Microwave-assisted Synthesis of fluorinated chalcones.

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Keywords: Chalcones, microwave and fluorinated.

Introduction

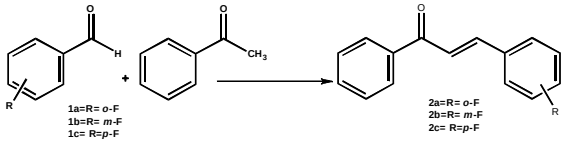
Chalcones constitute an important class of natural products belonging to the flavonoid family. Chemically, chalcones are 1, 3-diphenylpropenones in which the two aromatic rings are connected by a three carbon α, β-unsaturated carbonyl system[3].

Natural occurring or synthetic chalcones have been found to exhibit several pharmacological activities[2], including: anti-inflammatory, antioxidant, cytotoxicity, antimicrobial, analgesic, antipyretic, antimalarial and anti-allergic activities[5]. This wide-range of biological properties is mainly attributed to the *α, β*-unsaturated ketone moiety[3]. The introduction of various substituents into the two aryl rings has also been a subject of interest.

Traditionally, chalcones could be obtained via the Claisen–Schmidt condensation carried out in basic or acidic media under homogeneous conditions. These traditional conditions require long reaction times, a great expense of energy, and they need to prevent an efficient waste disposal scheme. Therefore it´s required new synthetic strategies[1].

In this work, we present the preparation of fluorinated chalcones, via the Claisen-Schmidt condensation between acetophenone and (*o, m, p*)-fluorobenzaldehyde, we compared two methods, one using conventional reflux and/ or agitation and another free solvent by microwave activation (scheme 1).

The structures of compounds were confirmed by spectral data (^{1}H NMR, ^{13}C NMR). The values found are consistent with those reported in the literature appear within the expected range according to the nature of protons.



Scheme 1: -Conditions 1: Synthesis of Chalcones using $NaOH/CH_3CH_2OH$, continued agitation and/or reflux.
-Conditions 2: Synthesis of Chalcones using *p-Ts*OH, free solvent and microwave activation.

Results and Discussion

A series of fluorine-substituted chalcones in the ring "B" at positions -*o*,-*m* and -*p* was obtained with good yields by Claisen-Schmidt condensation from the respective substituted benzaldehyde and acetophenone using green chemistry techniques.

In general, the solvent-free reaction of chalcones with microwave activation is carried out with high yields, while in the conventional synthesis yields were low and in some cases reaction no proceeded.

Table 1 presents the conditions of reactions and yields obtained for each experiment. These percentages correspond to the maximum time required for the transformation of reactants to products, which is limited to the appearance of subproducts.

The best yield percentages were obtained for solvent-free reactions activated by microwave radiation, the experiment 2 (2c) with 95.46% higher than that obtained by conventional techniques; experiment 1 (2c) with 83.62 %.

Even when the product 2b is obtained using conventional approaches (entry 3, 25.23%), the yields achieved are favored by using a microwave reactor (entry 5, 75%) which is comparable with the results of the reaction to use a home oven (entry 4, 65%).

Finally the product 2a are obtained satisfactorily in solvent-free conditions (entry 7, 70%) while the reaction with conventional techniques is not necessary.

Table 1: Experimental conditions in the synthesis of the compounds.

Entry	Product	Conditions of reaction	Time	Yield	Metting Point
1	2c	Continued Agitation[a]	2.25 hrs	83.62%	81 °C
2	2c	Free Solvent/ MW[b]	10 min	95.46 %	81 ° C
3	2b	Reflux[a]	3 hrs	25.23%	48 °C
4	2b	Free solvent/ MWH[b]	5 min.	65 %	48 °C
5	2b	Free solvent/ MW[c]	15 min	75%	48 °C
6	2a	Free Solvent/ MWH[b]	5 min	26.2%	44 °C
7	2a	Free Solvent/ MW[c]	15 min	70%	44°C

[a]Mixture: 1 eq. Acetophenone/ 1 eq. substituted benzaldehyde / 0.6 eq. NaOH aq. 0.1 mMol.

[b]Mixture: 1 eq. Acetophenone/ 1 eq. substituted benzaldehyde/ 0.5 eq. *p*-TsOH, Microwave Oven Home activation (MABE, model: HMM74MB, low power).
[c]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.

Analysis was carried out of the reaction depending on the complexity of the processing, according to the semiquantitative analysis tool proposed by Van Aken *et* al[4].

These parameters allow assessing the environmental impact of the chemical reaction through a Ecoscale.
The results obtained are shown in Table 2.

Table 2: Ecoscale assessment

Entry	Product	Ecoscale	Ranking
1	2c	81.81	excellent
2	2c	77.72	excellent
3	2b	39.62	unacceptable
4	2b	62.5	acceptable
5	2b	67.5	acceptable
6	2a	43.1	unacceptable
7	2a	64	acceptable

Is important to point out that with these modifications was to improve reaction time, yields and reduce environmental impact, which is evident with the analysis of Ecoscale reaching acceptable and excellent values.

Conclusion

The percentages obtained are satisfactory in solvent-free strategies by conventional techniques because the yields are lower due to the position of the substituent's in the starting materials.

The thermal condensation reaction is found to be sluggish and took longer time with low yields, in some cases no reaction proceeded.

The best results were obtained by using microwave activation; the use of the activation energy increases the yield and reduces the reaction time.

Yields were satisfactory even when the reaction was carried out with the home microwave other hand the use of the microwave reactor (Model VICHI: MW-600 MIC-1) provided a higher yield, that because household ovens (multimodal) have many drawbacks as the field distribution is not uniform, so that the radiation bounces off the walls and parts receive more radiation than others (hot spots), all this leads to a lack of reproducibility in these systems. Monomode systems have a single mode of radiation. Therefore radiation is better utilized and can work at lower power while maintaining a higher field density. Moreover on a monomode microwave is possible to control the irradiation power, so that one can have a better control of the reaction.

(*E*)-3-(4-Fluorophenyl)-1-phenylprop-2-en-1-one, (2c): Mp: 81 °C; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05-7.11(dd, 1H, J=8.6 Hz), 7.46-7.50 (m, 2H), 7.54-7.63 (m, 2H), 7.43-7.47 (d, 1H, J=15.64 Hz, Hβ), 7.74-7.78 (d,1H, J=15.72 Hz, Hα), 7.79-8.02 (m, 1H).
^{13}C NMR (400 MHz, $CDCl_3$): δ 116.23, 116.45, 121.89, 128.70, 128.88, 130.55, 130.63, 131.34, 133.09, 138.31, 143.66, 163.00, 194.49.
(*E*)-3-(3-Fluorophenyl)-1-phenylprop-2-en-1-one, (2b): Mp: 48 °C; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 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, J= 15 Hz).
^{13}C NMR (400 MHz, $CDCl_3$): δ 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.
(*E*)-3-(2-Fluorophenyl)-1-phenylprop-2-en-1-one, (2a): Mp: 44 °C; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-7.19 (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 (400 MHz, $CDCl_3$): δ.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.

Acknowledgements

This research paper was conducted with key support of the project PFICA UJAT-2011-C07-22.

References

1 Anastas PT. Green Chemistry, Theory and practice. Oxford University Press, New York. (1998).

2 Fang Dong, Cheng Jian, Fei Zhenghao, Gong Kai, Liu Zuliang. Synthesis of chalcones via Claisen–Schmidt condensation reaction catalyzed by acyclic acidic ionic liquids. Catalysis Communications 9 (2008) 1924–1927.

3 Hormaza A. Angelina; Arbeláez, Oscar Felipe; Montes Valencia Nancy. Síntesis y caracterización de una serie de Chalconas. Scientia Et Technica, vol. XV, núm. 43, diciembre, 2009, 316-320.

4 K. Van Aken, L. Strekowski, L. Patiny, Beilstein J. Org.Chem., 2006, 2-3.

5 Y. Xia, Z.Y. Yang, K.F. Bastow, Y. Nakanishi, K.H. Lee, *Bioorg. Med. Chem. Lett.* 10 (2000) 699.