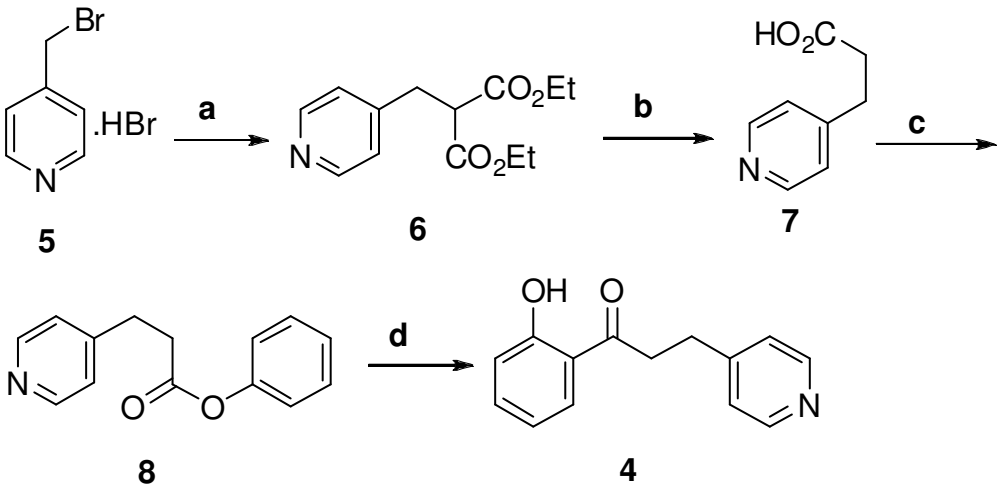
Synthetic outline for 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one **4**

Figure-2



General methods for synthesis of ortho hydroxy DHC

Figure-3



Reagents and conditions: (a) $CH_2(CO_2Et)_2$ NaOMe, DMF, rt, 6h, 79%; (b) i. KOH, EtOH, rt, 2h, 90%; ii. 6 *N* HCl, 16h, 92%; (c) EDC, HOBt, Et_3N, DMF, rt, 2h, 76%; (d) $AlCl_3$, 150 ^{0}C- 160 ^{0}C, 2h, 68%

SCHEME-1

aldehydes or aryl ketones, typically Claisen-Schmidt condensation affords low yields[7]. In the second method, alkylation of 2-hydroxy acetophenone would require a protection/deprotection sequence to preclude alkylation of the phenolic moiety. Based on these drawbacks the need for alternate and efficient strategies to access dihydrochalcones from hetroaryl or hydroxy-appended aryl ketones exists[8].

Towards the synthesis of **4**, commercially available and inexpensive 4-bromomethyl pyridine hydrobromide **5** was alkylated with diethyl malonate in the presence of sodium methoxide and DMF to provide **6** in 79% yield[9]. Competing side reaction of polymeric quaternization of **6** was avoided by adding excess amount of sodium methoxide[10]. Hydrolysis of the ester **6** with aqueous potassium hydroxide, followed by decarboxylation in the presence of 6*N* HCl afforded the 2-(4-pyridyl) acetic acid **7**[11].

Our initial efforts focused on the preparation of ester **8** from **7** with phenol in the presence of DCC and DMAP. Although, ester was obtained in good yields, a chromatography purification of the ester was required, owing to the presence of dicyclohexyl urea as byproduct. To overcome this problem we have employed EDC/HOBt for esterification and obtained the desired ester **8** in 76% yield, without the need for column chromatography purification. Ester **8** served as the key precursor for Fries Rearrangement.

Interestingly, synthesis of *o*-hydroxy substituted dihydrochalcones *via* Fries rearrangement has been previously used in pharmaceutical industry for preparation of important intermediates[12]. First report was in 1990 by Miguel and co-workers for photochemical studies of α-2-Diacetoxystyrenes[13]. Later in 2012 Merck & Co. developed a process for synthesis of hydroxy aryl ketones by Fries Rearrangement employing with methanesulfonic acid and methanesulfonic anhydride[14]. However, synthesis of hetero aryl dihydrochalcones *via* Fries Rearrangement is not reported in the literature. In this regard, we have attempted Fries Rearrangement of **8** with $AlCl_3$ and nitrobenzene as a solvent at reflux temperature and obtained desired **4** in 61% yield[5]. The yield for the Fries Rearrangement improved when the reaction was performed with $AlCl_3$ at 150^o under solvent-free conditions without the formation any side-

products. The nature of dihydrochalcone motif was evident from its ^{1}H NMR spectrum, which displayed characteristic triplets at δ 3.31 and 3.52 ppm for aliphatic protons and in ^{13}C indicated at 28.92 and 38.69 ppm and consonance with literature reports[5].

Experimental

Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO solutions using a Varian 400 NMR instrument. Proton chemical shifts (δ) are relative to tetra methyl silane (TMS, δ = 0.0) as internal standard. and expressed in parts per million. Coupling constants (J) are given in hertz. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were obtained on a mass spectrometer..

Diethyl 2-(pyridin-4-ylmethyl)malonate (6)

To 50 mL of DMF (50 mL) at RT was gradually added with stirring NaOMe (4.13g, 76 mmol) and the resulting reaction mixture was cooled to 5-10°. Diethyl malonate (11.6 mL, 76 mmol) was added to the reaction mixture and stirred at RT for 1h. 4-(Bromomethyl) pyridine hydrobromide **5** (12g, 47 mmol) dissolved in DMF (22 mL) was added to the reaction mixture over a period of 10 min at 5 -10 °. The resulting reaction mixture was stirred for 6h at RT. After completion of the reaction by TLC, the reaction mixture was quenched with ice cold water (500 ml) and extracted with DCM (2 x 250 mL). The combined organic layers were dried over Na_2SO_4. Filtered the organic layer and concentrated under reduced pressure to give crude product as pale red color oil. The obtained crude compound was purified by column chromatography (SiO_2, 60-120 mesh, 40% EtOAc/hexane) to get diethyl 2-(pyridin-4-ylmethyl)malonate **6** (9.4g, 79%) as pale red color oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.19 (t, 6H, *J* = 7.2 Hz), 3.22 (d, 2H, *J* = 7.6 Hz), 3.63 (t, 1H, *J* = 7.6 Hz), 4.14 (m, 4H) 7.23 (d, 2H, *J* = 6.4 Hz) 8.51 (d, 2H, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.91, 14.05, 33.80, 52.46, 52.65, 61.78, 124.01, 124.18, 146.93, 149.86, 149.94, 168.32; Mass: *m / z* = 252.1 $[M+H]^+$.

3-(Pyridin-4-yl)propanoic acid (7)

To a stirred solution of ethanol (65 mL) was added diethyl-2-(pyridine-4-ylmethyl) malonate **6** (6.5g, 25.5 mmol), KOH (2.9g, 51 mmol) and H_2O (10 mL) at RT. The resulting reaction mixture was stirred for 2h at RT. After completion of the reaction by TLC, the reaction mixture was concentrated under reduced pressure and the aqueous solution was acidified using 6N HCl to pH ~ 2. The obtained solid was filtered and washed with EtOH (10 mL) and dried under vacuum to furnish 2-(Pyridin-4-ylmethyl)malonic acid (4.5g, 90% yield) as an off white solid. ^{1}H NMR (400 MHz, D_2O): 3.30 (d, 2H, *J* = 6 Hz), 3.90 (t, 1H), 7.87 (d, 2H, *J* = 6 Hz), 8.73 (d, 2H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, D_2O): 35.61, 47.65, 59.04 124.49, 148.33, 151.41, 177.33, 178.19; Mass: *m / z* 196.0 $[M+H]^+$.

The mixture of 6*N* HCl (90 mL) and 2-(pyridine-4-ylmethyl) malonic acid (4.5g, 23 mmol) was stirred at 100° for 16h. After completion of the reaction by TLC, the reaction mixture was concentrated under reduced pressure to get the off-white color semi solid. The obtained solid was triturated using EtOH (50 mL) and filtered the solid, dried under vacuum to furnish 3-(Pyridin-4-yl)propanoic acid **7** (3.2g, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 2.70 (t, 2H, *J* = 7.6 Hz), 3.01 (t, 2H *J* = 7.6 Hz), 7.74 (d, 2H, *J* = 4.8 Hz), 8.70 (d, 2H, *J* = 4.8 Hz) 12.4 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), 30.63, 33.26, 127.16, 127.37, 141.58, 141.79, 162.02, 173.52; Mass: *m / z* 152.1 $[M+H]^+$.

Phenyl 3-(pyridin-4-yl)propanoate (8)

The mixture of 3-(pyridin-4-yl) propionic acid **7** (3.2g, 21 mmol), diisopropylethylamine (3.74 mL, 21 mmol), HOBt (1.43g, 10 mmol) and EDC (8.2g, 52 mmol) in DMF was stirred for 2h at RT. After completion of the reaction by TLC, the reaction mixture was diluted with ice cold water and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and organic layer was dried over by anhydrous Na_2SO_4. Organic layer was concentrated under reduced pressure to obtained phenyl 3-(pyridin-4-yl) propanoate **8** (3.5g, 76% yield) as pale yellow color liquid. ^{1}H NMR (400 MHz, $CDCl_3$), 3.12 (t, 2H, *J* = 7.2 Hz), 3.30 (t, 2H, *J* = 7.2 Hz), 7.04 (d, 2H, *J* = 7.6 Hz), 7.21 (d, 2H, *J* = 7.2 Hz) 7.23 (t, 1H), 7.37 (t, 2H), 8.72 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) , 30.03, 34.51, 121.31, 123.65, 123.97, 125.82, 126.15, 129.28, 129.66, 149.12, 149.78, 150.44, 170.77; Mass: *m / z* 227.8 $[M+H]^+$.

1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one (4)

The mixture of phenyl 3-(pyridine-4-yl) propanoate **8** (900 mg, 3.96 mmol) and $AlCl_3$ (1.6g, 11.7 mmol) was heated to 150–160° and stirred for 2h. After completion of the reaction by TLC, the reaction mixture was cooled to RT and diluted with DCM (50 mL) and the organic layer was washed with 6*N* HCl (2 x 20 mL) and brine solution (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to obtain a crude compound. The crude compound was purified by column chromatography (SiO_2, 60-120 mesh) to get 1-(2-hydroxyphenyl)-3-(pyridin-4-yl)propan-1-one **4** (613 mg, 68% yield) as a pale brown color oil. ^{1}H NMR (400 MHz, $CDCl_3$): 3.31 (t, 2H), 3.52 (t, 2H), 6.87 (m, 1H), 6.98 (d, 1H, *J* = 8.0 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.48 (t, 1H), 7.75 (d, 1H, *J* = 8.0 Hz), 8.68 (d, 2H, *J* = 7.8 Hz), 11.86 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), 28.92, 38.69, 118.63, 118.70, 119.06, 123.83, 129.49, 132.41, 136.72, 149.69, 150.03, 162.40, 167.78, 204.16; Mass: *m / z* = 227.9 $[M+H]^+$.

In conclusion, we have demonstrated a short and expedient synthesis for the artificial sweetener **4** exploiting Fries rearrangement as a key step. The choice of readily available starting materials, simple work-up with easy purification and waste minimization make this route a 'green-approach' which can be applied to the synthesis of other hetero aryl dihydrochalcone motifs constituted by hydroxy containing aryl and hetero aryl rings.

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