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Efficient Synthesis of Substituted 2-Nitrochalcone Derivatives †

Alam Yair Hidalgo [1,2], Quirino Torres-Sauret [1], Carlos Ernesto Lobato-García [1], Miguel Ángel Vilchis-Reyes [1,*], Abraham Gómez-Rivera [1], Oswaldo Hernandez-Abreu [1] and Nancy Romero-Ceronio [1,*]

[1] División Académica de Ciencias Básicas, Universidad Juárez Autónoma de Tabasco, Carretera Cunduacán-Jalpa km 1, Col. La Esperanza, Cunduacán 86690, Tabasco, Mexico; alam.yair.hidalgo@gmail.com (A.Y.H.); quirino.torres@ujat.mx (Q.T.-S.); carloslobatogarcia@gmail.com (C.E.L.-G.); abraham.gomez@ujat.mx (A.G.-R.); oswaldo.hernandez@ujat.mx (O.H.-A.).

[2] Instituto Tecnológico Superior de Comalcalco, Tecnológico Nacional de México, Carretera Vecinal, Comalcalco-Paraíso Km 2, R/a Occidente 3ra Sección, 86650 Comalcalco, Tabasco, Mexico

* Correspondence: miguel.vilchis@ujat.mx (M.Á.V.-R.); nancy.romero@ujat.mx (N.R.-C.)

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Abstract: Organic synthesis plays a fundamental role in medicinal chemistry, allowing the production of compounds with desirable pharmacological properties. In this context, new synthesis methods, such as the use of ultrasound, are continuously being explored to improve the efficiency and sustainability of these processes. In this work, the synthesis and structural characterization of 2-nitrochalcone derivatives substituted with electron-withdrawing (fluoro) and electron-donating (methoxy) groups in the three isomeric positions of the B ring via nuclear magnetic resonance and ultrasound are presented; both a conventional method and a non-conventional ultrasound-assisted method are used. The results show that both methodologies are effective for obtaining these compounds, but the conventional method presents some additional advantages in the case of these nitrochalcones, such as shorter reaction times and better reaction yields.

Keywords: synthesis; ultrasound; 2-nitrochalcones

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1. Introduction

Organic synthesis plays a fundamental role in medicinal chemistry, allowing the production of compounds with desirable pharmacological properties [1]. In this context, the search for more efficient and sustainable synthesis methods is an active area of research [2]. The use of unconventional techniques, such as ultrasound irradiation, has gained attention in recent years because of its potential to improve efficiency and reduce energy consumption in chemical reactions [3].

Chalcones, particularly 2-nitrochalcone derivatives, are compounds of interest because of their promising pharmacological properties [4], including antioxidant, anti-inflammatory [5] and anticancer activities [6]. Modification of these compounds with electron-donating and electron-accepting groups can significantly influence their physical and chemical properties [7].

The synthesis of chalcones is generally carried out by the condensation of aromatic aldehydes with aromatic ketones in the presence of a base, such as sodium hydroxide or potassium carbonate [8,9]. However, the efficiency of these reactions can vary depending on the reaction conditions and methods employed [10].

In this work, we present the results of the synthesis and structural characterization of 2-nitrochalcone derivatives substituted with fluorinated and methoxylated groups in the isomeric positions of the B-ring using both a conventional method and an unconventional ultrasound-assisted method (Figure 1). The comparison of these methods allows us to evaluate their efficiency in terms of yield and sustainability.

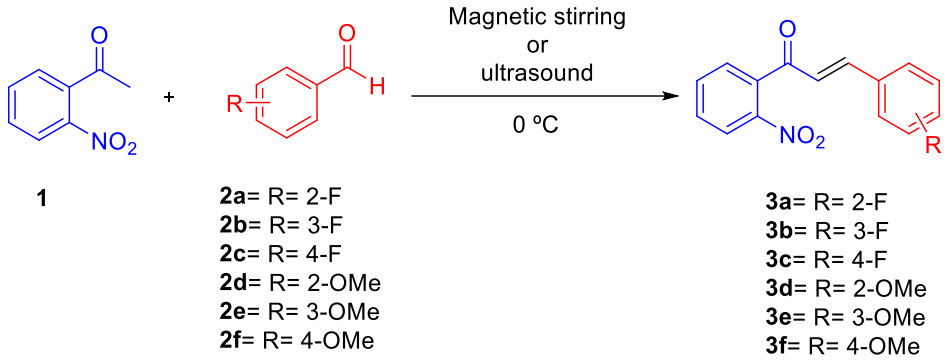

Figure 1. Synthesis of 2-nitrochalcone derivatives.

2. Materials and Methods

2.1. Physical Measurements

All chemicals were purchased from (Sigma Aldrich, St. Louis, MO, USA). All manipulations were performed at room temperature without any special purification of solvents or reagents. Melting points were determined via a Stuart SMP10 apparatus with the open capillary technique and are uncorrected. ^{1}H NMR and DEPTQ NMR spectra were recorded at 600 MHz and 150 MHz, respectively, in $CDCl_3$ via a Bruker Ascend™ Spectrometer (Fällanden, Switzerland). The progress of the reaction was monitored by thin-layer chromatography (TLC) using hexane:ethyl acetate as the eluent (8:2). IR spectra were obtained via an FT-IR spectrometer (Spectra One, Perkin Elmer, Foster City, CA, USA).

2.2. Synthesis and Characterization of Compounds **3a–e**

2.2.1. Conventional Conditions (Method A)

In a 10 mL flask, 0.6 mmol of 2-nitroacetophenone together with 0.6 mmol of the respective fluorinated or methoxylated benzaldehyde was added, and the mixture was dissolved in 3 mL of methanol or ethanol at 0 °C. Then, 1.0 equivalent of NaOH in the solution was added, and the mixture was allowed to react for 1 h Under vigorous magnetic stirring at 0 °C. At the end of the reaction, a solid was obtained, which was separated by decantation and washed twice with cold water. Finally, the solid was crystallized by a 3:1 dichloromethane:hexane solvent pair.

2.2.2. Ultrasound Irradiation (Method B)

In a round-bottom flask, equimolar amounts (0.6 mmol) of 2-nitroacetophenone and the respective fluorinated or methoxylated benzaldehyde were added. These reactants were dissolved in 3.0 mL of methanol or anhydrous ethanol. Once the starting materials were dissolved, 0.4 equivalents of K_2CO_3 were added. The reaction mixture was subjected to ultrasonic irradiation for 2 h. The formed solid was filtered and washed with cold water (2 × 15 mL). Finally, the product was characterized.

(*E*)-3-(2-Fluorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3a). White crystals, yield (71%) (method A), yield (62%) (method B), mp 107–109 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (method A), J = 8.2 Hz, 1H), 7.70 (td, J = 7.5, 1.4 Hz, 1H), 7.59 (m, 1H), 7.49 (td, J = 7.6, 1.7 Hz, 1H), 7.44 (dd, J = 7.5, 1.4 Hz, 1H), 7.41 (d, J = 16.5 Hz, 1H), 7.31, (m, 1H), 7.10 (td, J = 7.6, 1.1 Hz, 1H), 7.01 (d, J = 16.4 Hz, 1H) 7.01 (m, 1H). DEPTQ NMR (150 MHz) δ 192.6, 162.2, 146.7, 138.2, 136.1, 134.0, 132.5, 130.6, 129.0, 128.7, 128.2, 124.5, 122.1, 116.2, 116.1. FTIR: $^{\nu}$max/cm^{-1}: 1651 cm^{-1} (C=O), 1527 cm^{-1} (C=C), 1604 cm^{-1} (N-O), 977 cm^{-1} (C=C *trans*).

(*E*)-3-(3-Fluorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3b). White crystals, yield (90%) (method A), yield (71%) (method B), mp 95–98 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7. 8 Hz, 1H), 7.43 (d, J = 8.82 Hz, 1H), 7.26 (m, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 16.2, 1H), 7.10, (s, 1H), 7.01 (t, J = 7.4 Hz, 1H), and 6.90 (d, J = 16.2 Hz, 1H). DEPTQ NMR (150 MHz) δ 192.6, 163.8, 162.2, 146.7,

144.5, 136.2, 134.2, 130.8, 130.6, 128.8, 127.4, 124.6, 118.0, 114.7. FTIR: ᵛmax/cm⁻¹: 1658 cm⁻¹ (C=O), 1523 cm⁻¹ (C=C), 1580 cm⁻¹ (N-O), 976 cm⁻¹ (C=C *trans*).

(*E*)-3-(4-Fluorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3c). White crystals, yield (95%) (method A), yield (73%) (method B), mp 113–115 °C; ¹H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, J = 8.8 Hz, 1H), 7.76 (td, J = 7.5, 1.0 Hz, 1H), 7.65 (m, 1H), 7.50 (m, 3H), 7.26 (m, 1H), 7.22 (d, J = 16.2 Hz, 1H), 7.07 (t, J = 8.6, 2H), 6.92 (d, J = 16.2 Hz, 1H). DEPTQ NMR (150 MHz) δ 192.5, 165.1, 146.8, 144.7, 136.3, 134.0, 130.6, 130.5, 130.2, 128.8, 125.9, 124.5, 116.3, 116.1. FTIR: ᵛmax/cm⁻¹: 1651 cm⁻¹ (C=O), 1525 cm⁻¹ (C=C), 1584 cm⁻¹ (N-O), 996 cm⁻¹ (C=C *trans*).

(*E*)-3-(2-Methoxyphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3d). Yellow crystals, yield (74%) (method A), yield (70%) (method B), mp 91–93 °C; ¹H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 7.4 Hz, 1H), 7.71 (m, 1H), 7.62 (m, 1H) 7.60 (d, J = 16.4, 1H), 7.49 (m, 2H), 7.33 (m, 1H), 7.09 (d, J = 16.4 Hz, 1H), 6.92 (t, J = 7.6, 1H), 6.86 (d, J = 8.2 Hz, 1H), 3.78 (s, 3H). DEPTQ NMR (150 MHz) δ 193.4, 158.6, 146.9, 142.0, 136.5, 133.9, 132.5, 130.5, 129.1, 128.9, 126.6, 124.4, 122.9, 120.8, 111.3, 55.5. FTIR: ᵛmax/cm⁻¹: 1642 cm⁻¹ (C=O), 1529 cm⁻¹ (C=C), 1591 cm⁻¹ (N-O), 985 cm⁻¹ (C=C *trans*).

(*E*)-3-(3-Methoxyphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3e). Yellow crystals, yield (70%) (method A), yield (61%) (method B), mp 89–91 °C; ¹H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 8.22 Hz, 1H), 7.76 (td, J = 7.5, 1.1 Hz, 1H), 7.65 (m, 1H) 7.50 (dd, J = 7.5, 1.3, 1H), 7.28 (t, J = 7.9, 1H), 7.21 (d, J = 16.2 Hz, 1H), 7.08 (d, J = 7.6, 1H), 7.01 (s, 1H), 6.97 (d, J = 16.2 Hz, 1H) 6.94 (m, 1H), 3.81 (s, 3H). DEPTQ NMR (150 MHz) δ 193.3, 160.5, 147.3, 146.6, 136.9, 135.8, 134.5, 131.1, 130.5, 129.3, 127.1, 125.0, 121.8, 117.6, 113.7, 55.8. FTIR: ᵛmax/cm⁻¹: 1640 cm⁻¹ (C=O), 1521 cm⁻¹ (C=C), 1598 cm⁻¹ (N-O), 989 cm⁻¹ (C=C *trans*).

(*E*)-3-(4-Methoxyphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (3f). Yellow Crystals, yield (93%) (method A), yield (78%) (method B), mp 109–111 °C; ¹H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, J = 8.22 Hz, 1H), 7.74 (td, J = 7.5, 1.1 Hz, 1H), 7.64 (m, 1H) 7.50 (dd, J = 7.5, 1.3, 1H), 7.44 (m, 2H), 7.21 (d, J = 15.5 Hz, 1H), 7.08 (d, J = 7.6, 1H), 7.01 (s, 1H), 6.97 (d, J = 16.2 Hz, 1H) 6.94 (m, 1H), 3.81 (s, 3H), 6.90 (m, 2H), 6.87 (d, J = 15.5 Hz, 1H), 3.83 (s, 3H). DEPTQ NMR (150 MHz) δ 192.9, 162.2, 147.0, 146.3, 136.7, 134.0, 130.5, 129.0, 126.8, 124.6, 124.1, 114.6, 55.6. FTIR: ᵛmax/cm⁻¹: 1649 cm⁻¹ (C=O), 1523 cm⁻¹ (C=C), 1599 cm⁻¹ (N-O), 993 cm⁻¹ (C=*C trans*).

3. Results and Discussion

Chemistry

Compounds derived from 2-nitrochalcone were obtained by two different methods: a conventional method (magnetic stirring) and a nonconventional method (ultrasound). Both methods produced satisfactory yields. The results of both methods are summarized in Table 1.

Table 1. Optimal conditions for the synthesis of 2-nitrochalcones **3a–f**.

Compounds	Method A			Method B		
	Base	Time (h)	Yield (%)	Base	Time (h)	Yield (%)
3a *	NaOH	1	71	K_2CO_3	2	62
3b *	NaOH	1	90	K_2CO_3	2	71
3c *	NaOH	1	95	K_2CO_3	2	73
3d *	NaOH	2	74	K_2CO_3	2	70
3e *	NaOH	2	70	K_2CO_3	2	61
6f *	NaOH	2	93	K_2CO_3	2	78

* Temperature: 0 °C, NaOH compounds **3a–c** 1 equiv. and 3**d–f** 1.2 equiv. (Method A), K_2CO_3 0.4 equiv. (Method B).

When comparing both methods, the magnetic stirring method stands out for its better performance and operational simplicity. However, ultrasound is more efficient in terms of sustainability because it reduces energy consumption. However, in the case of these molecules, no decrease in reaction times or better yields was observed with the B method. Therefore, it would be advisable to continue improving the ultrasound conditions for these reactions.

In ultrasound, although dispersion is enhanced and cavitation can accelerate reactions, the short duration of these high-energy events may not be sufficient for all reagents to fully interact, especially if the reagents are less soluble or have lower reactivity. On the other hand, with magnetic stirring, prolonged exposure of the reactants to a constant temperature and continuous mixing ensure enhanced diffusion, which may explain the higher yields in the reactions of 2-nitrochalcone derivatives.

The 2-nitrochalcone derivatives were characterized by NMR (^{1}H and DEPTQ), highlighting the following important points: Compounds **3a–f** show characteristic chemical shifts in the NMR spectra, which confirm the structure of the chalcones, mainly the signals of the α-β-unsaturated system. The shift values (δ) correspond appropriately to the expected hydrogens and carbons in each derivative. DEPTQ analysis and two-dimensional experiments, such as COSY and HSQC, confirmed the presence of key functional groups, including substituents on the aromatic rings.

4. Conclusions

Reactions carried out by magnetic stirring were shown to be more effective than those carried out by ultrasonication in terms of yield. However, the use of nonconventional techniques such as ultrasound remains promising from a sustainability perspective. NMR spectroscopy provided crucial information for structural confirmation of the derivatives, showing alignment between chemical shifts and expected structures.

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