Short Communication

Sonochemistry: A good, fast and clean method to promote the synthesis of 5-arylidene-2,4-thiazolidinediones

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Sonochemistry: A good, fast and clean method to promote the synthesis of 5-arylidene-2,4-thiazolidinediones.

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ABSTRACT

The efficient synthesis of sixteen 5-arylidene-2,4-thiazolidinediones by aldol condensation reaction of 2,4-thiazolidinedione, mono- and di-substituted arenealdehydes and KOH using ultrasound irradiation is reported. The desired compounds were obtained in a few min (10-30 min) with moderate to good yields (25-81%).

Keywords: thiazolidinediones; sonochemistry; aldol condensation

1 INTRODUCTION

Many studies have described the biological properties of 5-arylidene-2,4-thiazolidinediones [1] such as: anti-inflammatory activity due to the capacity of PPARγ ligands [2], reduction of retinal neovascularization activity [3], aldose reductase inhibitor [4,5], anti-inflammatory and antioxidant properties [6] and antifungal action [7].

With all these promising biological activities, it would be useful if the synthesis of these compounds were easy, fast and showed goods yields. The literature reports several methods for the synthesis of 5-arylidene-2,4-thiazolidinediones such as sodium acetate in acetic acid under reflux conditions [8], KOH and ethanol under reflux [9], piperidine in ethanol under reflux [10-12], polyethene glycol (PEG-300) under reflux [13] and ethylenediamine diacetate as catalyst at room temperature [14].

Under all previously mentioned reaction conditions, products were formed after several hours of reaction. Currently, studies are performed looking for new methods that facilitate and speed up some reactions. The literature shows the emerging use of microwave irradiation to promote synthesis, including the synthesis of 5-arylidene-2,4-thiazolidinediones which takes 10-30 min [15-17].

Likewise, another good possibility is the use of sonochemistry. Ultrasound irradiation produces the cavitation effect that accelerates some synthetic reactions. Cavitation is the formation, growth and violent collapse of bubbles in liquid medium that cause high temperatures and pressures inside the bubbles promoting chemical and physical transformations by enhancing mass transfer and turbulence in the liquid [18,19]. Due to this capacity, ultrasound irradiation is used in a great number of chemical reactions such as: acetylation of alcohols [20], synthesis of stilbenes by Suzuki cross-coupling [21], synthesis of ketones from aryl tannanes [22] and Michael addition [23]. The aldol condensation reaction was also reported [24, 25] and provides good support for performing this work. Our research group also showed the efficiency of ultrasound energy for the synthesis of thiazolidinones in good yields for 5-35 min [26, 27]. Recently, a few 5-arylidene-2,4-thiazolidinediones were synthesized in good yields using an ultrasound bath at 80°C for 20 min in the presence of ionic liquids [28], however, this is the first time that such compounds have been synthesized using the more efficient ultrasound irradiation by probe.

Therefore, continuing our research program, the aim of this paper is to reduce the reaction time for the synthesis of 5-arylidene-2,4-thiazolidinediones using the non-conventional ultrasonic methodology.

2 RESULTS AND DISCUSSION

All compounds were previously published in the literature according to: **3a** [29];**3b**, **3f**, **3j** [14]; **3c**, **3h**, **3i** [11]; **3d**, **3e, 3k** [9];**3g** [30]; **3l** [31]; **3m** [32]; **3n** [33]; **3o** [34]; **3p** [35].

First of all, we synthesized the compound **3c** (yield 59%) by reaction of 2,4-thiazolidinedione **1**, 4-methoxybenzaldehyde **2c** and KOH (excess) in reflux of ethanol for 6 hours according to Venkatesan et al. [8]. The study of the conditions for the synthesis of compound **3c** using ultrasound irradiation is summarized in Table 1 and the progress of reactions was monitored by GC analysis. The reaction carried out only with

ultrasound irradiation did not result in the desired product (Entry 1) and a base was needed, applying the Knoevenagel condensation. Thus, the reaction with triethylamine and sodium acetate showed a small amount of **3c** (Entry 2-5). The best condition found was the reaction using excess potassium hydroxide as a base for 20 min (Entry 8). It is interesting to note that only trace of compound **3c** was observed when the reaction was carried out with refluxing ethanol for 20 min. The formation of product **3c** was confirmed by CG/MS and NMR [36].

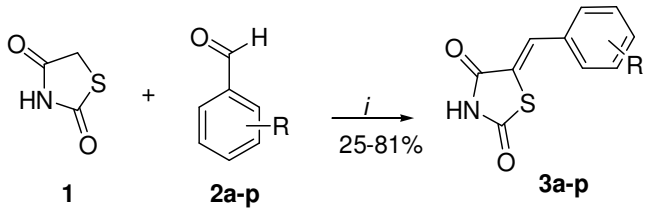
Table 1. Study of reaction conditions to synthesis of compound **3c**

Entry	Base	Equimolar proportion (**1**:**2c**:base)	Time (min)	GC-analysis (%) **3c**
1	-	1:1	30	None
2	Triethylamine	1:1:1	20	Trace
3	Triethylamine	1:1:2	30	19
4	Sodium acetate	1:1:1	20	Trace
5	Sodium acetate	1:1:2	20	Trace
6	Potassium hydroxide	1:1:1	15	Trace
7	Potassium hydroxide	1:1:2	15	84
8	Potassium hydroxide	1:1:2	20	100
9	Potassium hydroxide	1:1:3	20	100

Thus, all the compounds **3a-p** were synthesized from reaction of 1 mmol of 2,4-thiazolidinedione **1**, 1 mmol of arenealdehyde **2a-p** and 2 mmol of potassium hydroxide (Scheme 1). The reaction times of all arenealdehydes were continuously monitored and the final times for each of them were shown in Table 2. The crude products were purified by a simple washing with a hot solution mixture of hexane:ethyl acetate (9:1)

All compounds were obtained from moderate to good yields and were submitted to GC–MS analysis which proves the aldol condensation, with exception of compound **3n** [37] that was analyzed by ^{1}H and ^{13}C NMR due to the fact that it is only soluble in DMSO. The configuration of 5-arylidene-2,4-thiazolidinediones might be *Z* according to previously studies found in the literature [11,17].

Scheme 1.



1 **2a-p** **3a-p**

i: KOH, ethanol, ultrasonic irradiation, 10-30 min.

Table 2: Yields and selected physical properties of 5-arylidene-2,4-thiazolidinediones **3a-p** synthesized by ultrasonic methodology.

Comp.	R	Time (min)	m.p. (C)[a]	Yield (%)[b]	GC–MS analysis m/z (%)
3a	2-OCH_3	15	235-237	51	235 (M^+, 65), 164 (100), 149 (45), 121 (40), 77 (35).
3b	3-OCH_3	15	195-196	65	235 (M^+, 40), 164 (100), 134 (15), 121 (20), 77 (20).
3c	4-OCH_3	20	205-207	34	235 (M^+, 35), 164 (100), 149 (60), 121 (25), 77 (27).
3d	2-Cl	30	217-220	43	239 (M^+, 15), 204 (90), 168 (100), 133 (30), 89 (45).
3e	3-Cl	15	211-213	81	239 (M^+, 30), 168 (100), 133 (20), 89 (35), 84 (15).
3f	4-Cl	15	228-230	72	239 (M^+, 25), 168 (100), 133 (20), 84 (15), 66 (10).
3g	2-F	15	194-196	50	223 (M^+, 20), 180 (10), 152 (100), 107 (20), 76 (15).
3h	3-F	15	167-169	62	223 (M^+, 28), 152 (100), 107 (20), 76 (15), 69 (10).
3i	4-F	10	214-215	54	223 (M^+, 20), 152 (100), 107 (20), 76 (15), 69 (5).
3j	4-CH_3	15	225-226	40	219 (M^+, 35), 148 (100), 115 (15), 91 (15), 74 (15).
3k	3-OH	15	239-240	25	221 (M^+, 30), 150 (100), 121 (25), 77 (15), 39 (10).
3l	2,3-OCH_3	20	163-165	51	235 (M^+ - OCH_3, 45), 164 (100), 149 (60), 121 (25), 77 (20).
3m	2,4-OCH_3	10	241-243	69	265 (M^+, 4), 235 (50), 164 (100), 149 (40), 121 (20), 77 (37).
3n	2,5-OCH_3	15	147-149	58	[c]
3o	2,6-Cl	15	147-149	79	273 (M^+, 10), 238 (100), 202 (80), 167 (30), 123 (30), 101 (20).
3p	2-Cl, 6-F	10	148-150	80	257 (M^+, 15), 222 (90), 186 (100), 151 (25), 93 (30).

[a] - melting points are uncorrected; [b] - yields of isolated compounds; [c] - not determined because it is only soluble in DMSO.

We tried to obtain the 5-arylidene-2,4-thiazolidinediones from there action of electron-withdrawn nitrobenzaldehydes (*orto*, *meta* and *para*), however to our surprise we only identified the starting materials by CG analysis. Furthermore, these reactions produce an emulsion that can be harmful to ultrasound equipment.

3 EXPERIMENTAL

All common reagents and solvents were used as obtained from commercial suppliers without further purification. The reactions were carried out with a microtip probe (3 mm) connected to a 500W Sonics Vibra-cell ultrasonic processor operating at 20 kHz at 25% of the maximum power output. The progress of reactions was monitored by TLC and by a Shimadzu Gas Chromatograph GC-2010, Column I.D., 0.25 mm; Columnlength, 30 m; Column Head Pressure, 14 psi, program: T_0 = 50 °C; t_0 = 2.0 min; rate 16.0 °C/min; T_f = 250 °C; t_f = 10.0 min; Inj. = 250 °C; Det. = 270 °C. Melting points were determined using open capillaries on a Fisatom model 430 apparatus and are uncorrected. GC–MS analyses were performed on a GC 2010-plus GC–MS-QP2010SE System AOC-20i – auto injector. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Ac-200F spectrometer (^{1}H at 200MHz and ^{13}C at 50 MHz) in DMSO.

*3.1 General procedure for the preparation of 5-arylidene-2,4-thiazolidinediones **3a-p**.*

A mixture of 2,4-thiazolidinedione **1** (1 mmol), corresponding arenealdehyde **2a-p** (1 mmol) and 2 or 3 mmol KOH in ethanol (10 mL) were placed in a 25 mL beaker. The reaction mixture was then sonicated by an ultrasonic probe with a frequency of 24 kHz at room temperature from 10 to 30 min according to arenealdehyde. After reaction time, the solvent was evaporated, the resultant solid was neutralized with solution of HCl 1 mol/L and filtrated under reduced pressure. When necessary, the compounds were washed with a hot solution of hexane:ethyl acetate (9:1) to supply the pure products (**3a, 3l, 3n** and **3o**).

4 CONCLUSIONS

In summary, ultrasound irradiation is an excellent method to promote the clean and fast synthesis of sixteen 5-arylidene-2,4-thiazolidinediones in moderate to good yields, in some cases without any further purification. This methodology reduces the amount of solvent and diminishes the reaction time.

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[36] Selected NMR data for *(Z)*-5-4-(methoxybenzylidene)thiazolidine-2,4-dione **3c**: ^{1}H NMR (200 MHz, DMSO, $J_{H\text{-}H}$=Hz): 7.47 (d, 2H, ^{3}J=8.7); 7.29 (s, 1H, CH vinylic); 7.01 (d, 2H, ^{3}J=8.8); 3.77 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, ppm): 182.2 (C=O); 175.4

(C=O); 158.9, 132.8, 130.4 (2C), 128.8, 122.5 and 114.1 (2C) (aryl and vinylic); 55.1 (OCH_3).

[37] Selected NMR data for *(Z)*-5-(3,5-dimethoxybenzylidene)thiazolidine-2,4-dione **3n**: ^{1}H NMR (200 MHz, DMSO, J_{H-H}=Hz): 7.90 (s, 1H, CH vinylic); 7.06 (s, 2H), 6.87 (s,1H); 3.81 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, ppm): 167.7 (C=O); 167.1 (C=O); 152.9, 152.2, 126.3, 123.6, 121.8, 117.4, 113.1 and 112.9 (aryl and vinylic); 55.9 (OCH_3); 55.4 (OCH_3).

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> Sixteen 5-arylidene-2,4-thiazolidinediones were synthesized by ultrasound irradiation> The desire products were obtained in short reaction times (10-30 min)> Ultrasound irradiation is efficient to aldol condensation reaction.