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UTILITY OF SUPERACID IN HETEROCYCLIC CHALCONE SYNTHESIS

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ABSTRACT

Chalcones and chromenones (heterocycle) constitute major sub-classes of naturally occurring flavonoids. In view of their variety of pharmacological activites, it has been decided to synthesis chromenone chalcone derivatives. Therefore, chalcone condensation reaction is standardized utilizing different reaction media. In literature, most of chalcone derivatives have been synthesised in alkaline conditions by heating, whereas, chromenone ring opens in alkaline condition. Therefore, the reaction was carried out in acidic media, employing number of acids. It has been found that the reaction yield is huge when superacid *viz.* Perchloric acid was employed.

KEYWORDS: Acid catalysed, Chromone, Chalcone, perchloric acid, synthesis.

INTRODUCTION

Chalcones have been reported to possess many useful properties, including anti-inflammatory, antimicrobial, antifungal, antioxidant, antitumor and anticancer activities.[1,2] On the other side, Chromen-4-one constitute one of the major class of naturally occurring heterocyclic compounds[3] and interest in their chemistry is unabated because of their useful biological activities such as cytotoxic (anticancer)[4], neuroprotective[5], HIV-inhibitory[6] antimicrobial[7], antifungal[8], analgesic and/or anti-inflammatory[9], antiallergic[10], hypoglycaemic[11] and antioxidant activity.[12] In view of the variety of pharmacological

properties exhibited by chalcones and Chromen-4-one, we were prompted to undertake the synthesis of new chromen-4-one based chalcone compounds which may show different or better physiological activities.

A large number of chalcones have been prepared by Claisen-Schmidt condensation of aldehydes with methyl ketones under acidic/basic conditions.[13] Most of these synthetic routes have been modified time to time to generate heterocyclic chalcone systems *viz.* K.C. Nicolaou *et al.* (2000) prepared heterocyclic chalcone derivatives by using selenium-based solid-phase synthesis.[14] P. Kumar *et al.* (2011) reported an easy, safe, solvent free and effective method for the synthesis of pyrazole-substituted chalcones by grinding reactants in the presence of activated barium hydroxide (C-200).[15]

Claisen-Schmidt condensation between substituted acetophenones and corresponding aldehydes using KOH/EtOH (72 hrs) was reported by Y.R. Lee *et al*. (2012), wherein, hydroxyl group protection is done viabenzopyran-6-yl-ethanone derivative preparation using catalyst ethylenediamine diacetate (EDDA), while, deprotection was done with Dowex 50X2 resin (68% yield).[16] Indole-based and quinolinyl chalcone derivatives synthesis have been reported with ultrasonic method.[17,18] Similarly, microwave irradiation methods have also been employed in heterocyclic chalcone synthesis.[19] Pd-catalyzed dehydrogenative cross-coupling reaction of (hetero)arenes with (hetero)aryl ethyl ketones has been developed by Y. Shang *et al*. (2013).[20] Whereas, O. K. Gataeva *et al.* (2014) proposed a Knoevenagel condensation of phenacylazides with the furfurals to give the azidochalcones using piperidine acetate at room temperature for 48 h.[21] Recently, rhodium (III)-catalyzed dehydrogenative Heck reaction[22] and phase transfer catalytic synthesis have also been reported.[23]

In another study, series of chromonyl chalcones from 3-formylchromones and different cyclic active methyl compounds, employing Zn(L-proline)$_2$ as a recyclable Lewis acid catalyst published, however, most of these routes require high cost.[24] Also, ring opening and polymerisation of chromenone nucleus takes place in alkaline conditions.[25] Therefore, acid catalysed Claisen-schmidt condensation has been proposed.

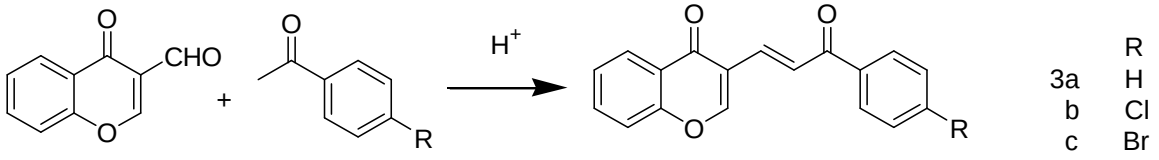
MATERIALS AND METHODS

Starting materials, reagents and solvents were purchased from commercial suppliers Aldrich Chemical Company (U.S.A) and purified/distilled/crystallized before use if found necessary.

A Bruker AVANCEII 400 NMR spectrometer was used to record the ^{1}H-NMR. Chemical shifts (δ) are reported as downfield displacements from TMS used as internal standard and coupling constants (*J*) are reported in Hz. Ion trap (Agilent) AP 2000 (SCIEX) spectrometer was also used to record the mass spectra. All melting points are uncorrected and measured in open glass-capillaries on a Veego (make) MP-D digital melting point apparatus. A SHIMADZU UV/VIS 1800 spectrophotometer was used for UV analysis. Weighing balance, (CY220) of Denver Instruments was used for weighing of compounds. TLC was performed on pre-coated silica gel G TLC plates.

General Procedure for Synthesis of Heterocyclic Chalcones

A mixture of 3-formyl-4H-chromen-4-one 1 (1.5 mol approx.) and acetophenone 2 (1 mol) were taken in a RBF. To this glacial acetic acid (10 ml) and one drop of perchloric acid were added and heated for few minutes (monitored by TLC, EthOAc: Hexane).



1 **2** **3**

Scheme 1

The reaction mixture was cooled to obtain the solid product. This was filtered, washed with distilled water and dried. It was further purified by crystallization or (eluent Hexane: EtOAc) to yield the desired products (3a-c). Purified products were characterized with the help of various spectral techniques (^{1}H NMR, ^{13}C-NMR, UV, IR and Mass Spectroscopy) (Scheme 1, Table 1).

Table 1: Reaction time and % yield of Heterocyclic Chalcones (3a-c).

S. No.	Compd.	R	Molecular weight	Reaction time(mins)	TLC Mobile Phase	Rf	Yield (%)	Melting point(^{0}C)
1	**3a**	H	276.08	9	EtOAc: Hexane :: 4:6	0.7	85	147-149
2	**3b**	Cl	310.04	15	EtOAc: Hexane :: 4:6	0.6	79	151-153
3	**3c**	Br	354.63	25	EtOAc: Hexane :: 4:6	0.6	70	178-180

Characterization

1-phenyl-3-(chromen-4-one-3-yl)-prop-2-en-1-one (3a)

Compound (**3a**) is light yellow solid; Yield: 85%; mp: 147-149^{o}C; UV (MeOH) λ_{max}: 215 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz) :δ 8.59 (d, 1H, *J* = 15.24 Hz, $C_{1'}$-H), 8.28 (dd, 1H, *J* = 8.04 Hz and 1.6 Hz, C_5-H), 8.22 (s, 1H, C_2-H), 7.92-7.89 (m, 2H, Ar-H), 7.75-7.72 (m, 1H, C_7-H), 7.55-7.51 (m, 3H, $C_{2'}$-H, C_6-H and C_8-H), 7.47 - 7.42 (m, 3H, Ar-H); ESI-MS: m/z 277.92 $[M + 1]^+$ (92.5%).

1-(4-chlorophenyl)-3-(chromen-4-one-3-yl)-prop-2-en-1-one (3b)

Compound (**3b**) is yellow solid; Yield: 79%; mp: 151-153^{o}C; UV (MeOH) λ_{max}: 242 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz) :δ 8.65 (d, 1H, *J* = 15.24 Hz, $C_{1'}$-H), 8.30 (dd, 1H, *J* = 8.04 Hz and 1.6 Hz, C_5-H), 8.22 (s, 1H, C_2-H), 7.96-7.93 (m, 2H, Ar-H), 7.75-7.71 (m, 1H, C_7-H), 7.56 - 7.52 (m, 2H, Ar-H), 7.50-7.46 (m, 3H, $C_{2'}$-H, C_6-H and C_8-H); ESI-MS: m/z 311.82 $[M + 1]^+$ (99.3%), 313.07 $[M + 1 + 2]^+$ (33.5%).

1-(4-bromophenyl)-3-(chromen-4-one-3-yl)-prop-2-en-1-one(3c)

Compound (**3c**) is yellow solid; Yield: 70%; mp: 178-180^{o}C; UV (MeOH) λ_{max}: 244 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz) :δ 8.66 (d, 1H, *J* = 15.24 Hz, $C_{1'}$-H), 8.31 (dd, 1H, *J* = 8.04 Hz and 1.6 Hz, C_5-H), 8.22 (s, 1H, C_2-H), 7.99-7.96 (m, 2H, Ar-H), 7.75-7.71 (m, 1H, C_7-H), 7.66 - 7.63 (m, 2H, Ar-H), 7.53-7.48 (m, 3H, $C_{2'}$-H, C_6-H and C_8-H); ESI-MS: m/z 355.91 $[M + 1]^+$ (52.5%), 357.93 $[M + 1 + 2]^+$ (54.4%).

RESULTS AND DISCUSSION

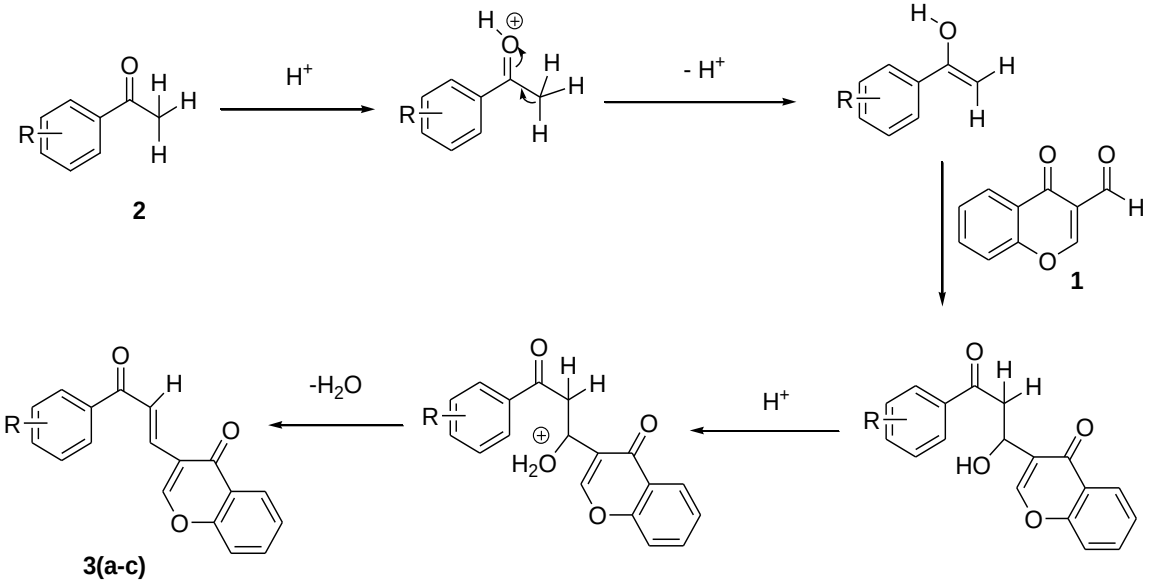
As illustrated in Scheme 1, the designed molecules were synthesized by the reaction of 3-formyl-4H-chromen-4-one derivative with acetophenones in acidic condition. Earlier the reactions were tried using Hydrochloric acid solution, dry HCl and $SOCl_2$, but none of these reagents yielded desired products in sufficient amount (Table 2). Therefore, the concerned reaction was carried out using perchloric acid and slight warming which produced the products in good yield only by filtration and re-crystallisation.

Table 2: Reaction %yield using different reagents

S. No.	Compd	R	%yield			
			HCl solution	Dry HCl	$SOCl_2$	perchloric acid
1	3a	H	26	35	30	85
2	3b	Cl	16	22	12	79
3	3c	Br	15	25	10	70

^{1}H-NMR spectra of all the synthesized compounds in common showed a downfield ^{1}H doublet for $C_{1'}$-H of propenone moiety at ~ δ8.6 ppm. Corresponding $C_{2'}$-H proton displayed ^{1}H doublet at ~δ7.4-7.5 ppm in all the compounds (appeared as a multiplet as merged with other peaks); *J* values for these doublets came out to be ~ 15.2 Hz which is a characteristic of the protons having *trans* configuration. This confirms the formation of chalcone system.

A plausible mechanism of synthesis of desired products **(3a-c)** is given in Scheme 2.



Scheme 2

This study has described the synthesis of heterocyclic chalcone derivatives, where, chromone heterocycle is incorporated in chalcone system. The synthetic route produce very less yield when reactions are carried out with strong acids and heat but when same reaction was carried out with superacid: perchloric acid with slight warming the reaction gives very good yield of desired products. This clearly specifies the efficacy of superacids to facilitate the reactions.

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