

Green synthesis of chalcones derivates of acetophenone.

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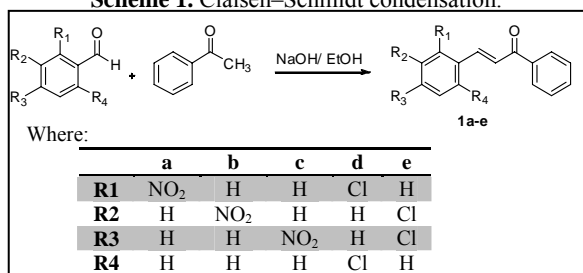
The chalcones, are precursors of open chain flavonoids and isoflavonoids which are present in several nature products, and their derivatives have been showed increasing attention due to numerous potential biological and pharmacological activities such as antiinflammatory, antituberculosis, antifungal, antimalarial, antiproliferative, antimicrobial, antibacterial, antileish-manicidal and anticancer¹⁻⁶. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity.

In this report we present the synthesis of a series of α , β -unsaturated carbonyl compounds (chalcones), and also report the evaluation of this synthesis by EcoScale, which is a semi-quantitative analysis base on safety, economical and ecological features.

Chalcones **1a-e** (Scheme 1) were synthesized via Claisen-Schmidt condensation reaction with acetophenone and 2-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, 2,6-dichlorobenzaldehyde and 3,4-dichlorobenzaldehyde, aqueous NaOH (0.05M) in ethanol, at room temperature (rt). After completion of the reaction, the mixture was filtered to collect the precipitates and purification by recrystallization affords the pure chalcones (Table 1, entry 1-5).

The green chemistry foments the use of auxiliary substances should be made unnecessary wherever possible and innocuous when used, due to we use ethanol instead methanol, because is obtained from renewable resources.

Scheme 1. Claisen-Schmidt condensation.



Reagents and Conditions: NaOH (0.05M), acetophenone (1 eq.), substituted benzaldehydes (1 eq.); EtOH, rt.

Table 1: Results and Reaction conditions

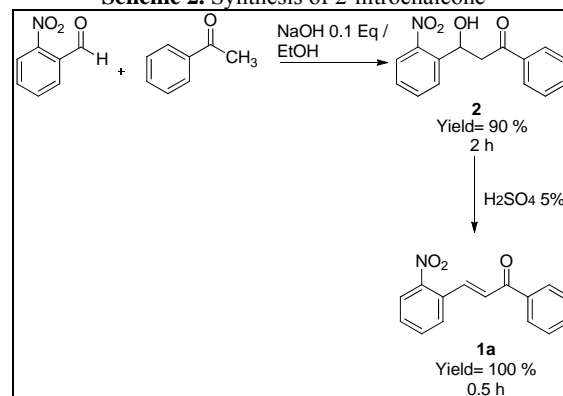
Entry	Compounds	Conditions	Time	Yield (%) ^a
1	1a	0.5 Eq NaOH	3 h	34 %
2	1b	0.1 Eq NaOH	3.5 h	92 %
3	1c	0.1 Eq NaOH	2 h	82 %
4	1d	1 Eq NaOH	3.5 h	92 %
5	1e	1 Eq NaOH	2 h	89 %
6	1a	1) 0.1 Eq NaOH 2) H ₂ SO ₄ 5%	2 h 0.5 h	90% ^b

^a Yield refers to pure products after filtration.

^b Global Yield.

On the other hand we improve the yield of the compound **1a** (90%), when the reaction was carried out in two steps, first the condensation reaction followed by the dehydration phase of the compound **2** (Scheme 2). (Table 1, entry 6).

Scheme 2. Synthesis of 2-nitrochalcone



Several metrics are used to evaluate the chemical reactions and the environmental impact of the synthesis pathway, in order to evaluate quality of the organic preparation we used the parameters established by Aken *et al* in EcoScale. The results listed in table 2 show that the most values of EcoScale over than 80 points, which are considered as excellent, described by the ranking of reaction conditions⁸ (entry 2-6).

Table 2: Evaluation of EcoScale

Entry	Compounds	EcoScale
1	1a	59
2	1b	88
3	1c	83
4	1d	88
5	1e	86
6	1a	85

The spectroscopic characterization of these molecules was performed using the conventional techniques such as nuclear magnetic resonance (¹H- and ¹³C-NMR) and infrared spectroscopy (IR).

This reactions produce the corresponding chalcones in good yields (up to 80 %) with excellent levels of Ecoscale (up to 80 points).

Acknowledgements

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Characterization data:

(E)-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one, 1a: Mp: 116 °C; blue solid; IR (neat): ν 1663, 1600, 1568, 1511, 1434, 1372, 1337, 1283, 1209, 1006, 968, 855, 745, 737, 678 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.36 (d, 1H), 7.48-7.61 (m, 4H), 7.68-7.76 (m, 2H), 8.00-8.05 (m, 3H), 8.11-8.14 (d, 1H); ¹³C NMR (400 MHz, CDCl₃):

δ 124.87, 127.04, 128.62, 128.65, 129.14, 130.31, 131.12, 133.08, 133.54, 137.24, 140.02, 190.22.

(E)-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one, 1b: Mp: 133 °C; white solid; IR (neat): ν 2922, 1661, 1607, 1529, 1450, 1354, 1309, 733, 704, 683 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.50-7.55 (m, 2H), 7.66 (s, 1 H), 7.8-7.85 (d, 1H), 7.91-7.94 (dd, 1H), 8.03-8.06 (m, 2H), 8.22-8.26 (dd, 1H), 8.49-8.50 (t, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 122.27, 124.43, 124.56, 128.50, 128.71, 129.95, 133.22, 134.25, 136.51, 137.42, 141.52, 148.57, 189.52.

(E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one, 1c: Mp: 157 °C; yellow solid; IR (neat): ν 2927, 1659, 1607, 1515, 1342, 1219, 1107, 1049, 1016, 842, 781, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.51-7.55 (t, 2H), 7.60-7.62 (m, 1H), 7.63-7.67 (d, 1H), 7.77-7.79 (d, 1H), 7.79-7.83 (d, 2H), 8.02-8.05 (m, 2H), 8.25-8.27 (d, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 124.12, 125.60, 128.51, 128.74, 128.87, 133.30, 137.42, 140.95, 141.41, 148.44, 189.53.

(E)-3-(2, 6-dichlorophenyl)-1-phenylprop-2-en-1-one, 1d: Mp: 75 °C; yellow solid; IR (neat): ν 3070, 1669, 1610, 1584, 1432, 1302, 1259, 1214, 1173, 1011, 973, 774, 961, 603 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.17-7.21 (t, 1H), 7.36-7.38 (d, 2H), 7.48-7.52 (m, 2H), 7.57-7.61 (m, 1H), 7.64-7.68 (d, 1H), 7.83-7.87 (d, 1H), 8.01-8.03 (m, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 128.63, 128.65, 128.78, 129.66, 129.79, 130.36, 132.52, 133.07, 133.52, 135.10, 137.53, 137.74, 190.06.

(E)-3-(3, 4-dichlorophenyl)-1-phenylprop-2-en-1-one, 1e: Mp: 96 °C; white solid; IR (neat): ν 3062, 1665, 1601, 1547, 1504, 1470, 1396, 1312, 1214, 1132, 1077, 1023, 977, 881, 821, 775, 684 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.74 (d, 1H), 7.48-7.49 (d, 1H), 7.49-7.5 (m, 1H), 7.51-7.53 (dd, 2H), 7.58-7.63 (m, 1H), 7.76 (s, 1H), 7.71-7.73 (m, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 123.46, 127.50, 128.50, 128.71, 129.73, 130.93, 133.12, 141.90, 189.82.

3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one 2: Mp: 88 °C; white solid; IR (neat): 3440, 2979, 1597, 1523, 1346, 1122, 1043, 757, 746, 686 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.94-7.99 (m, 4H), 7.68-7.70 (t, 1H), 7.58-7.60 (t, 1H), 7.44-7.48 (m, 4H), 5.84-5.87 (dd, 1H), 3.68-3.73 (dd, 1H), 3.19-3.25 (dd, 1H); ¹³C NMR (400 MHz, CDCl₃): δ 199.76, 140.15, 138.53, 136.19, 133.74, 128.66, 128.33, 128.23, 128.15, 124.35, 65.80, 46.92.