



MICROWAVE-ASSISTED SYNTHESIS OF SOME HALO-SUBSTITUTED CHALCONES

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Abstract

An efficient microwave-assisted synthesis of halosubstituted chalcones were presented by the condensation of halosubstituted ketones and substituted aldehydes. These reactions were found to be economically cheap in comparison with classical synthesis.

Keywords: Synthesis, halosubstituted chalcones, microwave technique.

1. Introduction

Microwave organic reaction enhancement (MORE) has captured the interest of researchers as a non-conventional technique towards the rapid synthesis of novel biological compounds [1]. Many researchers have described accelerated organic reactions towards proving the synthetic utility of MORE chemistry in routine organic synthesis. It can be termed as '4e-chemistry' because it is easy, effective, economical, and eco-friendly and is believed to be a step towards green chemistry [2].

The presence of α , β - unsaturated carbonyl compounds is one of the main structural components in various naturally occurring biologically active substances known as chalcones, analogs of 1,3-diarylprop-2-ene-1-one form a wide class of compounds containing two aromatic rings bound with vinyl ketone fragment. It is well known that most natural or synthetic chalcones are highly active with extensive pharmaceutical and medicinal applications. Chalcones are found to be effective as antitumor [3], anticancer [4], antibacterial [5], antioxidant [6], antileishmanial [7], cytotoxicity [8], antiproliferative [9], anti-inflammatory [10], antimicrobial [11], tyrosinase inhibitory [12], and insecticidal [13] activities.

In view of application of microwave organic reaction enhancement chemistry and importance of chalcones, we plan to synthesize some novel halo-substituted chalcones. The condensation of 1-(1-hydroxy-4-halonaphthalen-2-yl)ethanone and differently substituted aromatic aldehydes using mild basic conditions under microwave irradiation gives halo-substituted chalcones (Scheme 1).

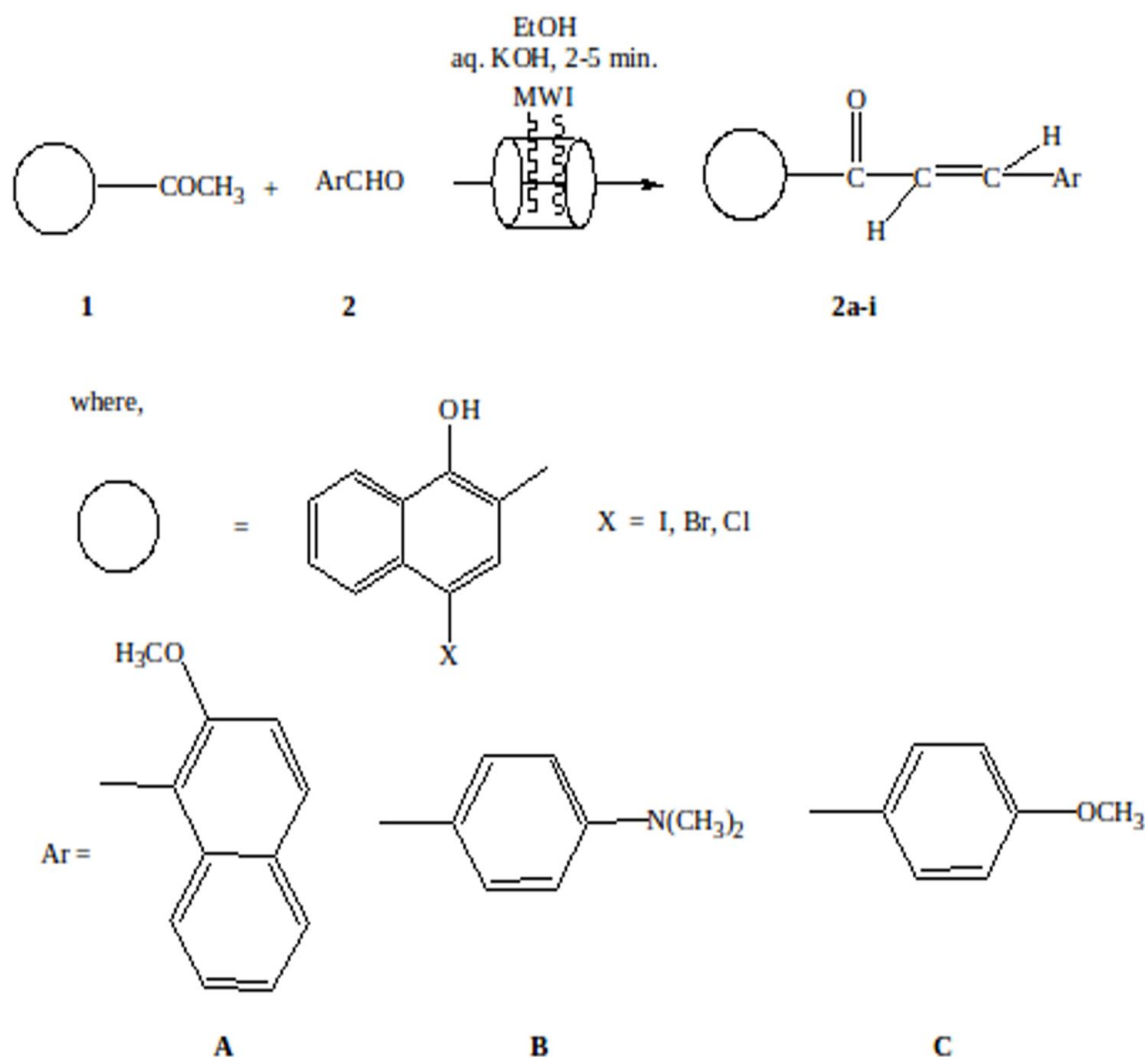
2. Materials and Methods

2.1. Chemicals and apparatus

Melting points were uncorrected and determined in an open capillary tube. FT-IR spectra were recorded on FT-IR Shimadzu spectrometer. $^1\text{H-NMR}$ spectra were recorded in CDCl_3 on an Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer. Synthos-3000, Anton Paar reaction system was used for microwave syntheses.

2.2. Typical procedure for synthesis of chalcones

An equimolar mixture of 1 and 2 were dissolved in 15 mL of ethanol with stirring and the aqueous solution of potassium hydroxide (50% 10 mL) was added drop wise. Resulting reaction mixtures were irradiated in microwave for 2-5 minutes, with a short interval of time for 10 sec. to avoid evaporation of excess solvent. Reaction progress was monitored on TLC using n-hexane/ethyl acetate/petroleum ether combination (1:1:1, v/v/v) as the mobile phase. On completion of reaction, the reaction mixture was diluted with cold water and acidified with 10% HCl. The separated solid was filtered and crystallized from a mixture of ethanol and DMF to obtain the pure samples **2a-i**.



Scheme 1. Microwave-assisted synthesis of chalcones.

1-(1-Hydroxy-4-iodonaphthalen-2-yl)-3-(2-methoxynaphthalen-1-yl) propenone, **2a**: FT-IR (KBr, ν , cm^{-1}): 3410 (OH), 1630 (C=O), 1455, 1550 (C=C), 1278 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6 , δ , ppm): 11.8 (s, 1H, OH), 6.7-7.4 (m, 11H, ArH), 6.9 (d, $J=16$ Hz, 1H, H_α), 7.6 (d, $J=16$ Hz, 1H, H_β), 3.8 (s, 3H, OCH₃). (EI, m/z (%): 480 (M^+ , 42%). Anal. calcd. for C₂₄H₁₇IO₃: C, 60.0; H, 3.54; I, 26.45. Found: C, 60.13; H, 3.57; I, 26.56.

1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(2-methoxynaphthalen-1-yl) propenone, **2b**: FT-IR (KBr, ν , cm^{-1}): 3412 (OH), 1633 (C=O), 1467, 1542 (C=C), 1274 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.4 (m, 11H, ArH), 6.8 (d, $J=16.5$ Hz, 1H, H_α), 7.6 (d, $J=16$ Hz, 1H, H_β), 3.9 (s, 3H, OCH₃). (EI, m/z (%): 433 (M^+ , 70%). Anal. calcd. for C₂₄H₁₇BrO₃: C, 66.51; H, 3.92; Br, 18.47. Found: C, 66.62; H, 3.90; Br, 18.46.

1-(4-Chloro-1-hydroxynaphthalen-2-yl)-3-(2-methoxynaphthalen-1-yl) propenone, **2c**: FT-IR (KBr, ν , cm^{-1}): 3412 (OH), 1634 (C=O), 1470, 1557 (C=C), 1276 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO- d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.4 (m, 11H, ArH), 6.9 (d, $J=16$ Hz, 1H, H_α), 7.7 (d, $J=16.5$ Hz, 1H, H_β), 3.8 (s, 3H, OCH₃). (EI, m/z (%): 388 (M^+ , 63%). Anal. calcd. for C₂₄H₁₇ClO₃: C, 74.22; H, 4.38; Cl, 9.02. Found: C, 74.27; H, 4.40; Cl, 8.98.

3-(4-Dimethylaminophenyl)-1-(1-hydroxy-4-iodonaphthalen-2-yl)propenone, **2d**: FT-IR (KBr, ν , cm^{-1}): 3416 (OH), 1629 (C=O), 1448, 1578 (C=C), 1275 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.8 (s, 1H, OH), 6.7-7.3 (m, 9H, ArH), 6.9 (d, $J=16$ Hz, 1H, H_α), 7.6 (d, $J=16$ Hz, 1H, H_β), 3.3 (s, 6H, two CH_3). (EI, m/z (%): 443 (M^+ , 60%). Anal. calcd. for $\text{C}_{21}\text{H}_{18}\text{INO}_2$: C, 56.88; H, 4.06, I, 28.66. found: C, 56.96; H, 4.10; I, 28.71.

1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(4-dimethylaminophenyl)propenone, **2e**: FT-IR (KBr, ν , cm^{-1}): 3414 (OH), 1629 (C=O), 1443, 1575 (C=C), 1272 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.8 (s, 1H, OH), 6.7-7.3 (m, 9H, ArH), 6.8 (d, $J=16$ Hz, 1H, H_α), 7.6 (d, $J=16.5$ Hz, 1H, H_β), 3.3 (s, 6H, two CH_3). (EI, m/z (%): 396 (M^+ , 82%). Anal. calcd. for $\text{C}_{21}\text{H}_{18}\text{BrNO}_2$: C, 63.63; H, 4.54; Br, 20.28. Found: C, 63.67; H, 4.58; Br, 20.24.

1-(4-Chloro-1-hydroxynaphthalen-2-yl)-3-(4-dimethylaminophenyl)propenone, **2f**: FT-IR (KBr, ν , cm^{-1}): 3415 (OH), 1629 (C=O), 1452, 1572 (C=C), 1274 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.4 (m, 9H, ArH), 6.9 (d, $J=16.5$ Hz, 1H, H_α), 7.6 (d, $J=16.5$ Hz, 1H, H_β), 3.3 (s, 6H, two CH_3). (EI, m/z (%): 351 (M^+ , 70%). Anal. calcd. for $\text{C}_{21}\text{H}_{18}\text{ClNO}_2$: C, 71.79; H, 5.12; Cl, 9.97. Found: C, 71.83; H, 5.15; Cl, 9.94.

1-(1-Hydroxy-4-iodonaphthalen-2-yl)-3-(4-methoxyphenyl)propenone, **2g**: FT-IR (KBr, ν , cm^{-1}): 3412 (OH), 1631 (C=O), 1450, 1565 (C=C), 1270 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.3 (m, 9H, ArH), 6.9 (d, $J=16.5$ Hz, 1H, H_α), 7.6 (d, $J=16.5$ Hz, 1H, H_β), 3.9 (s, 3H, OCH_3). (EI, m/z (%): 430 (M^+ , 85%). Anal. calcd. for $\text{C}_{20}\text{H}_{15}\text{INO}_3$: C, 55.81; H, 3.48; I, 29.53. Found: C, 55.78; H, 3.51; I, 29.57.

1-(4-Bromo-1-hydroxynaphthalen-2-yl)-3-(4-methoxyphenyl)propenone, **2h**: FT-IR (KBr, ν , cm^{-1}): 3414 (OH), 1634 (C=O), 1457, 1562 (C=C), 1271 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.3 (m, 9H, ArH), 6.9 (d, $J=16.5$ Hz, 1H, H_α), 7.6 (d, $J=16.5$ Hz, 1H, H_β), 3.8 (s, 3H, OCH_3). (EI, m/z (%): 383 (M^+ , 58%). Anal. calcd. for $\text{C}_{20}\text{H}_{15}\text{BrNO}_3$: C, 62.66; H, 3.91; Br, 20.88. Found: C, 62.62; H, 3.94; Br, 20.84.

1-(4-Chloro-1-hydroxynaphthalen-2-yl)-3-(4-methoxyphenyl)propenone, **2i**: FT-IR (KBr, ν , cm^{-1}): 3416 (OH), 1634 (C=O), 1462, 1570 (C=C), 1273 (C-O-C). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , δ , ppm): 11.9 (s, 1H, OH), 6.7-7.3 (m, 9H, ArH), 6.9 (d, $J=16.5$ Hz, 1H, H_α), 7.6 (d, $J=16.5$ Hz, 1H, H_β), 3.8 (s, 3H, OCH_3). (EI, m/z (%): 339 (M^+ , 58%). Anal. calcd. for $\text{C}_{20}\text{H}_{15}\text{ClNO}_3$: C, 70.79; H, 4.42; Cl, 10.32. Found: C, 70.87; H, 4.47; Cl, 10.39.

3. Results and Discussion

The classical Claisen-Schmidt condensation synthesis of chalcones involves aldehyde reacted with acetophenone in the presence of aqueous bases, $\text{Ba}(\text{OH})_2$ / LiOH [14, 15]. Chalcones are also synthesized by using microwave irradiation, ultrasound irradiation [16] and by Suzuki reaction [17]. Various modified methods for synthesis of chalcones has been reported using different catalyst such as SOCl_2 [18], natural phosphate / lithium nitrate [19], KF / natural phosphate [20], acyclic acidic ionic liquid [21], Na_2CO_3 [22], high-temperature water [23], sodium carbonate [24], ZrCl_4 and ionic liquid [25],

silica-sulfuric acid [26], NaOH / Al₂O₃ [27], and silica chloride [28].

Table 1. Microwave assisted synthesis of halosubstituted chalcones, **2a-i**.

Compound	Color	Conventional	Method ^a	Microwave	Method ^b	Melting Point (°C)
		Time (h)	Yield (%)	Time (min)	Yield (%)	
2a	Yellow	14	68	2	90	143-147
2b	Yellow	14	72	4	87	137-139
2c	Yellow	12	70	5	91	153-156
2d	Orange	14	65	4	85	163-165
2e	Red	12	67	3	82	160-162
2f	Red	14	70	5	84	155-157
2g	Yellow	12	74	4	88	167-169
2h	Yellow	13	72	3	90	146-148
2i	Orange	12	67	4	86	173-175

A classical synthesis of these compounds involves the condensation of acetophenones and aldehydes to give chalcones. The combination of solvents and long reaction time, costly chemicals / catalyst makes this method environmentally hazardous. This provided the stimulus to synthesize some new chalcones using microwave irradiation technique [29]. Microwave irradiation has been used to accelerate organic reactions because of high heating efficiency, providing remarkable rate enhancement, dramatic reduction in reaction times with improvement in yield and quality of products. Reactions that require hours or even days by conventional heating can often be accomplished in seconds or minutes by microwave heating [30]. Initially, we attempted the condensation of 1-(1-hydroxy-4-iodonaphthalen-2-yl)ethanone (**1**) with 2-methoxy-naphthalene-1-carbaldehyde (**2**) using an aqueous solution of KOH in ethanol as the reaction solvent. The reaction went to completion within 2 minutes and the corresponding product **2a** was obtained in 90% yield.

In order to optimize the reaction conditions, we carried out the same condensation reaction using conventional Claisen-Schmidt method [11]. We found that microwave technique [30] has several advantages including clean reaction conditions, not expensive nature, yields and environmentally eco-friendliness. The structures of newly synthesized compounds **2a-i** were established on the basis of spectroscopic data and elemental analysis. In the FT-IR spectra of condensed products, it displays the absorption band near 1632 cm⁻¹ due to α,β -unsaturated carbonyl stretching. The ¹H-NMR spectroscopic analysis display the singlet due to -OH proton appears at δ 11.9 ppm. The α,β -unsaturated olefinic proton shows trans configuration with J value 16.5 Hz and display a doublet near δ 6.9 for H _{α} and δ 7.6 for H _{β} .

4. Conclusion

In summary, we have carried out a simple Claisen-Schmidt condensation between halo-substituted ketones with different aldehydes using aq. KOH under microwave irradiation technique. The advantages of present protocol are simplicity of operation, time saving, high yields of products, avoidance of expensive catalyst, and usage of volatile organic solvent.

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