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Monomodal *vs* Multimodal Microwave Irradiation Applied in the Synthesis of Fluorochalcones

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Abstract The synthesis of *o*-, *m*- and *p*-fluorine-substituted chalcones at the ring "B" was accomplished by a Claisen-Schmidt condensation between the benzaldehyde and acetophenone. The reaction was performed in solvent-free conditions with microwave activation and good yields (> 75%) were obtained. It is noteworthy that the application of conventional reaction conditions produced very low yields and in some cases, the reaction did not proceed at all. The methodology implemented considerably reduces reaction times.

Keywords Fluorine-substituted Chalcones, Claisen-Schmidt Condensation, Solvent-free reaction

1. Introduction

Chalcones constitute an important group of biomolecules, some of which exhibit a wide range of biological activities [1] for example: antifungal [2], antibacterial [3], anti-inflammatory [4, 5], antitumor [6], and antioxidant properties [7].

Structurally, the chalcone moiety is formed by two aromatic rings bonded by a three carbon skeleton which is present as a carbonyl α, β-insaturated system (Figure 1) [8].

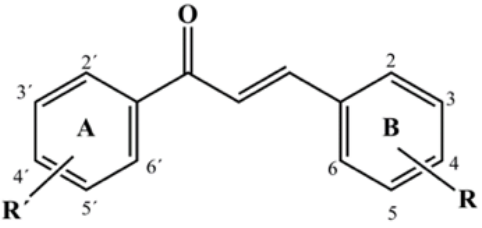

Figure 1. General structure of the chalcone moiety

The condensation between acetophenone derivatives and aromatic aldehydes is the general procedure to obtain chalcones. The Claisen-Schmidt condensation, either catalyzed by strong bases or Lewis acids, has been proved as one of the most efficient procedure for the synthesis of this kind of products [9]. There are several reports which present variations, such as: reflux conditions with organic solvents [10], free-solvent reactions [11], use of ultrasound as source of energy [12] and microwave activation [13]. Among the catalysts employed to perform this condensation are reports with bases such as NaOH [14], KOH/MeOH [15], $LiOH.H_2O$ [16], and $NaOH\text{-}K_2CO_3$ [17]; Lewis acids have also been reported for this reaction, for example: $SOCl_2$ [18]. There are also reports of the application of special reagents likewise: $SiO_2\text{-}H_2SO_4$ [19], $PdCl_2$ [20], $TiO_2\text{-}P25\text{-}SO_4^{-2}$ [21], or $I_2\text{-}Al_2O_3$ [22]. Several procedures described in the literature present methodological disadvantages such as prolonged reaction times, special infrastructural requirements or the preparation of specific reagents. These inconveniences have driven the search of eco-friendly synthetic procedures, according with the twelve principles of green chemistry [23, 24].

This paper reports the preparation of three fluoro-substituted chalcones at the ring B (compounds **2a**, **2b** and **2c**), through the Claisen-Schmidt condensation between acetophenone and (*o*, *m*, *p*)-fluorobenzaldehyde; both conventional and green chemistry procedures were applied.

2. Experimental

The synthesis of the three fluorochalcones (**2a**, **2b** and **2c**) was conducted by the Claisen-Schmidt condensation of *o*-fluorobenxaldehyde (**1a**), *m*-fluorobenzaldehyde (**1b**) and *p*-fluorobenzaldehyde (**1c**) with acetophenone. All the substances were analytical-grade reagents and were

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employed without further purification. The reactions were performed through conventional (use of solvents, stirring and/or reflux conditions) and green chemistry (free-solvent conditions, microwave irradiation) procedures (Figure 2).

Melting points were determined with a melting point apparatus (Scorpion Scientific A50360) and they are not corrected. The IR spectra were recorded on KBr pellets using a Perkin-Elmer Precisely Spectrometer. The NMR spectra were recorded on a Varian VX-400, using $CDCl_3$ as solvent and TMS as an internal standard.

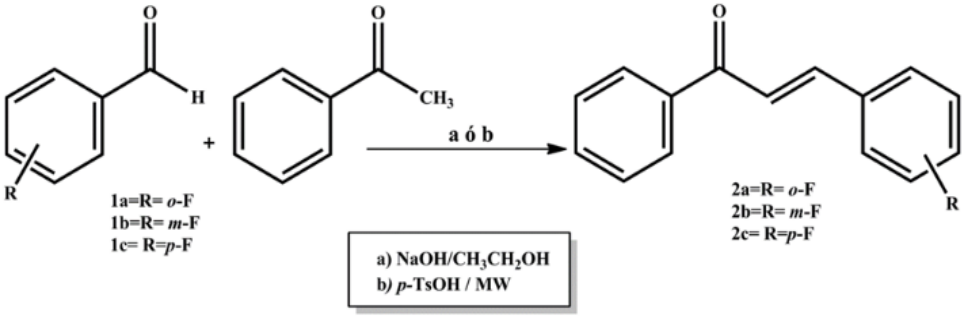

Figure 2. Reaction scheme for the synthesis of compounds **2a-2c**. Reaction conditions: a) $NaOH/CH_3CH_2OH$, continuous stirring and/or reflux; b) p-TsOH, free solvent, microwave activation

2.1. General Procedure for Conventional Synthesis of Chalcones 2a-c

The conventional procedure was performed by dissolving sodium hydroxide (0.6 eq. aq. 0.1 mMol) in ethanol (1mL), this mixture was put into an ice-bath at 0°C; once this temperature was reached, acetophenone (1 equivalent) and the corresponding fluorobenzaldehyde (1 equivalent) were slowly added. The reaction mixture was removed from the ice-bath and maintained with magnetic stirring until no further changes were observed. The reaction was monitored by TLC (silica gel 60 F254, hexane/ethyl acetate 95:5). Where no substantial changes were observed, the reaction mixture was heated under reflux conditions. The reaction crude was cooled at 0°C during 24 h; and the solid products were filtered and washed with cold ethanol. The crystallization was made from an ethanol/dichloromethane mixture. The recrystallized products were dried, weighed and characterized.

2.2. General Procedure for the Solvent-Free Synthesis of Chalcones 2a-c

The eco-friendly synthetic procedures were performed in solvent-free conditions and acid catalysis. A mixture of *p*-toluensulfonic acid (PTSA) (0.5 eq), acetophenone (1 eq) and the corresponding fluorobenzaldehyde (1 eq) were placed in a proper reactor. The system was microwaved irradiated employing a monomodal microwave system (MW) (VICHI, model: MW-600 MIC-1). For comparative purposes, a domestic microwave oven (MO) was also employed (MABE, model: HMM74MB). The reaction was monitored by TLC (silica gel 60 F254, hexane/ethyl acetate 95:5). The reaction crude was purified by CC (silica 60 mesh, hexane/ethyl acetate 98:2). The eluents were removed by vacuum distillation. The solid products were recrystallized from a mixture of hexane/ethyl acetate. The purified products were dried, weighed and characterized.

2.3. (*E*)-3-(2-Fluorophenyl)-1-Phenylprop-2-en-1-one, 2a

Pure product **2a** was obtained as a yellow solid (highest yield = 70%); m.p. 44°C (reported: 38° to 40°C, [25]). Spectroscopic analysis: νmax/cm^{-1} (neat KBr) = 1700 (s), 1600 (s), 1250-1300 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.09-7.19 (m, 2H), 7.33-7.39(m, 1H), 7.47-7.51 (m, 2H), 7.56-7.65 (m, 3H), 7.62-7.66(d, 1H, J=15.92 Hz, Hα), 7.88-7.92 (d, 1H, J=15.92 Hz), 8.00-8.8.03 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 116.18, 116.66, 124.74, 124.77, 124.80, 128.51, 128.99, 129.96, 132.06, 132.12, 133.08, 137.52, 138.19, 163.22, 190.60.

2.4. (*E*)-3-(3-Fluorophenyl)-1-Phenylprop-2-en-1-one, 2b

Pure product **2b** was obtained as a yellow solid (highest yield = 75%); m.p. 48°C (reported: 48°C, [26]). Spectroscopic analysis: νmax/cm^{-1} (neat KBr) = 1660 (s), 1590-1600 (s), 1200 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 7.11-7.06 (m, 1H), 7.31-7.38 (m, 3H), 7.51-7.59 (m, 3H), 7.53-7.49 (d, 1H, *J*=15 Hz, Hα), 7.72-7.72 (d, 1H, *J*=15 Hz, Hβ), 8.02-8.00 (d, 2H, 15 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 114.18, 117.27, 122.92, 124.39, 128.41, 128.58, 130.37, 132.79, 137.03, 137.76, 143.13, 164.11, 189.96.

2.5. (*E*)-3-(4-Fluorophenyl)-1-Phenylprop-2-en-1-one, 2c

Pure product **2c** was obtained as a yellow solid (highest yield= 95.5%); m.p. 79°C (reported: 78.85°C, [27] and 83 to 84°C, [28]). Spectroscopic analysis: νmax/cm^{-1} (neat KBr)= 1662 (s), 1605 (s), 1510 (s); 1217 (s). ^{1}H NMR (400 MHz, $CDCl_3$):8.01(2H, dd,1.2, *J*=8.4 Hz), 7.76 (1H,d, *J*=16Hz), 7.61(2H, ddt, *J*=2.0,5.2,8.4 Hz), 7.56 (1H, dt, *J*=1.2,6.4 Hz), 7.48 (2H, dd, *J*=6.4, 8.4 Hz), 7.45 (1H, d, *J*=16 Hz), 7.08 (2H, tt, *J*=2.0,8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 190.15, 165.19, 162.69, 143.38, 137.98, 132.77, 130.31, 130.22, 128.38, 121.58, 116.13, 115.91.

3. Results and Discussion

Chalcones **2a-2c** were prepared by a conventional procedure with basic catalysis in ethanol with mechanical stirring at room temperature and/or reflux conditions. A solvent-free procedure was also employed for the preparation of these compounds with acid catalysis using PTSA and MW or MO as energy source. Table 1, presents a resume of: reaction conditions, reaction yields, and physical appearance of products **2a-2c**. All of them were obtained as yellow solids, and their melting point varies from 44 to 79°C. The solvent-free synthesis mediated either by monomodal (MW) or domestic (MO) microwave irradiation presented higher yields (>65%) when compared with both the mechanical agitation and the reflux methods. It is noteworthy that for compound **2a** neither the conventional nor the domestic microwave irradiation procedures were suitable for its synthesis, which was only successful by monomodal microwave irradiation.

The spectroscopical data for compounds **2a-2c** are summarized in table 2. For the infrared spectra the identification of characteristic signals confirmed the presence of the functional groups expected. The carbonyl absorption band was recognized in the range of 1650-1700 cm^{-1}, and the carbon-carbon double bond vibration band was located around 1600 cm^{-1}. The bands corresponding to the aromatic rings, were observed around 1450-1500 cm^{-1} and the carbon-fluorine bond vibrations were observed in the region of 1230-1300 cm^{-1}.

The analysis of the ^{1}H NMR spectra of the three compounds showed that the hydrogen atoms of the α,β-insaturated system were observed as doublets with coupling constants larger than 15 Hz, which is consistent with a *trans* orientation of both hydrogen atoms around the double bond. The signals observed in the ^{13}C NMR spectra are consistent with the expected structures and with the data reported previously in the literature [6, 21].

Table 1. Experimental conditions, reaction yields and melting points of compounds **2a-2c**

Product	Reaction conditions	Time (min)	Yield (%)	P.F. (°C)
2a	Conventional	---	---	---
2a	Solvent-free / MO**	5	26.2	44
2a	Solvent-free / MW***	15	70	44
2b	Reflux *	180	25.2	48
2b	Free solvent/ MO**	5	65	48
2b	Free solvent/ MW***	15	75	48
2c	Continuous agitation*	5	83.6	79
2c	Free solvent/ MW***	15	95.5	79

*Mixture: 1 eq. Acetophenone/ 1 eq. substituted benzaldehyde / 0.6 eq., NaOH/ethanol 0.1 mMol.
**Mixture: 1 eq. Acetophenone/ 1 eq. substituted benzaldehyde/ 0.5 eq., *p*-TsOH, Reactor: Domestic Microwave Oven (MABE, model: HMM74MB, low power).
***Mixture: 1 eq. Acetophenone/ 1 eq. substituted benzaldehyde/ 0.5 eq. *p*-TsOH, Microwave Reactor (VICHI model: MW-600 MIC-1.): Temperature: 50°C, speed: 100 rxm, power: 90%, pressure: 1psi.

Table 2. IR absorption bands (KBr pellets), ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100MHz, $CDCl_3$) chemical shifts, for compounds **2a-2c**

Compounds	IR1/δ (cm^{-1})	NMR ^{1}Hδ(ppm), J(Hz)	NMR ^{13}Cδ (ppm)
2a	1700 C=O 1600 C=C 1250-1300 C-F	δ7.09-7.19 (m, 2H), 7.33-7.39 (m, 1H), 7.47-7.51 (m, 2H), 7.56-7.65 (m, 3H), 7.62-7.66(d, 1H, *J*=15.92, Hα), 7.88-7.92 (d, 1H, *J*=15.92, Hβ), 8.00-8.03 (d, 2H, J=12)	116.18, 116.66, 124.74, 124.77, 124.80, 128.51, 128.99, 129.96, 132.06, 132.12, 133.08, 137.52, 138.19, 163.22, 190.60.
2b	1660 C=O 1590-1600 C=C 1200 C-F	7.11-7.06 (m, 1H), 7.31-7.38 (m, 3H), 7.51-7.59 (m, 3H), 7.53-7.49 (d, 1H, *J*=15, Hα), 7.72-7.72 (d, 1H, *J*=15, Hβ), 8.02-8.00 (d, 2H, J= 8).	114.18, 117.27, 122.92, 124.39, 128.41, 128.58, 130.37, 132.79, 137.03, 137.76, 143.13, 164.11, 189.96.
2c	1662 C=O 1605 C=C 1510 C-C 1217 C-F	8.01(2H, dd, 1.2, *J*=8.4), 7.76 (1H, d, *J*=16), 7.61(2H, ddt, *J*=8.4,5.2, 2.0), 7.56 (1H, dt, *J*=6.4,1.2), 7.48 (2H, dd, *J*=6.4, 8.4), 7.45 (1H, d, *J*=16), 7.08 (2H, tt, *J*=8.4, 2.0).	190.15,165.19, 162.69, 143.38, 137.98, 132.77, 130.31, 130.22, 128.38, 121.58,116.13,115.91

Previously, we reported the crystal structure of **2c** as a second monoclinic polymorph (Figure 3) [27], The elucidation was performed at 293 K. The new polymorph crystallizes in space group P21/c, which is different from the first monoclinic polymorph, [29]. The cell parameters of the current monoclinic polymorph vary significantly from the earlier form [a = 24.926 (9), b = 5.6940 (19), c = 7.749 (3) A and β = 94.747 (5)°]. Compound **2c** shows an (*E*) configuration on the C═C bond with *p*-fluorophenyl group opposite to the 1-phenylketone. Torsion angle of *p*-fluorophenyl to 1-phenylketone group is 10.53 (6)°.

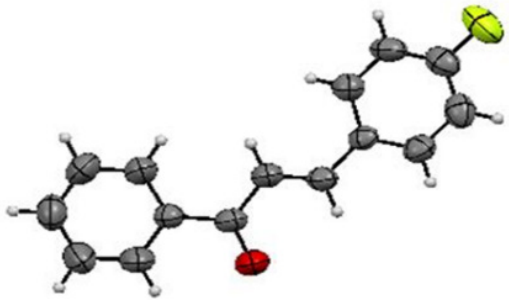

Figure 3. Molecular structure of 2c, with 30% probability displacement ellipsoids for non-H atoms

4. Conclusions

The solvent-free/microwave activation strategy proved to be a satisfactory procedure for the synthesis of fluoro-substituted chalcones; rather than the conventional methods which presented longer reactions times and poorer yields. The spectroscopic data are in accordance with the expected structures and previous reports in the literature.

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REFERENCES

[1] Nowakowska, Z. and Kedzia, B., Schroeder, G., 2008, Synthesis, physicochemical properties and antimicrobial evaluation of new (*E*)-chalcones. Eur. J. Med. Chem., 43, 707-713.

[2] Lahtchev, K. L., Batovska, D. I., Parushev, P., Ubiyvovk, V. M., Sibirny, A. A., 2008, Antifungal activity of chalcones: a mechanistic study using various yeast strains., Eur. J. Med. Chem., 43, 2220-2228.

[3] Khan, A. S., Asiri, A. M., Alamry, K. A., El-Daly, S. A., Zayed, M.A., 2013, Eco-friendly synthesis and in vitro antibacterial activities of some novel Chalcones., Russian J. of Bioorg. Chem., 39(3), 312-317.

[4] Yadav, H. L., Gupta, P., Pawar, S., R., Singour P., K. Patil U. K., 2011, Synthesis and biological evaluation of anti-inflammatory activity of 1,3-diphenyl-propenone derivatives., Med. Chem. Res., 20, 461-465.

[5] Gómez-Rivera, A., Aguilar-Mariscal, H., Romero-Ceronio, N., Roa de la Fuente, L. F., Lobato-Garcia, C. E., 2013, Synthesis and anti-inflammatory activity of three nitro chalcones., Bioorg. & Med. Chem. Letters, 23, 5519–5522.

[6] Kumar, D., Kumar, N.M., Akamatsu, K., Kusaka, E., Harada, H., Ito, T., 2010, Synthesis and biological evaluation of Indolylchalcones as antitumor agents., Bioorg. & Med. Chem. Letters, 20, 3916-3919.

[7] Padhye, S., Ahmad, A., Oswal, N., Dandawate, P., Rub, R. A., Deshpande, J., Swamy, K. V., Sarkar, F. H, 2010, Fluorinated 2-Hydroxychalcones as garcinol analogs with enhanced antioxidant and anticancer activities., Bioorg. & Med. Chem. Letters., 20, 5818-5821.

[8] Fang, X., Yang, B., Cheng, Z., Zhang, P., Yang, M., 2014, Synthesis and antimicrobial activity of novel chalcone derivatives., Res. Chem. Intermed., 40, 1715-1725.

[9] Patel, J., Malani, M. H., Dholakiya, B. Z., 2012, Silica sulfuric acid-catalyzed Claisen-Schmidt condensation of 1,3,4- trisubstitutedpyrrole 2,5-dione to chalcone., Res. Chem. Intermed., 38, 2371-2381.

[10] Hayat, F., Moseley, E., Salahuddin, A., Van Zyl, R. L., Azam, A., 2011, Antiprotozoal activity of chloroquinoline based chalcones., Eur. J. of Med. Chem., 46, 1897-1905.

[11] Thirunarayanan, G., Mayavel, P., Thirumurthy, K., 2012, Fly-ash: H2SO4 catalyzed solvent free efficient synthesis of some aryl chalcones under microwave irradiation. Spectrochimica Acta, Part A., 91, 18-22.

[12] Jarag, J. K., Pinjari, V. D., Pandit, A. B., Shankarling, G. S., 2011, Synthesis of chalcone (3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one): Advantage of sonochemical method over conventional method., UltrasonicSonochemistry., 18, 617-623.

[13] Zuo, Y., Yu, Yi, Wang, S., Shao, W., Zhou, B., Lin, L., Luo, Z., Huang, R., Du, J., Bo, X., 2012, Synthesis and cytotoxicity evaluation of biaryl-based chalcones and their potential in TNFα-induced nuclear facto-Kβ activation inhibition., Eur. J. of Med. Chem., 50, 393-404.

[14] Shakil, N. A., Singh, M. K., Sathiyendiran, M., Kumar, J. C., Pandaria, J., 2013, Microwave synthesis, characterization and bio-efficacy evaluation of novel chalcone based 6-carbethoxy-2-ciclohexen-1-one and 2H-indazol-3-ol derivatives., Eur. J. of Med. Chem., 59, 120-131.

[15] Tran, T-D., Do, T-H., Tran, N-C., Ngo, T-D, Phuong-Huynh, T-N., Tran, T-D., Thai, K-M., 2012, Synthesis and anti-methicillin resistant *Staphylococcus aureus* activity of substitute chalcones alone and in combination with non-beta-lactam antibiotics., Bioorg. & Med. Chem. Letters., 22, 4555-4560.

[16] Bhagat, S., Sharma, R., Sawant D. M., Sharma, L., Chakraborti A. K., 2006, $LiOH.H_2O$ as a novel dual activation catalyst for highly efficient and easy synthesis of 1,3-diaryl-2-propenones by Claisen-Schmidt condensation under mild conditions., Journal of Molecular Catalysis A: Chemical., 244, 20-24.

[17] Xing, S., Xiang, L. X., Lin, H., Yun H. X., 2010, New observation on a class of old reactions. Chemoselectivity for the solvent-free reaction of aromatic aldehydes with alkyketones catalyzed by a double-component inorganic base system., Schi. China Chem., 53(5), 1095-1101.

[18] Petrou, O., Ivanova, Y., Gerova, M., 2008, $SOCl_2$/EtOH: Catalytic system for synthesis of chalcones., Catalysis Comunications., 9, 315-316.

[19] Thirunarayanan, G., Sekar, K. G., 2014, SiO_2-H_2SO_4 catalized, microwave-assisted cyclization cum acetylation of 2-propenones under solvent-free condition: Synthesis and spectral correlations of some 1-acetyl pyrazolines., J. of Taibah University for Science., 8, 124–136.

[20] Al-Masum, M., Ng, E., Wai, M. C., 2011, Palladium-catalyzed direct cross-coupling of potassium styryltrifluoroborates and benzoyl chlorides – a one step method for chalcone synthesis., Tetrahedron Letters, 52, 1008-1010.

[21] Krishnakumar, B. and Swaminathan, M., 2011, Solvent free synthesis of quinoxalines, dipiridophenazines and chalcones under microwave irradiation with sulfated Degussa titania as a novel solid acid catalyst., Journal of Molecular Catalysis A: Chemical, 350, 16-25.

[22] Kakati, D. and Sarma, C., 2011, Microwave assisted solvent free synthesis of 1, 3-diphenylpropenones., Chemistry Central Journal, 5:8.

[23] Rajput, J.K. and Kaur, G., 2010, Silicotungstic acid catalysed Claisen Schmidt condensation reaction: an efficient protocol for synthesis of 1,3-diaryl-2-propenones., Tetrahedron Letters, 53, 646-649.

[24] P. T. Anastas and J. C. Warner, Green Chemistry: Theory and Practice, New York, USA: Oxford University Press, 2000.

[25] Dudhe, R., Pramod K. S., and Prabhakar K. V., 2014, Pyrimidine containing furanose derivative having antifungal, antioxidant, and anticancer activity. Organic and Medicinal Chemistry Letters 4:3.

[26] Díaz-Oliva, V., C. Síntesis y Evaluación de la actividad biológica de chalconas sustituidas con flúor. Thesis. Universidad Juárez Autónoma de Tabasco. México. 2015.

[27] Arias-Ruiz, S. N., Romero, N., Lobato-García, C. E., Gómez-Rivera, A., Mendoza, A., 2013, Second monoclinic form of (*E*)-3-(4-fluoro-phen-yl)-1-phenyl-prop-2-en-1-one., ActaCryst. E69, o1694-o1695.

[28] Fang, Fan; Li, Yuan; Tian, Shi-Kai, 2011, Stereoselective Olefination of N-Sulfonyl Imines with Stabilized Phosphonium Ylides for the Synthesis of Electron-Deficient Alkenes, European Journal of Organic Chemistry., 6, 1084-1091.

[29] Jing, L.-H., 2009, (*E*)-3-(4-Fluorophenyl)-1-phenyl-2-propen-1-one. ActaCryst. E65, o2515.