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RESEARCH ARTICLE

A MODIFIED CLAISEN-SCHMIDT PROTOCOL FOR SYNTHESIS OF 1,3-DIARYL-2-PROPEN-1-ONE (CHALCONE)

1#*Chowrasia Deepak; 1#Sharma Nisha; 2Arshad Md.; 3Viswanadham K.K Durga Rao

1. University Institute of Pharmacy, CSJM University, Kanpur, U.P.-208024, India
2. Moleular Endocrinology Lab, Department of Zoology, Lucknow University, Lucknow, U.P-226007, India
3. Pharmaceutics Division, CSIR-Central Drug Research Institute, Lucknow, U.P.-226031, India

Correspondence
Chowrasia Deepak University Institute of Pharmacy, CSJM University, Kanpur, U.P.-208024, India
Email Id: chowrasia.deepak@gmail.com

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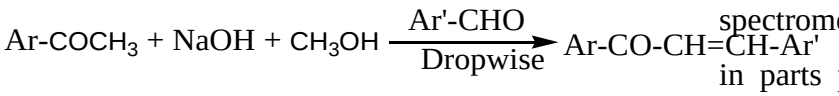
ABSTRACT

We here reports a modified improved method for synthesis of 1,3-diaryl-2-propen-1-one, rely on base catalyze condensation of arylmethyl ketone with aromatic aldehyde. This method however to an extent analogues to classical methodology thou minute changes in reactant charging sequence, prominent control over their dropping rate, and strict temperature regulation enhance its synthetic utility.

Introduction

1,3-diaryl-2-propen-1-ones (chalcone) are key pharmacophore in terms of pharmacological activities[1-11], acting as an universally accepted synthetic intermediate for yielding heteroaromatic ring systems as well as substituted steroidal derivatives[12-18]. Phytochemically, they are close conger (precursor) of bioactive flavonoid, isoflavonoids & their analogues, but unique among in terms of dual ring system connected each other via three carbon bridge enveloping keto-ethylenic moiety[19-21]. Generally occurs naturally, however extraction, isolation, and purification of these magical moiety employs tedious, time-consuming, complicated procedures, which are rarely comparable with synthetic procedure in terms of end product yield, purity, net reaction time, ease of procedure, & eco-handy technique. Thus numerous synthetic strategies were developed [22-26], each with their own pros & cons however utility of Claisen-Schmidt condensation (Scheme-01) is still undeniable as a synthetic feasible tool for this molecule.



Scheme-01

Adopting conventional Claisen-Schmidt procedure parallely in our lab we encountered problems such as prolong reaction time, excessive solvent requirement, sticky product formation, reaction failure, self condensation of ketonic-enolate, side reactions, impure product, & lower yield. Therefore in view of above restriction and our own intention towards synthesis of 1,3-diaryl-2-propen-1-one optimized various reaction parameters by blind shuffling the quantity of reactants, their time frame & sequence of charging, solvents, amount & nature of bases, reaction time, reaction temperature and thus ends-up our journey on an procedure extremely reliable both in terms of synthetic feasibility and eco-handy technique in synthesis of this molecule.

Materials & methods

All the reagents and solvents used in this experimentation are acquired from common store University Institute of Pharmacy, CSJM University, Kanpur, India and used as & their basis without any modification unless or until specified. The physiochemical & spectral properties of synthesized compounds were reported in table 02 & 03. ^{1}H NMR spectra were recorded with a Bruker Avence II 300 NMR spectrometer. The chemical shift were recorded in parts per million (ppm) and were reported relative to the TMS. Mass spectra data were recorded on Waters Q-TOF Premier-HAB213 system in ESI mode. The FT-IR spectra of synthesized compounds were recorded on PerkinElmer Spectrum version 10.03.06. The melting point was recorded by open capillary method and is uncorrected.

Experimental

Classical method[27]	**Modified method**	**General note**
Equimolar quantities (0.01M) of arylmethyl ketone & aromatic aldehydes were dissolved in ethanol (40ml) in a round bottom flask placed in ice bath. To this aqueous NaOH (10ml; 60%) were added dropwise with continuous stirring for 30-minutes. The mixing was continued for next 2-3 hrs at room temperature. The mixture was kept in refrigerator for overnight when it become quite thick. Then it was diluted with ice cold water, dried in air, and recrystallized from methanol.	In a clean conical flask (100ml), NaOH (10%; 5ml) was transferred followed by methanol (10ml). The flask was then immersed in an ice-chest and temperature was recorded with sensitive thermometer (50°C), once reading fixed at 0°C aromatic aldehyde (0.01M) was transferred; stirring initiated. Immediately, but slowly & steadily arylmethyl ketone (0.01M; 08-drops/min.) was dropped-in and stirring was continued while maintaining the reaction temperature not greater than 5°C. Soon reaction mixture becomes slightly yellowish color indicating reaction progression. Once addition was completed, ice-chest was replaced to cold water-bath (20°C), stirring resumed 2-hrs more. The content was refrigerated (if required) overnight, filtered off, and washed thoroughly from cold water and then from chilled ethanol. The product was air dried and washes from ethanol (10ml). Chalcone so obtained was sufficiently pure for further usage however its purity can be asses by thin layer chromatography (TLC) employing ethylacetate:petroleum ether in a ratio of 6:4.	*Reaction superiority* a. Required lesser amount of base & solvent compare to classical procedure for equal quantities of reactants. b. Condensation between enolates of arylmethyl ketone can be efficiently controlled. c. No problem of sticky product formation. e. Prevent side reactions. d. High quality product can be synthesized. e. Overall lesser reaction time. f. No need of intermittent reaction monitoring. g. Minimize reaction failure. h. Recrystallization may or may not be required. *Reaction limitation* a. Lethargy procedure. b.Drop-in rate of arylmethyl ketone must be optimum. c. Required strict control of reaction temperature.

Table 01

Results & discussion

A minor change in sequence of reactants charging, their dropping rate, and strict temperature control during overall reaction would yield a method highly versatile and reliable in terms of chalcone synthesis and its purity. Thus modified Claisen-Schmidt procedure (table 01) we herein reported is highly versatile, efficient, cost effective, and devoid of any reaction failure, side reactions, sticky product formation, inferior product yield, and purity problem comparatively (table 04). We also here suggest that this methodology is equally effective in synthetic procedure of various chalcones and their derivatives since this procedure enables an extraordinary command over generation and condensation of (nucleophile) with subsequent electrophile thereby enhance productivity along with purity gradification.

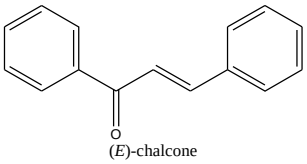
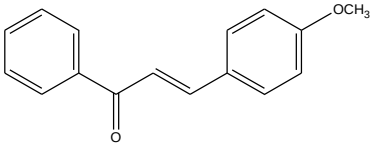
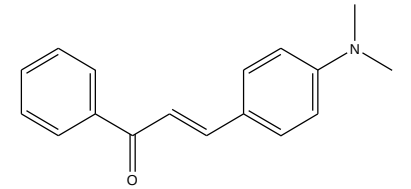
S. No	Reactants	Structure & chemical name	Formula & Mol. weight	Melting point (°C) Reported	Found	Yield (%)
01	Acetophenone & benzaldehyde	 (*E*)-chalcone	$C_{15}H_{12}O$; 208	56-57	57	87
02	Acetophenone & 4-Methoxy benzaldehyde	 (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one	$C_{16}H_{14}O_2$; 238	77-78	79	89
03	Acetophenone & 4-Dimethylamino benzaldehyde	 (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one	$C_{17}H_{17}NO$; 251	111-113	110	91

Table 02

S.No	Spectral data		
	IR (KBr) cm^{-1}	**NMR (δ, ppm)**	**Mass (m/e)**
01	3030 (CH-Ar), 1558 (C=O), 1598 (C=C)	7.7 (d 1Hα) 8.0 (1Hβ) 7.4-7.9 (m, 10H-Ar-H)	208
02	2955 (CH-Ar), 1658 (C=O), 1598 (C=C), 1111 ($-OCH_3$)	7 (d 1Hα) 8.1 (d,1Hβ) 6.4-8.1 (m, 9H-Ar-H), 3.6 (s, 3H, $-OCH_3$)	238
03	2906 (CH-Ar), 1661 (C=O), 1599 (C=C), 1313 (CN)	6.9 (d 1Hα) 8.0 (d,1Hβ) 7.0-7.5 (m, 9H-Ar-H), 2.6 (s, 6H, $-N(CH_3)_2$	251

Table 03

Reaction parameters	**Classical method**	**Modified method**
Reactants required	Aromatic ketone, aromatic aldehydes, & their substituted derivatives	Aromatic ketone, aromatic aldehydes, & their substituted derivatives
Reactants quantities	0.01M	0.01M
Reactant charging sequence	Both at same time	Aromatic aldehyde followed by aromatic ketone
Reactants charging rate	Not specified	Not more than 10-drops/min. incase aromatic ketone is liquid at room temperature and a pinch or slightly more if same exist as solid at room temperature

Base (Quantity & strength)	NaOH (10ml; 60%)	NaOH (5ml; 10%)
Solvent & its quantity	Ethanol; 40ml	Methanol; 10ml
Temperature control	Lacks specificity	Not greater than 5°C until addition of aromatic ketone & in-between15-20°C until completion of reaction
Reaction monitoring	Required	Required
Reaction time	210 min.	150 min.
Side reactions	Yes	No/least

Table 04

Conclusion

The modified Claisen-Schmidt reaction reported here can be used as an alternative for synthesis of chalcone owing to its superiority over classical method.

Conflict of interest

The authors declare they had no conflict of interest.

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