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A solvent-free protocol for the synthesis of fluorinated chalcone from formyl pyrazole as a green technique

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Abstract
Nine chalcones were prepared by grinding equimolar quantities of formyl pyrazole 3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde and various substituted o-hydroxy acetophenones in presence of potassium hydroxide in solvent free condition. This type of preparation method was found to be efficient, simple in terms of excellent yields, short reaction time and afford single product as illustrated in TLC. The prepared compounds were characterized by means of their IR, ^{1}H NMR spectral data and Mass spectrometry. This synthetic method shows potential alternative to the conventional methods.

Keywords: grinding, formyl pyrazole, chalcone, green synthesis

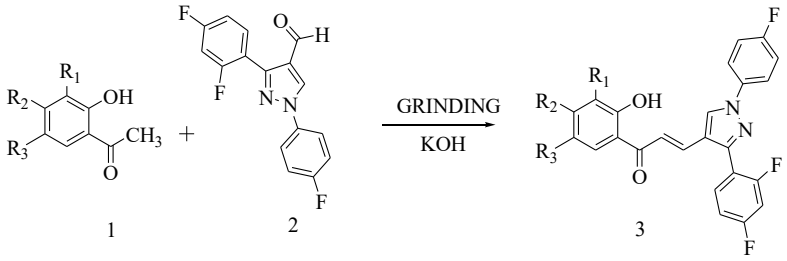
1. Introduction

The Green chemistry term is used in terms of the design and development of different chemical process to reduce or eliminate the employ and generation of chemicals harmful to the nature. In organic reactions, solvents used are often, expensive, toxic and disposal of such solvents is a serious threat to environment .Thus, design of solvent free organic synthesis has received tremendous attention in recent years. [1]

Chalcones are basically aromatic ketones that form the central core for a array of important biological compounds. Many heterocycles are synthesized from chalcones due the versatile nature of chalcone. Diverse biological activities like anti-ulcerative, anti-inflammatory, anti-viral analgesic, anti-fungal, anti-bacterial, anti-malarial and anticancer activities have been reported due to the backbone of chalcone [2-7] .Chalcone is the best synthons for the preparation of various heterocyclic compounds like pyridine, isoxazole, thiazine, oxazine, diazepine, pyrazole, pyrimidine. [8-9] Therefore, the preparation of chalcones continues to attract much attention in organic chemistry.

A number of methods have been reported for the synthesis of chalcones. The most commonly used method is the base- catalyzed Claisen Schmidt reaction of an aldehyde and methyl ketone using sodium hydroxide (NaOH),[10] potassium hydroxide (KOH),[11] barium hydroxide $Ba(OH)_2$[12] and lithium hydroxide ($LiOH\cdot H_2O$) [13].

Solvent free or solid state reaction may be carried out using the reactants alone or incorporating them in zeolites, clays, alumina, silica[14] . Herein, we report an atom efficient, a simple and eco-friendly method for the preparation of chalcones containing pyrazole ring. Nine chalcones were prepared by grinding equimolar quantities formyl pyrazole 3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde and various substituted o-hydroxy acetophenones in presence of potassium hydroxide in solvent free condition (scheme 1). All the nine compounds reported here were prepared in the absence of solvent and the reaction found to be simple, efficient in terms of short reaction time, excellent yields and afford single product as indicated in TLC.



Scheme 1: Synthesis of various substituted (*E*)-3-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one

Table-1: Physical data of compounds 3(a-i)

Compd.	R_1	R_2	R_3	M.P. (°C)	Conventional Method		Nonconventional Method	
					Time (hr)	Yield (%)	Time (min)	Yield (%)
3a	H	H	H	172-174	48	71	20	78
3b	H	H	CH_3	178-180	40	76	22	78
3c	H	H	Cl	194-196	40	60	24	65
3d	Cl	H	Cl	202-204	40	85	22	88
3e	H	H	F	200-202	40	62	22	69
3f	H	CH_3	Cl	138-140	40	64	26	70
3g	H	H	Br	226-228	40	76	24	80
3h	CH_3	H	CH_3	222-224	40	70	26	74
3i	H	H	OCH_3	214-216	40	72	26	72

Materials and Methods

Experimental

All the solvents and reagents used were of synthetic grade .The melting points were recorded in open capillary method and are uncorrected. IR spectra were recorded using FT-IR spectrophotometer. ^{1}H NMR spectrum was recorded using $CDCl_3$ on Bruker Avance (400 MHz) and their chemical shifts are recorded in δ (parts per million) units with respect to tetramethyl silane (TMS) as internal standard. Progress of the reactions was monitored using TLC, performed on precoated silica gel-60 F_{254} (Merck) plates using hexane-ethyl acetate (2:1, v/v) as solvent system.

Conventional Method

General procedure for the synthesis of (*E*)-1-(5-chloro-2-hydroxyphenyl)-3-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one (1c): A mixture of **1** (0.01 mol) and 2 (0.01 mol) was dissolved in 25 ml ethanol and contents were cooled to 0°C in ice bath. To this reaction mixture, powdered 1.5g KOH was added and temperature is maintained below 5°C. At room temperature the reaction mixture was stirred for 40hr. Then reaction mixture was diluted with water containing crushed ice and 2M HCl is added to acidify the mixture. Resulting product was separated by filtration and washed with ice cold water. Product was recrystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. Their physical data are given in **Table 1**.

Nonconventional Method

A mixture of 1 (0.01 mol) and 2 (0.01 mol) was mixed thoroughly then potassium hydroxide (1.5g) was added and ground with a pestle in an open mortar at room temperature for the time mentioned in **Table 1.**The mixture become solid and the solid broke up into small particles; the completion of the reaction was monitored by TLC. The reaction mixture containing solid product was poured over crushed ice and contents were acidified with 2M HCl. The product formed was washed with water to remove the traces of potassium hydroxide to give the corresponding chalcone. Product was crystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. Their physical data are given in **Table 1**.

Results

Spectral data of the synthesized compounds

IR (3c) (cm-1): 1067(C-Cl), 1230 (C-O), 1537 (C=C), 1585 (C=N), 1649 (C=O), 3139 (O-H).
1H-NMR (3c) (DMSO-d6) δ ppm: 6.9824-7.0045 (d, 1H, Ar-H, *J*=8.84 Hz), 7.1954-7.2624 (dd, 1H, Ar-H), 7.2938 7.3798 (m, 3H, Ar-H), 7.5034-7.5249 (d, 1H, Ar-H, *J*=8.6 Hz), 7.6216-7.6495 (d, 1H, CH=C-, *J*=11.16Hz), 7.6671-7.6874 (d, 1H, Ar- H, *J*=8.12 Hz), 7.8158-7.8538 (d, 1H, CH=C-, *J*=15.2 Hz), 7.9515-8.0784 (m, 3H, Ar- H), 9.4032 (s, 1H, pyrazole-H), 12.5869 (s, 1H, Ar–OH).
ES-MS (3c) (m/z): 455.38 (M+1), 457.40 (M+3).
IR (3f) (cm-1): 1059 (C-Cl), 1228 (C-O), 1536 (C=C), 1587 (C=N), 1651(C=O), 3143(O-H).
1H-NMR (3f) (DMSO-d6) δ ppm: 2.3618 (s, 3H, - CH_3), 7.0169 (s, 1H, Ar-H), 7.2683-7.3160 (m, 1H, Ar-H), 7.3784-7.4838 (m, 3H, Ar-H), 7.5039-7.5749 (m, 1H, Ar-H), 7.6628-7.7218 (dd, 1H, Ar-H, *J*=6.64 Hz & J=8.48 Hz), 7.8205-7.8589 (d, 1H, CH=C-, *J*=15.36 Hz), 7.9454-7.9570 (d, 1H, Ar-H, *J*=4.64 Hz), 7.9680-7.9797 (d, 1H, Ar-H, *J*=4.68 Hz), 8.0834 (s, 1H, Ar-H), 9.4339 (s, 1H, pyrazole-H), 12.5092 (s, 1H, Ar–OH).
ES-MS (3f) (m/z): 469.25 (M+1), 471.25 (M+3).

Discussion

The conventional preparation of chalcones from formyl pyrazole and various substituted o-hydroxy acetophenones involves dissolving the ketone in a basic ethanolic solution and this is subsequently added to an alcoholic solution of the pyrazole aldehyde that results in the formation of the product as a precipitate which is then neutralized with 2M HCl and washed with water several times and recrystallized from ethanol. We have found that grinding the reactants together in the presence of catalytic amount of potassium hydroxide, the aldol condensation proceeds as in solution by aggregating the reaction mixture using a mortar and pestle. Pyrazole aldehyde and various substituted o-hydroxy acetophenones upon the addition of KOH immediately turns yellow indicating the formation of enolate, upon gentle grinding the viscosity.

Conclusion

In conclusion, the method shown here is the eco-friendly, convenient, efficient and economical method for the preparation of heterocyclic chalcone and this method may be a shows potential alternative to the routine conventional methods.

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