Microwave-induced, Iodine-alumina catalyzed transformations of 1-(2'-hydroxyaryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one

P. VENKATESAN* and K. MOORTHY

Dept. of chemistry, Mahendra Institute of Technology, Namakkal – 637503

*Email: venkatesanps@yahoo.co.in

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Abstract: The chalcone derivatives, 1-(2'-hydroxyaryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one was transformed to corresponding flavone derivatives by iodine impregnated neutral alumina under microwave irradiation. The synthesized flavone derivatives were structurally confirmed by elemental analysis, UV, IR and ¹H-NMR spectral data, and the notable yield obtained was compared with previously reported method.

Keywords: Chalcone, Flavone, I₂-Al₂O₃, Solvent-free synthesis.

Introduction

Flavones (2-phenylchromones) is building block of many organic compounds and reported to show useful biological activities¹ such as leishmanicidal activity, oviposter stimulant, anti HIV, vasodilator, antiviral, antioxidants, bactericidal, DNA cleavage, anti-inflammatory, anti-mutagenic and anticancer. Substituted flavones like amino flavones have been studied as tyrosine kinase inhibitors and as anti-mitotic agents². Most of the flavones are synthesized by oxidative cyclization of 2'-hydroxy chalcones³, by the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione⁴, by auwers methods⁵ and via intermolecular Witting reaction⁶.

It has been observed that the substitution of five or six member heterocyclic group in C-2 position instead of phenyl group improves the biological activity of flavones⁷⁻⁹. Similarly, microwave (MW) irradiation is an efficient and environmentally-benign method to activate various organic transformations to afford products in higher yields in shorter reaction periods. Owing to its immense importance, we planned to synthesize new substituted flavone derivative, which was catalyzed by iodine impregnated neutral alumina (Al₂O₃) under microwave irradiation.

Experimental

All the common chemicals were obtained from Merck chemical company, SD fine chemicals and Sigma-Aldrich chemicals, India. The chalcone (**3a-e**) were prepared according to the procedure stated already.¹⁰

A Samsung domestic microwave oven was used at 400W power level for all the experiments. TLC was carried out using and spotting was done using iodine or UV light. Melting points of synthesized compounds were determined in open glass capillaries and were uncorrected.

UV spectra were recorded using Perkin-Elmer 402 UV-vis spectrophotometer. IR spectra were recorded on Perkin-Elmer 577 IR spectrophotometer using KBr pellets. ¹H spectra were recorded on Bruker 300 MHz NMR Spectrometer in CDCl₃ with tetramethyl silane as the internal standard and the chemical shifts were reported in ppm scale. Mass spectra were studied using Finnigan MAT 8230 mass spectrometer. Elemental analysis were done on Vario EL-III elemental analyzer and the analyzed reports were within ± 0.4 % of the theoretical values.

Synthesis of heterogeneous catalyst I₂-Al₂O₃

2.538 g (10 mmol) iodine was dissolved in minimum quantity of solvent dichloro methane. Then, 25 gm of neutral was added to iodine solution to adsorb. The mixture was air dried and stored in glass bottle until use.

Synthesis of 2-(2-Chloroquinolin-3-yl)-4H-chromen-4-one derivative (4a-e)

A mixture of 1-(2'-hydroxy-aryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (0.01 mol, **3a-e**) and 0.25 g of I₂-Al₂O₃ catalyst was irradiated in a microwave oven (400W) for appropriate time (3 to 5 min). After completion of reaction as monitored by TLC, the mixture was cooled, diluted with ethyl acetate and filtered to separate insoluble Al₂O₃. The filtrate was washed with a dilute solution of sodium thiosulphate to remove iodine and subsequently with water. After evaporation of ethyl acetate, the crude was purified by column chromatography hexane: ethyl acetate (9:1) eluent to afford pure 2-(2-Chloroquinolin-3-yl)-4H-chromen-4-one derivative (**4a-e**).

2-(2-Chloroquinolin-3-yl)-7-methoxy-4H-chromen-4-one (4a): Yellow solid; m.p. 110-112 °C; λ_{max} (CHCl₃, nm): 271, 382; IR (KBr, ν_{max} , cm⁻¹): 3166 (ArCH), 1672 (C=O), 1578 (C=N), 1238 and 1021 (C-O str), 731 (ArCl); ¹H NMR (300 MHz, CDCl₃): δ 3.85 (s, 3H, 7-OCH₃), 6.66-6.84 (m, 3H, 5-, 6- and 8-H), 6.56 (s, 1H, 3-H), 8.16-8.48 (m, 4H, 5'-, 6'-, 7'- and 8'-H), 8.81 (s, 1H, 4'-H); m/z: 338 (M⁺+1); Anal. calcd. (%) for C₁₉H₁₂NO₃Cl: C, 67.56; H, 3.58; N, 4.15. Found (%) C, 67.51; H, 3.57; N, 4.14.

2-(2-Chloroquinolin-3-yl)-6-methoxy-4H-chromen-4-one (4b): Pale yellow solid; m.p. 112-114 °C; λ_{max} (CHCl₃, nm): 271, 376; IR (KBr, ν_{max} , cm⁻¹): 3162 (ArCH), 1672 (C=O), 1582 (C=N), 1242 and 1026 (C-O str), 732 (ArCl); ¹H NMR (300 MHz, CDCl₃): δ 3.76 (s, 3H, 6-OCH₃), 6.74-6.96 (m, 3H, 5-, 7- and 8-H), 6.54 (s, 1H, 3-H), 8.22-8.44 (m, 4H, 5'-, 6'-, 7'- and 8'-H), 8.86 (s, 1H, 4'-H); m/z: 338 (M⁺+1); Anal. calcd. (%) for C₁₉H₁₂NO₃Cl: C, 67.56; H, 3.58; N, 4.15. Found (%) C, 67.54; H, 3.59; N, 4.13.

2-(2-Chloroquinolin-3-yl)-7,8-dimethoxy-4H-chromen-4-one (4c): Yellow solid; m.p. 108-110 °C; $\lambda_{\max}$ (CHCl₃, nm): 269, 358; IR (KBr, $\nu_{\max}$, cm⁻¹): 3184 (ArCH), 1674 (C=O), 1574 (C=N), 1241 and 1024 (C-O str), 732 (ArCl); ¹H NMR (300 MHz, CDCl₃): δ 3.77 (s, 3H, 8-OCH₃), 3.86 (s, 3H, 7-OCH₃), 6.58-6.82 (m, 2H, 5- and 6-H), 6.41 (s, 1H, 3-H), 8.25-8.57 (m, 4H, 5', 6', 7'- and 8'-H), 8.84 (s, 1H, 4'-H); m/z: 368 (M⁺⁺1); anal. calcd. (%) for C₂₀H₁₄NO₄Cl: C, 65.31; H, 3.84; N, 3.81. Found (%) C, 65.35; H, 3.83; N, 3.80.

2-(2-Chloroquinolin-3-yl)-5,7,8-trimethoxy-4H-chromen-4-one (4d): Yellow solid; m.p. 106-108 °C; $\lambda_{\max}$ (CHCl₃, nm): 267, 374; IR (KBr, $\nu_{\max}$, cm⁻¹): 3178 (ArCH), 1676 (C=O), 1576 (C=N), 1239 and 1028 (C-O str), 730 (ArCl); ¹H NMR (300 MHz, CDCl₃): δ 3.74 (s, 3H, 8-OCH₃), 3.86 (s, 3H, 5-OCH₃), 3.91 (s, 3H, 7-OCH₃), 6.89 (s, 1H, 6-H), 6.56 (s, 1H, 3-H), 8.18-8.52 (m, 5', 6', 7'- and 8'-H), 8.88 (s, 1H, 4'-H); m/z: 398 (M⁺⁺1); Anal. calcd. (%) for C₂₁H₁₆NO₅Cl: C, 63.40; H, 4.05; N, 3.52. Found (%) C, 63.44; H, 4.05; N, 3.54.

2-(2-Chloroquinolin-3-yl)-5,7-dimethoxy-4H-chromen-4-one (4e): Pale yellow solid; m.p. 102-104 °C; $\lambda_{\max}$ (CHCl₃, nm): 274, 386; IR (KBr, $\nu_{\max}$, cm⁻¹): 3182 (ArCH), 1672 (C=O), 1577 (C=N), 1241 and 1025 (C-O str), 732 (ArCl); ¹H NMR (300 MHz, CDCl₃): δ 3.74 (s, 3H, 5-OCH₃), 3.92 (s, 3H, 7-OCH₃), 6.52-6.96 (m, 2H, 6- and 8-H), 6.44 (s, 1H, 3-H), 8.24-8.46 (m, 4H, 5', 6', 7'- and 8'-H), 8.84 (s, 1H, 4'-H); m/z: 368 (M⁺⁺1); Anal. calcd. (%) for C₂₀H₁₄NO₄Cl: C, 65.31; H, 3.84; N, 3.81. Found (%) C, 65.33; H, 3.83; N, 3.81.

Results and Discussion

Our earlier work¹⁰ described the synthesis of the chalcone, 1-(2'-hydroxyaryl)-3-(2-chloroquinolin-3-yl)-prop-2-en-1-one (**3a-e**) by piperidine mediated Claisen-Schmidt condensation method as shown in Scheme 1.

Scheme 1. Synthesis of Chalcone derivatives (**3a-e**).

The IR spectra of compounds **3a-e** gave absorption about $1654\text{--}1630\text{ cm}^{-1}$ for the unsaturated keto group and absorption about $3436\text{--}3431\text{ cm}^{-1}$ for the presence of hydroxyl group. In addition, The ^1H NMR spectra gave two doublet centred about δ 7.6 ppm and δ 8.2 ppm with coupling constant about $J = 15\text{ Hz}$ were assigned to the *trans* olefinic proton at C_α and C_β position. The ^1H NMR signal about δ 14 ppm indicating the presence of hydroxyl group.

On oxidative cyclization of 2'-hydroxy chalcone using iodine impregnated neutral alumina under microwave irradiation, corresponding flavone derivatives **4a-e** were obtained in shorter reaction time as shown in Scheme 2.

Scheme 2. Synthesis of Flavone derivatives (**4a-e**).

The UV-vis absorption spectrum of the compounds **4a-e** in CHCl_3 showed λ_{max} at 265–275 nm and 358–386 nm indicating the presence of flavone moiety. IR spectra of compounds **4a-e** showed the absorption at $1664\text{--}1668\text{ cm}^{-1}$ for carbonyl groups and absence of hydroxyl absorption confirmed the oxidation of hydroxyl groups in chalcones **3a-e**. It was further supported by not observing corresponding ^1H NMR signals. The C-3 proton gave singlet about δ 6.42–6.44 ppm for the compounds **4a-e** showed that the $\text{C}_\beta\text{-H}$ of corresponding chalcone involved in cyclization of chalcone to form corresponding flavone. The entire mass spectral data and elemental analysis data were in accordance with the structure of expected compounds **4a-e** and they were given in experimental part.

On comparison of physical data, synthesis of compounds **4a-e** catalyzed by $\text{I}_2/\text{Alumina}$ under microwave condition gives comparably high yield with short time among the other conventional methods¹¹, and the physical data were given as given in Table 1.

Table 1. Physical Data of Flavone derivatives, 4a-e.

Compd.	m.p. (°C)	DDQ (Reflux) [Time*/ Yield [#]]	DMSO/I ₂ (Reflux) [Time*/ Yield [#]]	I ₂ /Al ₂ O ₃ (Reflux) [Time*/ Yield [#]]	I ₂ /Al ₂ O ₃ (MW) [Time ^s / Yield [#]]
4a	110-	7.5/1.96	4.5/1.23	5/2.09	4/3.16
	112	(58 %)	(66 %)	(62 %)	(94 %)
4b	112-	6/1.89	5/1.26	5/2.02	5/3.02
	114	(56 %)	(67 %)	(60 %)	(90 %)
4c	108-	7/2.1	5/2.5	6/2.50	5/3.38
	110	(57 %)	(68 %)	(68 %)	(92 %)
4d	106-	6/2.07	4.5/2.67	5/2.70	4/3.61
	108	(52 %)	(67 %)	(68 %)	(91 %)
4e	102-	6/2.06	5/2.43	7/2.27	5/3.38
	104	(56 %)	(66 %)	(62 %)	(92 %)

*In hour; ^sIn minute; [#]In grams.

In conclusion, synthesis of flavone renders comparably low yield using DDQ. The yield was notable increased while using I₂. Both DMSO/I₂ and Alumina/I₂ mixture gives moderate yield for conventional synthetic method. But, the considerable reaction time as well as yield was noted for the synthesis of flavone under microwave condition. However, the result showed that efficiency and yield of the reaction is high under Alumina/I₂ reaction condition as compared to other methods.

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