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A novel approach to Claisen Schmidt reaction - H_2SO_4 catalyzed microwave assisted synthesis of nitrochalcones

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ABSTRACT

A simple and mild method for the synthesis of substituted nitrochalcones using sulfuric acid as catalyst in acetic acid under microwave irradiation is described. High yields of the corresponding nitrochalcones were obtained.

KEYWORDS

Claisen-schmidt reaction;
Chalcones;
Microwave irradiation.

INTRODUCTION

α, β -Unsaturated ketones, especially 1,3-diarylprop-2-en-1-ones; commonly known as chalcones; have received much attention in medicinal chemistry. Chalcones are important owing to their biological properties, besides serving as precursors for the synthesis of a large number of heterocyclic systems such as aminopyrimidines, pyrazolines and isoxazolines[1]. Recent studies on biological evaluation of chalcones revealed some to be anti-cancer, anti-inflammatory, antimitotic, antimalarial and antileishmanial agents[2-6]. These findings explain significant interest of chemists, biochemists and pharmacologists in this particular group of compounds.

Many conventional methods are available for the synthesis of chalcones, the most widely used method is base catalyzed claisen–schmidt reaction in which condensation of a ketone with an aldehyde is carried out in presence of aq NaOH[7], KOH[8], $Ba(OH)_2$[9] The acid catalyzed methodologies include use of $AlCl_3$[10], $SOCl_2$/EtOH[11] and dry HCl[12]. In microwave methods, chalcones were reported to be prepared by using sodium hydroxide[13] and lithium chloride[14]. Most of these methods have disadvantages viz. longer reaction time, harsh reaction conditions with high probability of side reactions such as Cannizzaro reaction[15] or Aldol condensation and often from low yields[16], indicating that there is still scope for simpler and high yielding approaches towards this nucleus.

The use of microwaves in organic synthesis[17] has attracted considerable attention in recent years. It is emerging green technology that makes experimentally and industrially important organic synthesis more effectively and more eco-friendly than conventional reactions[18,19], hence we tried to exploit the microwave condition for the synthesis of nitrochalcones.

RESULTS AND DISCUSSION

For our initial study we selected 4-nitro acetophenone (1 equiv) and arylaldehydes (1 equiv) as model substrate and carried out reaction at room temperature using sulfuric acid (1 equiv) in acetic acid. We observed that, this system requires long reaction time (24-36 hrs.) to yield corresponding chalcone and the yield was poor

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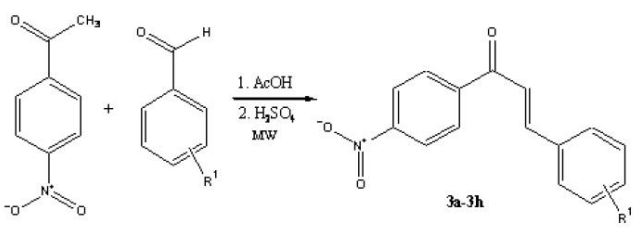
hence we tried to determine the best chalcone to sulfuric acid ratio. With this aim we carried out the synthesis of chalcone 3a using different equivalents of sulfuric acid with chalcones (*r*=1/1, 1/2, 1/3, 1/4, 1/5 etc.). The yields obtained after 24 hrs. of reaction (46, 58, 78, 70 and 67% respectively) show that sulfuric acid in the ratio of 1/3 to the chalcone was the optimal composition. Yields of corresponding chalcones using conventional method were poor and requiring long reaction time; therefore, we performed same condensation using catalyst scientific microwave oven with above equivalents of reactant and three equivalents of sulfuric acid as a catalyst in acetic acid at different power levels as well as temperatures. However; better results were obtained using equimolar ratios of 4-nitroacetophenone, arylaldehydes and three moles of sulfuric acid at 110 ^{0}C using microwave oven. By using sulfuric acid in acetic acid under microwave irradiation, we obtained chalcones exclusively within 1-10 min and moreover; we did not observe any side reactions. Thereafter, we carried out synthesis of several chalcones 3b-3h (Scheme-1) using 1/3 molar ratio of sulfuric acid to the chalcones (TABLE 1). All products were isolated, purified and analyzed by IR, ^{1}HNMR and some were confirmed by comparison of their Mps and spectral data (high-field 1H and 13C NMR spectra) with those of authentic samples[20-21].

TABLE 1: Synthesis of nitrochalcone derivatives using sulfuric acid using microwave

3	R^1	Reaction Time (mins.)	Yield (%)[a]	Mp °C (lit. Mp)
a	H	3.1	95	146-147 (146)
b	4-OCH_3	3.4	89.94	191-193 (192-194)
c	2-Cl	1.2	93.65	210-213 (213)
d	4-N-dimethylamino	4.5	88.00	212-214 (214)
e	4-NO_2	2.3	91.35	176-177 (175-178)
f	4-Cl	2.5	93.00	121-134
g	2-Furfuraldehyde	3.3	86.95	167-168
h	3,5-dimethoxy	2.5	91.24	165-167 (165-166)

a. Isolated yields. Structures of isolated products 3b, 3c, 3d, 3e and 3h were confirmed by comparison of their Mps and spectral data (high-field 1H and 13C NMR spectra) with those of authentic samples



Scheme 1 : General Route for synthesis of nitrochalcone derivatives

EXPERIMENTAL

Melting points were determined in open capillary tube using Elico Melting Point Apparatus and were uncorrected. IR spectra of compounds were recorded on 'Schimadzu IR 48' Spectrophotometer. ^{1}HNMR spectra on BROOT Spectrophotometer using duteriochloroform as solvent and tetramethylsilane as an internal standard. These reactions were performed using a scientific microwave oven (Catalyst electromagnetic System) with a power of 800W specially designed for organic synthesis.

Typical procedure for the preparation of 1-(4-nitrophenyl)- 3-phenyl-2-propene-1-one 3a is described as an example

A 100ml two-necked round bottomed flask equipped with a magnetic stirrer bar was charged with 4-nitroacetophenone (1 equiv), benzaldehyde (1 equiv) and glacial acetic acid 20 ml. To it concentrated H_2SO_4 (3 equiv) was added and the reaction mixture irradiated under microwave at 110 ^{0}C for few seconds. Reaction progress was monitored by TLC. When TLC shows nearly complete conversion to the corresponding chalcones, the precipitate formed was filtered off and washed with sodium bicarbonate solution and copious volume of water afforded 1-(4-nitrophenyl)-3-phenyl-2-propene-1-one (3a) in 95 % yield, Mp 146-147°C. The Product was recrystalized from ethanol.

(a) Spectral data for 1-(4-nitrophenyl)-3-phenyl-2-propene-1-one 3a

I.R. (KBr Pellets): 1680, 1597, 1516, 1334 (cm^{-1}); ^{1}H NMR ($CDCl_3$): δ (ppm) 8.37-834(d, 2H), 8.16 -8.13(d, 2H), 7.69 (d,1H), 7.844 (d, 1H), 7.51-7.44 (m, 5H).

(b) Spectral data for 1-(4-nitrophenyl)-3-(4-chlorophenyl)-2-propene-1-one 3f

I.R. (KBr Pellets): 1665, 1605, 1517, 1332 (cm^{-1}); ^{1}H NMR ($CDCl_3$): δ (ppm) 7.27-7.71(m, 6H, Ar-H, H-2 and H-3), 7.98-8.46(m, 4H).

(c) Spectral data for 1-(4-nitrophenyl)-3-(2-furfuryl)-2-propene-1-one 3g

I.R. (KBr Pellets): 1696, 1661, 1597, 1321 (cm^{-1}); ^1H NMR ($CDCl_3$): δ (ppm) 8.36 -8.33(d, 2H), 6.9 -6.5 (m, 3H), 7.61(d, 1H), 7.38(d, 1H).

CONCLUSION

A novel method has been developed for substituted nitrochalcones by condensation of 4-nitroacetophenone and substituted arylaldehydes using catalytic amount of sulfuric acid in acetic acid under microwave irradiation with advantages like simple work- up, shorter reaction times, no side reactions and high yields.

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