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Synthesis & Antioxidant Activity of Certain Chalcones & Their Derivatives

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ABSTRACT: Purpose: Purpose of this article is find out role of α,β- unsaturated carbonyl functionality on antioxidant activity. **Methods**: Chalcones were synthesized via claisen-schmidt condensation reaction and subsequent one step reduction to tetrahydrochalcones **(7-12)** was done by using sodium formate and 5% Pd/C in methanol at room temperature. Antioxidant activity was evaluated by Diphenyl Picryl Hydrazine (DPPH) scavenging method. **Results**: Chalcones were more potential than corresponding tetrahydrochalcones. **Conclusions**: One step reduction by using sodium formate and 5% Pd/C is very efficient and safe method. α,β-unsaturated carbonyl functionality imparts very significant role in antioxidant activity.

KEYWORDS: Chalcone; Claisen-Schmidt Condensation; Tetrahydrochalcones; Pd/C; Diphenyl Picryl Hydrazyl Radical (DPPH) Scavenging Activity.

INTRODUCTION

α,β–unsaturated ketone group containing moiety (Chalcones) has shows significant position in medicinal chemistry. The electron rich olefinic bond has shown involvement in Michel interaction and divers class of biological activities. To evaluate the role of reactive α,β–unsaturated ketone group in antioxidant activity, it is necessary to screen and compare tetrahydrochalcone with respective chalcones [1-5]. Several catalytic reducing agents have been employed for selective reduction including **palladium/ vinyl acetate, rhodium** (I) complexes, pincer-aryl ruthenium (II) complexes, magnesia, iridium/ formic acid, sodium hypophosphite, **palladium /ethylene atmosphere,** CeO_2-ZnO complex etc [6]. In this article, we highlight on one pot synthesis of tetrahdrochalcones by using sodium formate /5% palladium on carbon in methanol at room temperature. All synthesized test compounds were evaluated for antioxidative potential by diphenyl Picryl Hydrazine (DPPH) method. Results indicates that reduction of α,β-unsaturated carbonyl moiety imparts reduction in antioxidative potential.

MATERIALS & METHODS

Experimental

General

All melting points were measured on Mel-Temp apparatus and were uncorrected. Infrared (FT-IR) spectra were recorded on Shimadzu FTIR 8300 spectrometer. Proton (^{1}H) nuclear magnetic resonance spectroscopy was performed on a Brucker AMX-400 NMR spectrometer, operating at 300 MHz with TMS as internal standard. All chemical shifts were reported as δ (ppm) values. Compounds were also analyzed by GC-MS (QP 5010, Shimadzu Corporation, Japan). All reagents were purchased from Sigma Chemicals, India and were used without further purification. TLC analysis was carried out on aluminum foil precoated with silica gel 60 F254.

Chemistry

***General procedure for the synthesis of chalcone* (1-6)**

4-Hydroxyacetophenone (0.01mole) and p-substituted aromatic aldehyde (0.01 mole), were dissolved in 15 ml of absolute alcohol and potassium hydroxide (0.03 mole) dissolved in min. water was added to the solution. The solution was stirred at room temperature and progress of the reaction was monitored using TLC. After completion of reaction, the reaction mixture was diluted with water (200 ml),

and acidified with dilute hydrochloric acid to pH 3. The product obtained was filtered, washed with water, and crystallized from absolute alcohol [7].

***General procedure for the reduction of chalcone* (7-12)**

To a solution of chalcone (0.002mol) in methanol (5ml), sodium formate (0.016 mol) was added, followed by addition of 5% palladium on carbon (0.30 mol) and reaction mixture was stirred at room temperature. Stirring was continued until no starting material has left as confirmed by TLC. On completion of reaction, the reaction mixture was filtered to remove the catalyst and solvent was removed under reduced pressure. The crude product was purified by column chromatography (30 % EtOAc in hexane) [8].

***4-(1-hydroxy-3-phenylpropyl)phenol* (7)**

Yield: 80%; m.p.: 90-93^{0}C; FTIR (KBr pellet): 3352 (O-H str), 3045 (Ar C-H str), 2972 (C-H str), 1600 (C=O str), 1516, 1458 (Ar C=C str), 1363 (O-H sec.alcohol) ; ^{1}H NMR ($CDCl_3$), : 1.95-2.04 (m, 1H, H of CH_2-C_6H_5), 2.08-2.18 (m, 1H, H of CH_2-C_6H_6), 2.59-2.75 (m, 2H, CH_2 of CH_2-CH), 4.61-4.64 (t,1H, CH), 5.08 (s, 1H,OH), 6.79-6.82 (m, 2H, aromatic), 7.17-7.29 (m, 7H aromatic); m/z (rel.%) 229 (M+1).

***4-[1-hydroxy-3-(4-methylphenyl)propyl]phenol* (8)**

Yield: 78%; m.p.: 110-112^{0}C; FTIR (KBr pellet): 3321 (O-H str), 3092 (Ar C-H str), 2903 (C-H str), 1547 (C=O str), 1398 (O-H sec.alcohol) ; ^{1}H NMR ($CDCl_3$),: 1.93-2.04 (m, 1H, H of CH_2-C_6H_5), 2.05-2.15 (m, 1H, H of CH_2-C_6H_5), 2.31 (s, 3H, CH_3), 2.55-2.70 (m, 2H, CH_2 of CH_2-CH), 4.6-4.63 (t, 1H, CH), 5.01 (s, 1H,OH), 6.78-6.81(m, 2H,aromatic), 7.05-7.25(m, 6H aromatic), m/z (rel.%) 243 (M+1).

***4-[1-hydroxy-3-(4-methoxyphenyl)propyl]phenol* (9)**

Yield: 81%; m.p.: 115-117^{0}C; FTIR (KBr pellet): 3400 (OH str), 3024 (Ar C-H str), 2918 (CH_2 str), 1612 (C=O str), 1514, 1452 (Ar C=C str), 1232 (C-O-C str); ^{1}H NMR ($CDCl_3$), : 1.93-2.03 (m, 1H, H of CH_2-C_6H_5), 2.05-2.14 (m, 1H, H of CH_2-C_6H_6), 2.53-2.68 (m, 2H, CH_2 of CH_2-CH), 3.78 (s, 3H, OCH_3), 4.59-4.62 (t, 1H, CH), 5.21 (s, 1H, OH), 6.72-6.83 (m, 4H,aromatic), 7.02-7.25 (m, 4H aromatic); m/z (rel.%) 259 (M+1).

***4-[1-hydroxy-3-(4-fluorophenyl)propyl]phenol* (10)**

Yield: 69%; m.p.: 127-130^{0}C; FTIR (KBr pellet): 3401 (O-H str), 2992 (Ar C-H str), 2914 (C-H str), 1357 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.91-2.09 (m, 2H, $\underline{C}H_2C_6H_5$), 2.51-2.74 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.57-4.60 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.04 (s, 1H, OH), 6.76-7.19 (m, 8H, aromatic), m/z (rel.%) 245 (M+1).

***4-[1-hydroxy-3-(4-chlorophenyl)propyl]phenol* (11)**

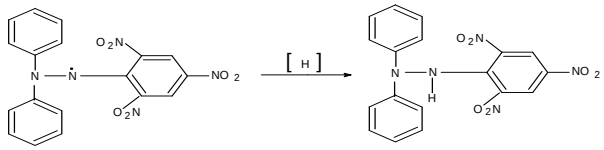
Yield: 73%; m.p.: 125-128^{0}C; FTIR (KBr pellet): 3463 (O-H str), 2897 (Ar C-H str), 2874 (C-H str), 1301 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.85-2.01 (m, 2H, $\underline{C}H_2C_6H_5$), 2.57-2.72 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.52-4.57 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.12 (s, 1H, OH), 6.81-7.25 (m, 8H, aromatic), m/z (rel.%) 263 (M+1).

***4-[1-hydroxy-3-(4-bromophenyl)propyl]phenol* (12)**

Yield: 71%; m.p.: 132-135^{0}C; FTIR (KBr pellet): 3348 (O-H str), 2951 (Ar C-H str), 2883 (C-H str), 1312 (O-H sec.alcohol); ^{1}H NMR ($CDCl_3$),: 1.87-2.14 (m, 2H, $\underline{C}H_2C_6H_5$), 2.42-2.57 (m, 2H, $\underline{C}H_2CH_2C_6H_5$), 4.45-4.63 (t, 1H, $\underline{C}HCH_2CH_2C_6H_5$), 5.16 (s, 1H, OH), 6.64-7.01 (m, 8H, aromatic), m/z (rel.%) 305 (M+1).

Antioxidant activity

Antioxidant potential of synthesized test compounds were evaluated by 2, 2-Diphenyl-1- picryl hydrazyl method [9]. DPPH (2, 2-Diphenyl-1- picryl hydrazyl) is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with suitable reducing agents and than electron becomes paired off and the solution losses colour stochiometrically with the number of electron taken up. Such reactivity has been widely used to test the ability of compound to act free radical scavengers.



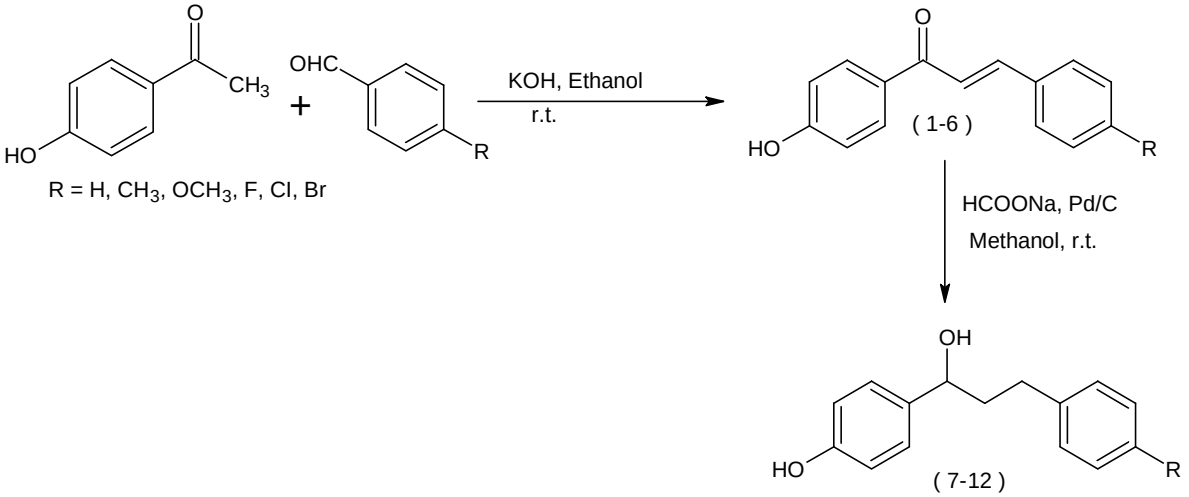
Hydrogen donating activity was quantified in presence of stable DPPH radical on the basis of Blois method. Stock solution of DPPH (3.9 mg in 50 ml), synthesized test compounds four serial dilution (14-112 µM) concentration were prepared in methanol. Absorbance was measured at 517 nm. Ascorbic acid was used as standard. The degree of discoloration indicates the scavenging efficiency of compound.

$$\% \text{ Scavenging} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

RESULTS & DISCUSSION

Chemistry

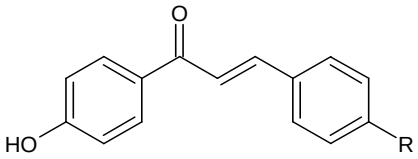
The sequence steps involved in synthesis of 4-hydroxy substituted Chalcones via Claisen–Schmidt condensation between 4-hydroxy acetophenone and various 4-substituted aromatic aldehydes are shown in Schem-1. The α,β–unsaturated carbonyl moiety (chalcone) was reduced to corresponding tetrahydrochalcone by using sodium formate and 5% palladium on carbon in methanol at room temperature to produce tetrahydrochalcone **7-12**. Compound **7** was obtained as white crystalline solid in 80 % yield. The FT-IR spectra of compound **7** showed absorption bands at 1363 cm^{-1} confirm the presence of OH group (secondary alcohol). The ^{1}H NMR spectra of **7** showed broad singlet at δ 5.08, which further confirmed the presence of OH group (secondary alcohol). This peak disappeared in D_2O exchange. The mass



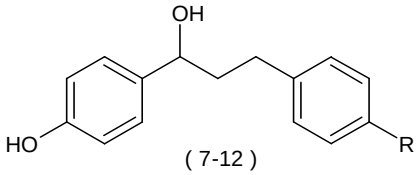
R = H, CH_3, OCH_3, F, Cl, Br

Scheme-1 Step wise synthesis of chalcones (1-6) and one step reduction to tetrahydrochalcones (7-12).

Table-1 Physical data of chalcones (1-6) and tetrahydrochalcones (7-12)



(1-6)



(7-12)

S.N	Structure	M.W.	m.p.(^{0}C)	%Yield	R_f value	Log P
1	H	224	170-172	70	0.48*	3.20
2	CH_3	238	180-182	65	0.34*	3.68
3	OCH_3	254	190-193	72	0.53*	3.07
4	F	240	175-177	60	0.44*	3.35
5	CI	258	195-198	50	0.34*	4.36
6	Br	300	200-202	70	0.37*	4.02
7	H	228	90-93	80	0.42*	3.48
8	CH_3	242	110-112	78	0.28*	3.97
9	OCH_3	258	115-117	81	0.47*	3.35
10	F	244	127-130	69	0.36*	3.64
11	CI	262	125-128	73	0.24*	4.04
12	Br	304	132-135	71	0.31*	4.31

* (30 % EtOAc in hexane)

Table-2 % DPPH free radical scavenging capacity of test compounds (1-12 and ascorbic acid).

S.N.	% scavenging	Code	% scavenging
1	15	**7**	12
2	12	**8**	9
3	17	**9**	13
4	6	**10**	7
5	12	**11**	8
6	9	**12**	6
		Ascorbic acid	50

spectrum of compound **7** showed peak at m/z 229 (M+1) which confirmed the reduction of both double bond and carbonyl group. The IR spectra of compound **4** & **10** showed C-F stretching at 1150-1100 cm^{-1}. Similarily compound **5** & **11**, **6** & **12** showed C-Cl and C-Br stretching at 800-700 and 700-600 cm^{-1} respectively. The calculated value of the logarithm of the octanol/water partition coefficient (log P) for this compound (3.48) is greater than that of corresponding chalcone (3.2), which indicate enhancement in lipophilicity on reduction of chalcone. The physiochemical dates of synthesized test compounds are summarized in Table 1.

Antioxidant activity

Antioxidant activities of synthesized test compounds **1-12** were evaluated by DPPH free radical scavenging method. Their activities were compared with Ascorbic acid. Results of % DPPH free radical scavenging capacity are summarized in Table 2. Reported IC_{50} of ascorbic acid is 56µM. None of the compounds exhibited significant antioxidant activity. Gradual reduction in antioxidant activity was observed on successive reduction process.

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