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SYNTHESIS OF NOVEL CHALCONES BY CHLOROMETHYLATION OF 1-HYDROXY ACETOPHENONE

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Abstract: Chloromethylation of ortho hydroxy acetophenone has been performed by using formaldehyde solution in the presence of concentrated hydrochloric acid and $ZnCl_2$ as a Lewis acid in chloroform as a solvent at around 35 to 40 °C temperature 1-(5-(chloromethyl)-2-hydroxyphenyl) ethanone Is obtained in good to better yield of the product. Further on reaction with substituted aromatic benzaldehyde in the presence of alcoholic KOH under reflux condition chalcones are obtained. The reaction is proceeding through Claisen–Schmidt condensation followed by crossed aldol condensation reaction. The synthesized chalcones are pharmacologically valuable because it's versatile reactivity, which can be converted into various bioactive heterocyclic compounds.

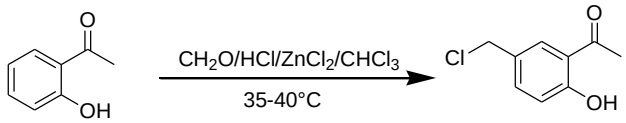
Introduction

Chalcones are a class of organic compounds characterized by their distinctive structure, which consists of a phenyl ring connected to an enone (an α, β-unsaturated carbonyl compound). Chalcones are important intermediates in the synthesis of various natural products and have garnered interest due to their diverse biological activities[i-iv]. The organic compound containing chalcome nucleus possesses medicinal properties such as anticancer, for the treatment Parkinson's disease, antiparasitic agents, antimicrobial potential, antituberculosis activity, cytotoxic and chemoprotective properties and in the treatment of unfolded protein response-mediated apoptosis in A549 lung cancer cells[v-xiii]. These compounds are often found in various plants and are involved in the biosynthesis of flavonoids, which play crucial roles in plant pigmentation, UV protection, and defense mechanisms[xiv]. Additionally, chalcones have been studied for potential applications in medicine, particularly in the development of new therapeutic agents. Chalcones can be prepared using several methods such as by Aldol condensation. This method involves the

reaction of an aromatic aldehyde with an α, β-unsaturated ketone (or another aldehyde) in the presence of a base[xv]. The reaction typically involves the formation of a β-hydroxy ketone intermediate, which then undergoes dehydration to form the chalcone, Claisen-Schmidt reaction, a classic method for chalcone synthesis, this involves the condensation of an aromatic aldehyde with a ketone in the presence of a base (like sodium hydroxide). The reaction proceeds through the formation of a β-hydroxy ketone, followed by dehydration to yield the chalcone[xvi-xviii], Crossed Aldol Reaction; Similar to the aldol condensation, this method involves two different carbonyl compounds, usually one being an aromatic aldehyde and the other being a ketone. It can lead to various chalcone derivatives. Some of the other reports in concerned with sustainability have also been reported[xix-xxiv]. These reported methods can vary in terms of efficiency, yield, and the specific chalcone derivatives produced, making the choice of method dependent on the desired outcome and available resources. Because of versatile nature of chalcones we have decided to prepare novel chalcones followed by chloromethylation reaction.

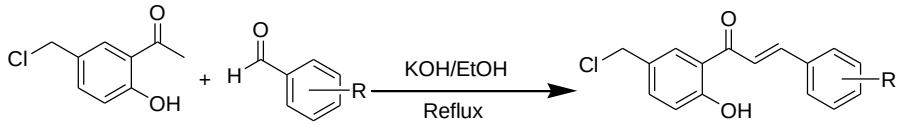
Result and Discussion

Initially we have synthesized 1-(5-(chloromethyl)-2-hydroxyphenyl) ethanone by chloromethylation reaction[-xxviii] of 1-hydroxy acetophenone (**Scheme 1**).



Scheme 1: Chloromethylation reaction of 2-hydroxy acetophenone.

Further, 1-(5-(chloromethyl)-2-hydroxyphenyl) ethanone have been condensed with substituted benzaldehydes in the presence of strong base KOH in ethanol under reflux condition it gives respective chalcones (**Scheme 2**).



Scheme 1: Synthesis of chalcones.

During the reaction course formation of product 1-(5-(chloromethyl)-2-hydroxyphenyl)-3-phenylprop-2-en-1-one have been monitored after each 30 minutes by means of thin layer chromatographic technique (TLC). The reaction is optimized at 50 to 55 °C temperature. This conventional route is more convenient and reliable. This is because KOH abstract acidic proton of acetyl carbon to form carbanion wherein, carbonyl carbon of benzaldehyde is more favorable for nucleophilic attack. This resulted in the formation of 1-(5-(chloromethyl)-2-hydroxyphenyl)-3-phenylprop-2-en-1-one through β-hydroxy ketone followed by dehydration reaction. Benzaldehyde with substitutions of electron withdrawing and electron donating group at different position were used to check the generality and viability of the reaction (**Table 1**.).

Table 1: Synthesis of chalcones from chloromethylated 2-hydroxy Acetophenone.

Sr No	Aldehyde (R)	Time (Hrs)	Yield (%)	M. P. (°C)
1	2-Cl	4:00	87 %	148-150
2	3-Cl	3:30	85%	160-162

3	4-OH	3:45	82%	179-181
4	3-OMe	3:30	85%	190-192
5	4- NO_2	3:30	78%	164-166
6	4-Me	3:30	80%	170-172
7	4-OH,3-OMe	4:15	76%	181-183
8	3-Me	4:00	74%	137-139

Experimental Section

Melting points of compounds were determined in open capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. Purity of compounds was monitored by TLC on silica F254 coated aluminum plates (Merck) as adsorbent and U.V. light and Iodine chamber as a visualizing agent. Chemicals and reagents are used as such without purification and purchased from commercial vender.

General procedure for chloromethylation of 2-hydroxy acetophenone catalyzed by zinc chloride:

In a 50 mL round bottom flask a mixture of ortho hydroxy acetophenone (0.50 g, 0.003 mol) and formaldehyde solution (0.16g, 0.005 mol) were mixed in the presence of $ZnCl_2$ catalyst in chloroform. The reaction mixture was then heated up to 40°C temperature up to the completion of reaction. The progress of reaction was monitored by TLC (ethyl acetate n-hexane) after each 30minutes. After completion of reaction the product was extracted in ethyl acetate and water, washed by brine solution twice, thus collected organic layer was dried on rotary evaporator. The obtained product was by using ethanol to get pure product.

Procedure for the synthesis of 1-(5-(chloromethyl)-2-hydroxyphenyl)-3-phenylprop-2-en-1-ones:

In a 50 mL round bottom flask 1-(5-(chloromethyl)-2-hydroxyphenyl) ethanone (0.20g, 0.0010 mol) was refluxed with alcoholic KOH for half an hour, later on Benzaldehyde (0.12 g, 0.0012 mol) was added, the reaction is refluxed up to the completion. The progress of reaction was monitored by TLC (ethyl acetate:n-hexane) after each 30minutes. After completion of reaction the product was poured on crushed ice, thus obtained product was filtered, dried and recrystallized by using ethanol
to get pure product.

Spectral analysis for representative Compound:1-(5-(chloromethyl)-2-hydroxyphenyl)-3-phenylprop-2-en-1-ones (Table 1 Sr. No.1); ^{1}H NMR (400 MHz, CDCl3, TMS, δ ppm): 4.80 (s, 1H, OH), 4.36 (s, 2H, CH2), 7.10-7.29 (m, 5H, Ar-H), 6.88-70.35 (m, 3H, Ar-H), 7.90 (d, J = 7.10, 1H, CH), 7.6 (d, J = 7.0, 1H, CH), HRMS (ESI); [M + H]+ for C16H13ClO2: 272.10. IR ν max/cm-1 (KBr): 3065 (C-H), 1699 (C-O), 1550 (C-C), 1315, 818 (C–Cl).

Conclusions

We have synthesized novel chalcones of diversified pharmacological applications by a smooth performance of conventional technique as a result the optimized protocol will offer significant contributions in the synthetic organic chemistry. The synthesized chalcones can be utilized for further synthesis of potent heterocyclic moieties. The current protocol offers remarkable contributions such as simplicity in the workup procedure, high yielding methodology, faster reaction rate, and more establishments of novel chalcones.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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