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Synthesis of Chiral Flavanones from Tricarbonyl (η^6-Arylbenzaldehyde)chromium(0)

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A synthesis of chiral flavanones *via* the condensation of tricarbonyl(η^6-arylbenzaldehyde)chromium(0) and *o*-hydroxyacetophenone in a shorter time at room temperature have been developed. The tricarbonylchromium(0) group was removed by virtue of light and the enantioenriched flavanones was formed with highly enantioselectivity (> 95 % ee).

Key Words: Synthesis, Chiral flavanones, Chiral tricarbonylchromium(0) aromatic aldehydes.

INTRODUCTION

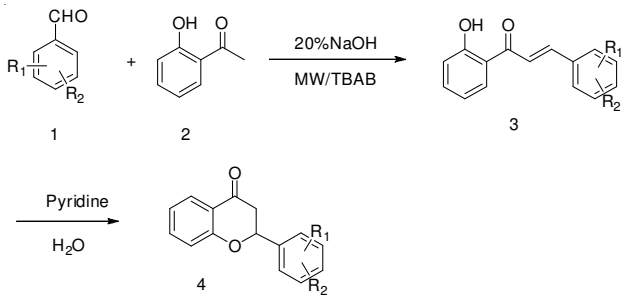
Flavanones constitute a large number of natural products with many medicinal applications[1]. Because of their broad range of biological activities such as anti HIV[2], anticancer[3], antioxidant[4], gastro-protective[5], antibacterial and antifungal[6,7], a variety of approaches have been developed to synthesize flavanones. The most commonly one was the intramolecular cyclodehydration of 1-(2-hydroxyphenyl)-1,3-diketones[8]. Although the diastereoselective flavanones has been shown to proceed, in some cases, with high to excellent diastereoselectivities, the enantioselective variation of this reaction is less developed. A limited number of strategies have been developed to obtain chiral flavanones, such as resolution of the related alcohols[9] or substitution reactions[10]. Due to its difficult synthesis and harsh experimental conditions, it is needed to find efficient method for the synthesis of chiral flavanones.

Herein we report an efficient synthesis of chiral flavanones *via* the reaction of tricarbonylchromium(0) and *o*-hydroxyacetophenone.

EXPERIMENTAL

Solvents were dried and liquid aromatic aldehydes were distilled prior to use. NMR spectra were recorded on a Bruker Avance DMX400 spectrometer in DMSO-d_6 with TMS as an internal standard. Infrared spectra were recorded on Bruker FTIR-Tensor27 spectrometer expressed in cm^{-1} (KBr). Mass was determined by using a Bruker Micro TOF-MS high resolution mass spectrometer. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm).

Experimental process: Synthesis of racemic flavanones (**Scheme-I**): Compound **3** (2-hydroxychalcones) was prepared through condensation of aromatic aldehyde **1** (5 mmol) and *o*-hydroxyacetophenone **2** (5 mmol) in 20 % NaOH aqueous solution (2 mL), using TBAB (tetrabutylammonium bromide, 0.15 mmol, 0.05 g) as phase transfer catalyst under microwave irradiation for 5 min. Then the reaction mixture was poured into ethyl acetate (20 mL) and washed with water for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) to give **3**.



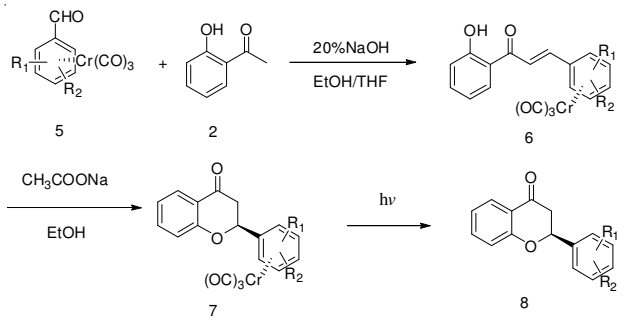
Scheme-I: Synthesis of enantiomers 2-phenychroman-4-ones

The mixture of **3** (2 mmol), hexahydropyridine (1 mL) and water (10 mL) was taken in a 50 mL round bottom flask and stirred at room temperature for 5-6 h. Then by filtering flavanones **4** was obtained (Table-1).

TABLE-1
SYNTHETIC RESULTS OF RACE-FLAVANONE **4**

Entry	R	Formula	m.p. (ºC)	Time	Yield (%)
4a	2 -OCH_3	$C_{16}H_{14}O_3$	106-107	3.0	85
4b	2,3(-OCH_3)$_2$	$C_{17}H_{16}O_4$	92-93	3.0	80
4c	3,4(-OCH_3)$_2$	$C_{17}H_{16}O_4$	73-74	3.5	85
4d	2-Br	$C_{15}H_{11}O_2Br$	97-98	3.0	89
4e	3-Br	$C_{15}H_{11}O_2Br$	95-96	3.0	90
4f	4-Cl	$C_{15}H_{11}O_2Cl$	81-82	2.0	92
4g	–	$C_{15}H_{12}O_2$	70-72	2.0	90

Synthesis of chiral flavanones (Scheme-II): In N_2 atmosphere the chiral tricarbonylchromium(0) aromatic aldehydes **5** (based on our previous work[11]) (5 mmol) and *o*-hydroxyacetophenone **2** (5 mmol) were stirred with 20 % NaOH solution (2 mL) in 95 % ethanol (10 mL) and THF (tetrahydrofuran 10 mL) at room temperature for 1 h. Then the reaction mixture was poured into ethyl acetate (20 mL) and washed with water for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by chromatography on silica gel (petroleum ether:ethyl acetate = 3:1) to give chiral tricarbonylchromium(0) 2-hydroxychalcones **6**.



Scheme-II: Synthesis of chiral 2-phenychroman-4-ones

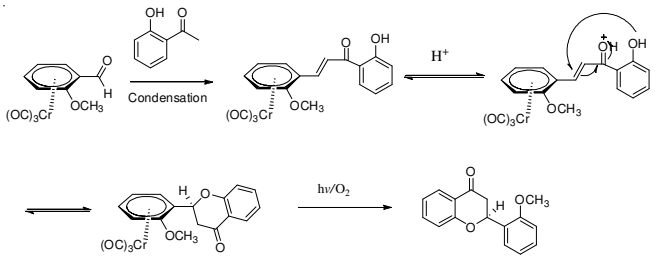
The mixture of **6** (2 mmol), sodium acetate and 95 % ethanol (10 mL) was taken in a 50 mL round bottom flask and stirred at room temperature for 5-6 h. Then by filtering we got chiral tricarbonylchromium(0) flavanones **7**. By virtue of light, the tricarbonylchromium(0) group was removed and obtained the chiral flavanones **8** (Table-2).

TABLE-2
SYNTHETIC RESULTS OF CHIRAL FLAVANONES

Entry	Time	Yield (%) [a]	e.e (%) [b]	Config.
+8a	2.0	65	96	R
-8a	2.0	65	98	S
+8b	2.0	60	95	R
-8b	2.0	60	94	S

[a]Isolated yields after chromography. [b]Determinede by chiral-HPLC using AD-H coloum.

Probable mechanism (Scheme-III): Firstly, the starting chalcone was accessed *via* Knoevenagel condensation, the chiral tricarbonylchromium(0) aromatic aldehydes reacted with *o*-hydroxyacetophenone in alkaling condition. Then, based on acid catalyzed the flavanones was formed upon intramolecular cyclization. At last the tricarbonylchromium(0) group was removed by virtue of light and the enantioenriched flavanones was formed (**Scheme-III**).



Scheme-III: Probable mechanism

Spectral data for new compounds

2,3-Dihydro-2-(2-methoxyphenyl)chromen-4-one (4a): colourless crystals, IR (KBr, ν_{max}, cm^{-1}): 3030, 2960, 2920, 2870, 1680, 1600, 1500, 1460, 1380, 1260. ^{1}H NMR (δ ppm, DMSO-d_6): 2.86 (dd, J_1 = 2.4Hz, J_2 = 16.8 Hz, C_3-H), 3.33 (t, J = 13.6Hz, C_3-H), 3.89 (s, 3H, CH_3O), 5.84 (dd, J_1 = 2.8 Hz, J_2 = 13.2 Hz, 1H, C_2-H), 7.70-7.13 (m, 8H, ArH). Anal. calcd. (%) for $C_{16}H_{14}O_3$: C 63.0, H 5.5; found (%): C 63.2, H 5.6.

2,3-Dihydro-2-(2,3-dimethoxyphenyl)chromen-4-one (4b): IR (KBr, ν_{max}, cm^{-1}): 3030, 2960, 2920, 2860, 1680, 1600, 1500, 1450, 1380, 1260, 1120. ^{1}H NMR (δ ppm, DMSO-d_6): 2.86 (dd, J_1 = 2.4 Hz, J_2 = 16.8 Hz, C_3-H), 3.32 (t, J = 13.6 Hz, C_3-H), 3.83 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 5.84 (dd, J_1 = 2.8 Hz, J_2 = 13.2 Hz, 1H, C_2-H), 7.70-7.13 (m, 7H, ArH). Anal. calcd. (%) for $C_{17}H_{16}O_4$: C 71.8, H 5.6; found (%): C 71.9, H 5.7.

2,3-Dihydro-2-(3,4-dimethoxyphenyl)chromen-4-one (4c): IR (KBr, ν_{max}, cm^{-1}): 3030, 2960, 2920, 2870, 1680, 1600, 1500, 1450, 1380, 1260, 1130. ^{1}H NMR (δ ppm, DMSO-d_6): 2.85 (dd, J_1 = 2.4 Hz, J_2 = 16.8 Hz, C_3-H), 3.32 (t, J = 13.6 Hz, C_3-H), 3.83 (s, 3H, CH_3O), 3.89 (s, 3H, CH_3O), 5.84 (dd, J_1 = 2.8 Hz, J_2 = 13.2 Hz, 1H, C_2-H), 7.70-7.13 (m, 7H, ArH). Anal. calcd. (%) for $C_{17}H_{16}O_4$: C 71.8, H 5.6; found (%): C 71.8, H 5.7.

2,3-Dihydro-2-(2-bromo)chromen-4-one (4d): IR (KBr, ν_{max}, cm^{-1}): 3030, 2920, 1680, 1600, 1500, 1450, 1260. ^{1}H NMR (δ ppm, DMSO-d_6): 3.33 (t, J = 13.6 Hz, C_3-H), 2.84 (dd, J_1 = 2.4 Hz, J_2 = 16.8 Hz, C_3-H), 5.86 (dd, J_1 = 2.8, J_2 = 13.2 Hz, 1H, C_2-H), 8.27-7.00 (m, 8H, ArH). Anal. calcd. (%) for $C_{15}H_{11}O_2Br$: C 59.4, H 3.6; found (%): C 59.5, H 3.4.

2,3-Dihydro-2-(2-chloro)chromen-4-one (4e): IR (KBr, ν_{max}, cm^{-1}): 3030, 2920, 1680, 1600, 1500, 1450, 1260. ^{1}H NMR (δ ppm, DMSO-d_6): 3.33 (t, J = 13.6 Hz, C_3-H), 2.84 (dd, J_1 = 2.4 Hz, J_2 = 16.8 Hz, C_3-H), 5.86 (dd, J_1 = 2.8, J_2 = 13.2 Hz, 1H, C_2-H), 8.27-7.00 (m, 8H, ArH). Anal. calcd. (%) for $C_{15}H_{11}O_2Cl$: C 59.4, H 3.6; found (%): C 59.5, H 3.4.

2,3-Dihydro-2-(4-chloro)chromen-4-one (4f): IR (KBr, ν_{max}, cm^{-1}): 3030, 2920, 1680, 1600, 1500, 1450, 1260, 1130. ^{1}H NMR (δ ppm, DMSO-d_6): 2.83 (dd, J_1 = 2.4 Hz, J_2 = 16.8 Hz, C_3-H), 3.35 (t, J = 13.6 Hz, C_3-H), 5.82 (dd, J_1 = 2.8 Hz, J_2 = 13.2 Hz, 1H, C_2-H), 7.70-7.13 (m, 8H, ArH). Anal. calcd. (%) for $C_{15}H_{11}O_2Cl$: C 69.6, H 4.3; found (%): C 69.7, H 4.4.

RESULTS AND DISCUSSION

In this work, it was found that the ee % of products were high when chiral tricarbonylchromium(0) aromatic aldehydes were used as chiral reactant. The results indicated that both (-)-tricarbonylchromium(0) aromatic aldehydes and (+)-

tricarbonylchromium(0) aromatic aldehydes played the same activity and stereoselective role in the synthesis of chiral flavanones.

Conclusion

In summary, we have developed an efficient method for the synthesis of chiral flavanones. This is a novel application of chiral tricarbonylchromium(0) aromatic aldehydes. Shorter total times (5-6 h) were taken with highly enantioselective (> 95 % ee) at room temperature comparing with previous methods. Our method for the synthesis of these natural products provided an efficient way and made significant improvment.

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