

Synthesis of Novel 2-Aryl-3-(2-morpholinoethyl)-1,3-thiazinan-4-ones Via Ultrasound Irradiation

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This study describes the synthesis of fourteen thiazinanones from a multicomponent reaction of 2-morpholinoethylamine (as primary amine), arenaldehydes (as carbonyl compound) and the mercaptopropionic acid using both conventional (thermal heating) and ultrasound methodologies. Through thermal heating methodology, the thiazinanones were obtained in 49 to 97% yields for 16 hours and through sonochemistry methodology, the reaction time was reduced for 25 minutes with yields 41 to 88%. The full identification and characterization of unpublished heterocycles were achieved by proton (¹H) and carbon 13 (¹³C) nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry and infrared. Some of them were also characterized by elemental analysis.

Keywords: thiazinanone, 2-morpholinoethylamine, multicomponent reaction, sonochemistry

Introduction

The cleaner ultrasound methodology has been very effective in organic synthesis, especially in cases where the reactions take too much time.¹ The effect of cavitation promotes the formation, growth and collapse of bubbles in the irradiated liquid. Consequently, the resulting high temperature and pressure inside the bubbles enhances mass transfer and a turbulent flow in the liquid and the reaction time is reduced.^{2,3}

Multicomponent reaction is a modern and environmental friendly synthetic strategy, wherein three or more starting materials are converted into one product. This kind of reaction has attracted interest in organic synthesis due the various advantages, such as reduction in reaction times, economy of the atoms and simplification of the synthetic procedures. This approach has also been widely exploited in medicinal chemistry for obtaining bioactive compound libraries⁴ including heterocycles.⁵

Small heterocyclic moieties containing atoms of nitrogen, sulfur and oxygen have been extensively studied due to their

diverse biological activities. Sonochemistry has been also studied to the synthesis of heterocycles, such as thiazoles,⁶ thiophenes,⁷ thiazines⁸ and thiadiazines.⁹ Our research group and others recently published the efficient ultrasound synthesis of thiazolidinones¹⁰⁻¹³ and thiazolidinediones.¹⁴ Thiazinanones also belongs to this heterocyclic class and it is important to note that, to our knowledge, the application of sonochemistry to the synthesis of thiazinanones has not been reported in the literature.

Six-membered thiazinanones show important biological properties as antioxidant, anti-inflammatory, anti-diabetic and antimicrobial.¹⁵⁻¹⁸ The strategies to the synthesis of thiazinanones are quite similar to the strategies to the synthesis of analogue five-membered thiazolidinones. Thus, thiazinanones could be obtained by a multicomponent reaction between a primary amine, an aldehyde (or ketone) and the mercaptopropionic acid^{15,17,19} or by a reaction between thioureas and β -propylhaloacetic acid.¹⁸ Moreover, these methods can be applied in two steps, multicomponent (all reactants together in the beginning of reaction) or one-pot reactions, under catalysis or not.

These observations associated to the crescent interest in multicomponent reactions encouraged us to evaluate

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the effect of ultrasound on the three component synthesis of novel thiazinanones from 2-morpholinoethylamine, arenealdehydes and mercaptopropionic acid. For comparative purpose, the reactions were performed in the presence and in the absence of ultrasonic irradiation, i.e., by conventional method.

Experimental

Material and methods

Reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA) and were used without additional purification. Reactions in ultrasound were carried out with a microtip probe (3 mm) connected to a 500 W Sonics Vibra-Cell ultrasonic processor (Sonics & Materials, Inc., Newtown, CT, USA), operating at 20 kHz (25% of the maximum power output). Reactions were monitored by thin layer chromatography (silica gel 60 F253, ultraviolet 254 nm) and gas chromatography, in a gas chromatograph (GC) GC-2010 (Shimadzu Corp., Kyoto, Japan) with a column ID of 0.25 mm and length of 30 m. The analyses were carried out with a 14 psi column head pressure. The temperature range was 50 °C (2 min) to 250 °C (10 min) with a 16 °C min⁻¹ rate. Temperatures of the injector and detector were 250 and 270 °C, respectively. Gas chromatography with mass spectrometer (GC-MS) analyses was performed on a GC-2010 plus GCMS-QP2010 SE system AOC-20i auto injector (Shimadzu, Kyoto, Japan). Proton (¹H) and carbon 13 (¹³C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX 400 spectrometer (400.14 MHz for ¹H and 100.61 MHz for ¹³C) or on a Bruker AVANCE 600 spectrometer (600.17 MHz for ¹H and at 150.91 MHz for ¹³C) or on a Bruker AC 200 F spectrometer (¹H at 200.13 MHz and ¹³C at 50.32 MHz; Billerica, MA, USA) in CDCl₃ containing tetramethylsilane (TMS) as internal standard. The ¹³C NMR spectrum of compound **5k** was recorded on Bruker AVANCE 500 spectrometer (125.75 MHz). The fids were processed in the MestReC 4.7.0.0 (Mestrelab Research SL, Santiago de Compostela, Spain) or in the TopSpin (Bruker, Billerica, MA, USA) softwares. Figure 1 shows the atom-numbering for thiazinanones **5a-n** to the identification of NMR signals. Infrared (IR) spectra were obtained in attenuated total reflectance (ATR) on a IV Agilent absorption spectrometer, model Cary 630 FTIR (Agilent Technologies, Santa Clara, CA, USA). The elemental analyses (C, H and N) were used for thiazinanones **5a**, **5b**, **5c** and **5g** on a 2400 Series II CHNS/O Analyser equipment (PerkinElmer, Waltham, MA, USA). Analyses were consistent within ca. 0.4 theoretical values.

General procedure for the synthesis of 2-(aryl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-ones

Synthesis of thiazinanones **5a-n** by thermal heating methodology

In a 100 mL flask with a Dean-Stark apparatus, toluene (50 mL), 2-morpholinoethylamine [4-(2-aminoethyl) morpholine] **2** (1 mmol) and corresponding arenealdehyde **1a-n** (1 mmol) were added and the reaction mixture was heated at 110 °C for 3 h. After this time, the mercaptopropionic acid **4** (2 mmol) was added and the mixture was heated for additional 16 h. The reaction mixture was washed with saturated solution of NaHCO₃ (3 × 30 mL), dried with MgSO₄ and concentrated *in vacuo* to give the expected thiazinanones. When necessary, the compounds were washed with a hot hexane to furnish the pure compounds.

Synthesis of thiazinanones **5a-n** by ultrasound methodology

A mixture of 2-morpholinoethylamine **2** (1 mmol), arenealdehyde **1a-n** (1 mmol) and mercaptopropionic acid **4** (3 mmol) in toluene (10 mL) was sonicated for 25 min in an ultrasonic probe with frequency of 20 kHz. The organic layer was washed with a saturated solution of NaHCO₃ (3 × 30 mL), dried with MgSO₄ and concentrated *in vacuo* to generate the products without purification.

Selected data for the thiazinanones **5a-n**

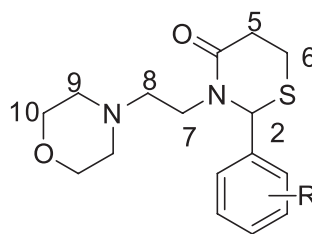


Figure 1. Atom-numbering for thiazinanones **5a-n**.

3-(2-Morpholinoethyl)-2-(2-nitrophenyl)-1,3-thiazinan-4-one (**5a**)

Yellow oil; IR (ATR) ν_{\max} / cm⁻¹: 2951 (C-H_{sp2} stretch), 2866-2816 (C-H_{sp3} stretch), 1615 (C=O stretch), 1528-1462 (aromatic C=C stretch), 1525 and 1357 (NO₂ stretch), 1121 (C-O stretch); ¹H NMR (400 MHz, J_{H-H} Hz) δ 2.45-2.35 (m, 5H, H-8b, H-9), 2.51-2.54 (m, 2H, H-5b, H-6b), 2.72-2.64 (m, 2H, H-7b, H-8a), 2.79-2.74 (m, 2H, H-5a, H-6a), 3.63 (t, 4H, J 4.6, H-10), 4.16 (dt, 1H, J 13.0, 4.2, H-7a), 6.85 (s, 1H, H-2), 7.19 (d, 1H, J 8.6, Ph-H), 7.44 (td, 1H, J 7.7, 1.2, Ph-H), 7.56 (td, 1H, J 7.6, 1.1, Ph-H), 8.01 (dd, 1H, J 8.0, 1.2, Ph-H); ¹³C NMR (125 MHz) δ 21.5 (C-6), 34.1 (C-5), 44.8 (C-7), 53.9 (2C, C-9), 56.9 (C-8), 58.3 (C-2),

66.9 (2C, C-10), 126.9, 128.9, 132.7, 135.4, 169.9 (C-4); anal. calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96; found: C, 54.98; H, 6.40; N, 12.01; GC-MS m/z (%): 351 (M^+ , 1.5), 113 (42.86), 100 (100), 56 (8).

3-(2-Morpholinoethyl)-2-(3-nitrophenyl)-1,3-thiazinan-4-one (**5b**)

White oil; IR (ATR) ν_{max} / cm^{-1} : 3062 (C-H_{sp2} stretch), 2947 and 2816 (C-H_{sp3} stretch), 1660 and 1454 (aromatic C=C stretch), 1525 and 1348 (NO₂ stretch), 1663 (C=O stretch), 1117 (C-O stretch); ¹H NMR (400 MHz, J_{H-H} Hz) δ 2.47-2.30 (m, 8H), 2.79-2.69 (m, 1H), 3.66-3.65 (m, 4H, H-9), 4.06-3.81 (m, 2H), 5.83 (s, 1H, H-2), 7.57 (m, 2H, Ph-H), 8.13 (q, 2H, J 7.6, Ph-H); ¹³C NMR (100 MHz) δ 20.1 (C-6), 39.6 (C-5), 42.3 (C-7), 53.6 (2C, C-9), 55.7 (C-8), 61.3 (C-2), 66.8 (2C, C-10), 121.9, 123.9, 130.3, 132.7, 141.9, 148.6, 174.2 (C-4); anal. calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96; found: C, 54.40; H, 5.97; N, 11.82; GC-MS m/z (%): 351 (M^+ , 0.98), 113 (32.21), 100 (100), 56 (9.14).

3-(2-Morpholinoethyl)-2-(4-nitrophenyl)-1,3-thiazinan-4-one (**5c**)

Brown oil; IR (ATR) ν_{max} / cm^{-1} : 3065 (C-H_{sp2} stretch), 2952-2812 (C-H_{sp3} stretch), 1596 and 1456 (aromatic C=C stretch), 1519 and 1348 (NO₂ stretch), 1631 (C=O stretch), 1119 (C-O stretch); ¹H NMR (400 MHz, J_{H-H} Hz) δ 2.48-2.33 (m, 5H, H-9, H-8b), 2.66-2.60 (m, 3H, H-5b, H-6b, H-8a), 2.81-2.79 (m, 3H, H-5a, H-6a, H-7a), 3.61-3.58 (m, 4H, H-10), 4.20 (dt, 1H, J 14.0, 5.6, H-7b), 5.90 (s, 1H, H-2), 7.45 (d, 1H, J 8.6, Ph-H), 8.24 (d, 2H, J 8.8, Ph-H); ¹³C NMR (100 MHz) δ 21.8 (C-6), 34.3 (C-2), 44.9 (C-7), 53.6 (2C, C-9), 56.6 (C-8), 62.0 (C-2), 67.0 (2C, C-10), 124.3, 127.3, 130.4, 147.6, 171.8 (C-4); anal. calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.69; H, 6.02; N, 11.96; found: C, 54.42; H, 6.10; N, 11.84; GC-MS m/z (%): 351 (M^+ , 1.12), 113 (13.12), 100 (100), 44 (2.02).

2-(2-Fluorophenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (**5d**)

Yellow oil; IR (ATR) ν_{max} / cm^{-1} : 2959 (C-H_{sp2} stretch), 2925 and 2863 (C-H_{sp3} stretch), 1650 (C=O stretch), 1584-1422 (aromatic C=C stretch), 1116 (C-O stretch); ¹H NMR (400 MHz, J_{H-H} Hz) δ 2.44-2.34 (m, 5H, H-9, H-8b), 2.60-2.54 (m, 2H, H-5b, H-6b), 2.67 (dt, 1H, J 13.9, 6.1, H-8a), 2.84-2.74 (m, 3H, H-5a, H-6a, H-7b), 3.62-3.60 (m, 4H, H-10), 4.06 (dt, 1H, J 13.8, 5.4, H-7a), 6.10 (s, 1H, H-2), 7.00 (m, 2H, Ph-H), 7.27 (2d, 2H, J 7.2, 6.2, Ph-H); ¹³C NMR (100 MHz, J_{C-F} Hz) δ 21.5 (C-6), 34.5 (C-2), 44.0 (C-7), 53.7 (C-8), 56.0 (2C, C-9), 57.0 (C-2), 67.0 (2C, C-10), 116.2 (J 20.9), 126.8 (d, J 2.4), 127.0 (d,

J 11.9), 129.68 (d, J 8.3), 159.5 (d, J 248.5), 169.3 (C-4); GC-MS m/z (%): 324 (M^+ , 1.65), 113 (43.12), 100 (100), 86 (5.77), 44 (1.96).

2-(3-Fluorophenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (**5e**)

Yellow oil; IR (ATR) ν_{max} / cm^{-1} : 2961 (C-H_{sp2} stretch), 2947 and 2929 and 2818 (C-H_{sp3} stretch), 1618 (C=O stretch), 1590 and 1402 (aromatic C=C stretch), 1117 (C-O stretch); ¹H NMR (600 MHz, J_{H-H} Hz) δ 2.45-2.34 (m, 5H, H-8b, H-9), 2.60-2.53 (m, 2H, H-6b, H-8a), 2.81-2.71 (m, 4H, H-5a, H-6a, H-5b, H-7b), 3.62-3.57 (m, 4H, H-10), 4.07 (dt, 1H, J 13.9, 5.1, H-7a), 5.75 (s, 1H, H-2), 6.98-6.91 (m, 3H, Ph-H), 7.28 (2d, 1H, J 7.9, 5.8, Ph-H); ¹³C NMR (150 MHz, J_{C-F} Hz) δ 21.8 (C-6), 34.4 (C-2), 44.6 (C-7), 53.8 (C-8), 55.5 (2C, C-9), 62.2 (C-2), 67.1 (2C, C-10), 113.7 (d, J 22.7), 115.1 (J 21.2), 122.1 (J 2.8), 130.2 (J 8.4), 142.6 (J 6.5), 162.9 (d, J 247.3), 169.2 (C-4); GC-MS m/z (%): 324 (1.56), 113 (30.74), 100 (100), 86 (5.58), 56 (9.32).

2-(2-Chlorophenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (**5f**)

White oil; IR (ATR) ν_{max} / cm^{-1} : 2951 (C-H_{sp2} stretch), 2868 and 2818 (C-H_{sp3} stretch), 1668 (C=O stretch), 1594 and 1409 (aromatic C=C stretch), 1113 (C-O stretch); ¹H NMR (200 MHz, J_{H-H} Hz) δ 2.41-2.30 (m, 5H, H-8b, H-9), 2.68-2.51 (m, 3H, H-5b, H-6b, H-8a), 2.78-2.70 (m, 1H, H-7b), 2.82-2.78 (m, 2H, H-5a, H-6a), 3.61 (t, 4H, J 4.7, H-10), 4.03-4.01 (m, 1H, H-7a), 6.16 (s, 1H, H-2), 7.01 (dt, 1H, J 4.7, 3.1, Ph-H), 7.22 (dt, 2H, J 4.6, 4.4, Ph-H), 7.39 (dt, 1H, J 4.6, 3.8, Ph-H); ¹³C NMR (50 MHz) δ 21.1 (C-6), 34.4 (C-5), 44.1 (C-7), 53.8 (2C, C-9), 56.9 (C-8), 59.6 (C-2), 67.0 (2C, C-10), 126.5, 126.6, 129.3, 130.27, 132.6, 136.3, 169.3 (C4); GC-MS m/z (%): 340 (M^+ , 1.81), 113 (47.70), 100 (100), 56 (9.89).

2-(3-Chlorophenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (**5g**)

Yellow oil; IR (ATR) ν_{max} / cm^{-1} : 3050 (C-H_{sp2} stretch), 2935-2809 (C-H_{sp3} stretch), 1619 (C=O stretch), 1597 and 1465 (aromatic C=C stretch), 1109 (C-O stretch); ¹H NMR (400 MHz, J_{H-H} Hz) δ 2.46-2.33 (m, 4H, H-8b, H-9), 2.61-2.52 (m, 2H, H-6b, H-8a), 2.81-2.69 (m, 4H, H-5a, H-6a, H-7b, H-5b), 3.60 (q, 4H, J 4.7, H-10), 4.06 (dt, 1H, J 13.9, 5.2, H-7a), 5.73 (s, 1H, H-2), 7.07 (dt, 1H, J 6.6, 1.7, Ph-H), 7.23 (dt, 2H, J 7.9, 6.4, Ph-H); ¹³C NMR (100 MHz) δ 169.3 (C-4), 141.9, 134.7, 129.8, 126.6, 124.6, 67.0 (2C, C-10), 62.2 (C-2), 56.6 (C-8), 53.8 (2C, C-9), 44.6 (C-7), 34.4 (C-5), 21.8 (C-6); anal. calcd. for $C_{16}H_{21}N_2ClO_2S$: C, 56.38; H, 6.21; N, 8.22; found: C, 56.57; H, 6.23; N, 8.35; GC-MS m/z (%): 340 (M^+ , 1.20), 113 (32.21), 100 (100), 56 (9.14).

2-(4-Chlorophenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5h**)

White oil; IR (ATR) ν_{\max} / cm^{-1} : 2940 (C-H_{sp2} stretch), 2858-2825 (C-H_{sp3} stretch), 1508 (C=O stretch), 1576 and 1463 (aromatic C=C stretch), 1102 (C-O stretch); ¹H NMR (250 MHz, *J*_{H-H} Hz) δ 2.46-2.36 (m, 5H, H-9, H-8b), 2.59-2.52 (m, 2H, H-6b, H-8a), 2.79-2.68 (m, 4H, H-5a, H-5b, H-6a, H-7b), 3.61-3.59 (m, 4H, H-10), 4.08 (dt, 1H, *J* 13.7, 5.6, H-7a), 5.75 (s, 1H, H-2), 7.13 (d, 2H, *J* 8.0, Ph-H), 7.29 (d, 2H, *J* 8.3, Ph-H); ¹³C NMR (100 MHz) δ 169.3 (C-4), 138.3, 133.9, 128.8, 127.9, 67.0 (2C, C-10), 62.2 (C-2), 56.5 (C-8), 53.8 (2C, C-9), 44.5 (C-7), 34.5 (C-5), 21.3 (C-6); GC-MS *m/z* (%): 340 (M⁺, 1.14), 113 (28.16), 100 (100), 86 (5.83), 56 (8.93).

2-(2-Methoxyphenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (**5i**)

Yellow oil; IR (ATR) ν_{\max} / cm^{-1} : 2947 (C-H_{sp2} stretch), 2846-2811 (C-H_{sp3} stretch), 1634 (C=O stretch), 1599 and 1458 (aromatic C=C stretch), 1110 (C-O stretch); ¹H NMR (600 MHz, *J*_{H-H} Hz) δ 2.42-2.34 (m, 5H, H-8b, H-9), 2.58-2.51 (m, 2H, H-6b, H-8a), 2.62 (m, 1H, *J* 13.9, 5.0, H-7b), 2.81-2.76 (m, 3H, H-5, H-6a), 3.62 (q, 4H, *J* 4.4, H-10), 3.93 (s, 3H, OCH₃), 4.03 (dt, 1H, *J* 13.6, 4.7, H-7a), 6.05 (s, 1H, H-2), 6.87 (q, 2H, *J* 7.1, Ph-H), 6.92 (dd, 1H, *J* 7.5, 1.7, Ph-H), 7.21 (dt, 1H, *J* 7.7, 1.8, Ph-H); ¹³C NMR (150 MHz) δ 21.5 (C-6), 34.6 (C-5), 44.2 (C-7), 53.7 (2C, C-9), 56.5 (C-8), 58.6 (C-2), 67.0 (2C, C-10), 111.0, 119.9, 126.0, 129.2, 155.9, 169.6 (C4); GC-MS *m/z* (%): 336 (M⁺, 3.71), 222 (6.20), 113 (66.26), 100 (100), 56 (11.51).

2-(3-Methoxyphenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5j**)

Brown oil; IR (ATR) ν_{\max} / cm^{-1} : 2958 (C-H_{sp2} stretch), 2852-2807 (C-H_{sp3} stretch), 1611 (C=O stretch), 1507 and 1458 (aromatic C=C stretch), 1111 (C-O stretch); ¹H NMR (400 MHz, *J*_{H-H} Hz) δ 2.45-2.34 (m, 5H, H-8b, H-9), 2.60-2.50 (m, 2H, H-7a, H-8a), 2.79-2.68 (m, 4H, H5, H-6a, H-7b), 3.61-3.58 (m, 4H, H-10), 3.74 (s, 3H, OCH₃), 4.05 (dt, 1H, *J* 13.8, 5.2, H-6b), 5.71 (s, 1H, H-2), 6.91 (dd, 2H, *J* 8.7, 2.0, Ph-H), 7.10 (dd, 1H, *J* 8.6, 1.7, Ph-H); ¹³C NMR (100 MHz) δ 21.5 (C-6), 34.6 (C-5), 44.2 (C-7), 53.7 (2C, C-9), 55.3 (OCH₃), 56.3 (C-8), 62.3 (C-2), 66.9 (2C, C-10), 114.0, 127.8, 131.3, 159.4, 169.4 (C-4); GC-MS *m/z* (%): 336 (M⁺, 2.55), 222 (1.68), 113 (42.86), 100 (100), 56 (9.69).

2-(4-Methoxyphenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5k**)

Yellow oil; IR (ATR) ν_{\max} / cm^{-1} : 2941 (C-H_{sp2} stretch), 2851 (C-H_{sp3} stretch), 1601 and 1460 (aromatic C=C stretch), 1627 (C=O stretch), 1115 (C-O stretch); ¹H NMR (400 MHz,

*J*_{H-H} Hz) δ 2.45-2.33 (m, 5H, H-9, H-8b), 2.62-2.50 (m, 2H, H-6b, H-8a), 2.78-2.71 (m, 4H, H-7b, H-5, H-6a), 3.6-3.56 (m, 4H, H-10), 3.74 (s, 3H, OCH₃), 4.05 (dt, 1H, *J* 13.8, 5.3, H-7a), 5.71 (s, 1H, H-2), 6.81 (d, 2H, *J* 8.7, Ph-H), 7.09 (d, 2H, *J* 8.7, Ph-H); ¹³C NMR (125 MHz) δ 21.8 (C-6), 34.5 (C-5), 53.8 (2C, C-9), 55.4 (OCH₃), 56.4 (C-8), 62.45 (C-2), 67.0 (2C, C-10), 114.0, 127.8, 132.3, 159.4, 169.5 (C4); GC-MS *m/z* (%): 336 (M⁺, 2.14), 222 (6.70), 113 (36.21), 100 (100), 86 (5.48), 44 (2.70).

2-(2-Hydroxyphenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5l**)

Brown oil; IR (ATR) ν_{\max} / cm^{-1} : 3344 (OH stretch), 3070 (C-H_{sp2} stretch), 2950 and 2899 (C-H_{sp3} stretch), 1615 (C=O stretch), 1591 and 1441 (aromatic C=C stretch), 1115 (C-O stretch); ¹H NMR (600 MHz, *J*_{H-H} Hz) δ 2.51-2.42 (m, 5H, H-8b, H-9), 2.60-2.54 (m, 2H, H-6b, H-8a), 2.83-2.70 (m, 4H, H5, H-6a, H-7b), 3.62 (q, 4H, *J* 4.2, H-10), 4.08 (dt, 1H, *J* 13.8, 5.3, H-7a), 5.65 (s, 1H, H-2), 6.73 (dd, 2H, *J* 7.9, 1.8, Ph-H), 7.00 (d, 2H, *J* 7.9, Ph-H); ¹³C NMR (150 MHz) δ 21.7 (C-6), 34.4 (C-5), 44.4 (C-7), 62.5 (C-2), 53.6 (2C, C-9), 56.1 (C-8), 66.7 (2C, C-10), 115.5, 127.8, 129.8, 156.7, 170.0 (C4); GC-MS *m/z* (%): 322 (M⁺, 0.50), 113 (43.55), 100 (100), 86 (2.17), 44 (20.68).

2-(3-Hydroxyphenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5m**)

Brown oil; IR (ATR) ν_{\max} / cm^{-1} : 3244 (OH stretch), 2949 (C-H_{sp2} stretch), 2944 (OH stretch), 2861 and 2820 (C-H_{sp3} stretch), 1605 (C=O stretch), 1526-1456 (aromatic C=C stretch), 1108 (C-O stretch); ¹H NMR (400 MHz, *J*_{H-H} Hz) δ 2.50-2.38 (m, 5H, H-8b, H-9), 2.60-2.54 (m, 2H, H-6b, H-8a), 2.84-2.72 (m, 4H, H-5, H-6a, H-7a), 3.61 (q, 4H, *J* 4.2, H10), 4.09 (dt, 1H, *J* 13.8, 5.3, H7b), 5.69 (s, 1H, H2), 6.62 (d, 1H, *J* 1.8, Ph-H), 6.71 (dd, 2H, *J* 7.9, 1.8, Ph-H), 7.24 (d, 2H, *J* 7.9, Ph-H); ¹³C NMR (100 MHz) δ 21.6 (C-6), 34.5 (C-5), 44.8 (C-7), 54.7 (2C, C-9), 57.3 (C-8), 63.6 (C-2), 67.9 (2C, C-10), 114.1, 116.3, 119.5, 131.2, 141.9, 157.7, 170.9 (C4); GC-MS *m/z* (%): 322 (M⁺, 1.23), 113 (35.67), 100 (100), 86 (6.93), 44 (2.00).

2-(4-Hydroxyphenyl)-3-(2-morpholinoethyl)1,3-thiazinan-4-one (**5n**)

Yellow oil; IR (ATR) ν_{\max} / cm^{-1} : 3305 (OH stretch), 3056 (C-H_{sp2} stretch), 2970 and 2869 (C-H_{sp3} stretch), 1636 (C=O stretch), 1610 and 1461 (aromatic C=C stretch), 1112 (C-O stretch); ¹H NMR (600 MHz, *J*_{H-H} Hz) δ 2.50-2.42 (m, 5H, H-8b, H-9), 2.60-2.54 (m, 2H, H-6b, H-8a), 2.84-2.70 (m, 4H, H-5, H-6a, H-7b), 3.44 (dt, 1H, *J* 13.3, 5.7, H-7a), 3.71 (q, H4, *J* 4.6, H-10), 4.16 (dt, 1H, *J* 13.7, 5.6, H-6b), 5.74 (s, 1H, H-2), 6.82 (d, 2H, *J* 8.6, Ph-H), 7.08 (d, 2H,

J 8.5, Ph-H); ^{13}C NMR (150 MHz) δ 21.7 (C-6), 34.5 (C-5), 44.4 (C-7), 53.7 (2C, C-9), 56.2 (C-8), 62.5 (C-2), 66.7 (2C, C-10), 115.6, 127.9, 156.8, 170.1 (C-4); GC-MS *m/z* (%): 322 (M^+ , 1.36), 113 (32.58), 100 (100), 86 (7.14), 44 (3.09).

Results and Discussion

One-pot synthesis of thiazinanones by the conventional thermal heating method

To the synthesis of thiazinanones **5a-n**, three components were used as the starting materials: the mercaptoacetic acid, arenaldehydes bearing electron-withdrawn or electron-releasing groups, and the 2-morpholinoethylamine. The choice for 2-morpholinoethylamine as amine core was due the biological importance of heterocyclic morpholine. Compounds with this scaffold feature a wide range of biological activities, recently reviewed by Paľchkov.²⁰

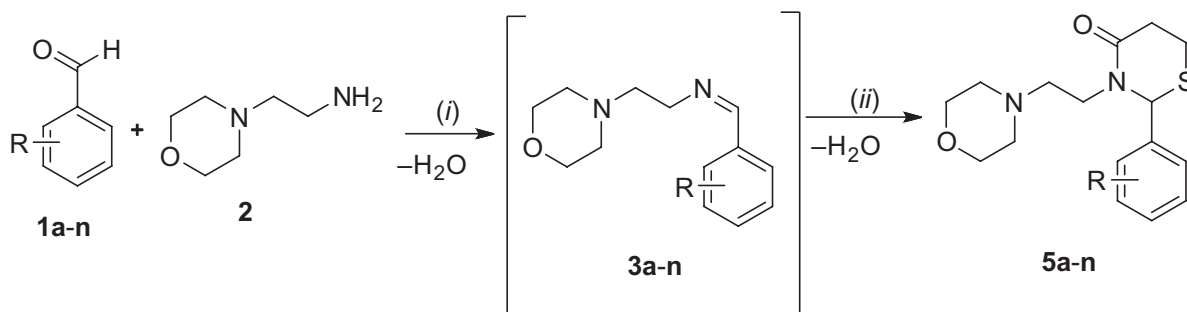
Our first purpose was the synthesis of heterocycles by the conventional thermal heating methodology (Scheme 1). The expected compounds were synthesized through the one-pot reaction procedure in toluene refluxing. In this procedure, the intermediate imine was completely formed (3 h) before the cyclocondensation step to the thiazinanones (16 h). The water was removed by azeotropic distillation using a Dean-Stark apparatus and the progresses of all reactions were monitored by thin layer chromatography (TLC) and/or by GC. The heterocycles were obtained in moderate to excellent yields after the purification by washing with hot hexane/ethyl acetate (9:1).

Sonification effect on the multicomponent synthesis of thiazinanones

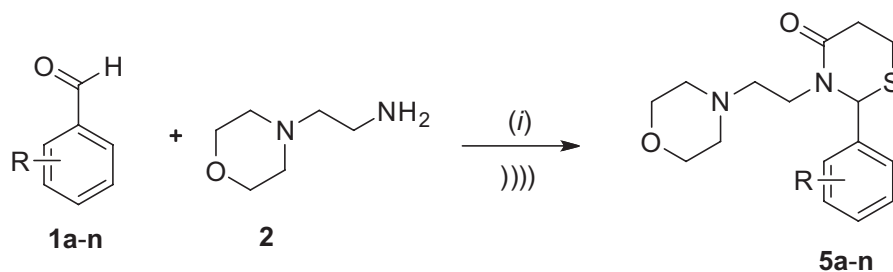
The six-membered thiazinanone has structural similarity to the five-membered thiazolidinone, so the reaction condition using ultrasound was based in such heterocycle, according to a recent work published by us.¹² 2-Morpholinoethylamine is an aliphatic amine and the first experiment was carried out in a multicomponent reaction of amine **2**, 2-nitrobenzaldehyde **1a** and mercaptopropionic acid **4** (3 equivalents) in toluene for 5 min. However, it was observed the starting material aldehyde in TLC and GC. The next experiment was monitored by TLC in ten, fifteen, twenty and twenty-five minutes. The complete formation of thiazinanone **5a** (up to 99% in GC) was observed in 25 min. The product was isolated and all spectrometric and spectroscopic data are identical to those for thiazinanone **5a** prepared by the conventional method. Further, the proportion of the mercaptopropionic acid **4** was also studied and no significant difference on yields was found when 1, 2 or 3 equivalents of acid were used.

Found the best condition, the synthesis of all thiazinanones **5a-n** were carried out in a mixture of 1 mmol of arenaldehydes **1a-n**, 1 mmol of amine **2** and 1 mmol of the mercaptopropionic acid **4** that was sonicated for 25 min in toluene (Scheme 2). The heterocycles **5a-n** were obtained in a range of 41-88%, without further purification.

The comparative yields of thiazinanones **5a-n** are summarized in Table 1. The electronic nature of arenaldehyde substituent did not affect the yields



Scheme 1. (i) Toluene, 110 °C, 3h; (ii) HSCH₂CH₂COOH, 110 °C, 16h (49-97%).



Scheme 2. (i) Toluene, HSCH₂CH₂COOH, ultrasound, r.t., 25 min (41-88%).

of products as well the position, with exception for thiazinanones **5l-n** bearing a phenolic group that showed lower yields. A possible explanation is the polar hydroxyl group that increase water solubility and an amount of product might be lost in the extraction procedure.

As we expected, the sonochemistry methodology afford the pure thiazinanones in lower reaction times than conventional heating (25 minutes to 19 hours) in quite similar yields. Other important advantage of ultrasound methodology is the absence of water remove procedure, e.g., azeotropic distillation, desiccant agents.

Table 1. Yields of thiazinanones **5a-n** synthesized by ultrasound and thermal heating methodologies

entry	R	Yield ^a / %	
		Thermal heating	Ultrasound
5a	2-NO ₂	87	71
5b	3-NO ₂	79	86
5c	4-NO ₂	89	73
5d	2-F	97	82
5e	3-F	74	48
5f	2-Cl	85	46
5g	3-Cl	91	86
5h	4-Cl	64	78
5i	2-OCH ₃	88	85
5j	3-OCH ₃	87	75
5k	4-OCH ₃	84	88
5l	2-OH	60	53
5m	3-OH	72	55
5n	4-OH	49	41

^aYield of isolated compounds.

The fourteen unpublished thiazinanones were identified and characterized by mass spectrometry and ¹H and ¹³C NMR spectroscopy. The 2D NMR techniques heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) were necessary to the correct assignments of hydrogens and carbons. The ¹H NMR spectrum shows that the aromatic signals appear in the range of 8.24-7.00 ppm, the H2 hydrogen as a singlet at 6.85-5.68 ppm. The H10 and H9 of the morpholine ring are assigned as a triplet or multiplet at 3.63-3.57 ppm and as a multiplet in the range of 2.48-2.33 ppm, respectively. The H7a of ethylene bridge is shown as a double triplet at 4.20-4.06 ppm (²J = 14.0-13.0 Hz, ³J = 5.6-4.2 Hz) and H7b and H8 appear as multiplets with superposition of signals. The four diastereotopic H5 and H6 of thiazinanone ring are shown as multiplets due the superposition of signals in

the range of 2.82-2.51 ppm. In ¹³C NMR, the C10 and C9 of morpholine ring appear at 66.7-67.9 ppm and 53.6-56.0 ppm, respectively. The chemical shift of ethylene carbons shows that C8 is deshielded at 67.9-66.7 ppm and C7 are shielded at 56.0-53.6 ppm, according to HMQC spectra. The carbons of thiazinanones are assigned as 174.2-169.2 ppm for the carbonyl (C4), 62.2-57.0 ppm for the C2, 34.6-34.1 ppm for C5 and 21.8-21.5 ppm for C6. The HMBC confirm the assignment of C5 and C6.

Conclusions

Therefore, the sonochemistry was efficient as an attractive strategy to promote the synthesis of thiazinanones through a multicomponent reaction. The products were obtained in good yields in shorter reaction times (25 min) when compared to thermal heating methodology (19 h). In addition, no water removal was necessary when the ultrasound was used.

Supplementary Information

Supplementary information with analytical data (mass, ¹H and ¹³C NMR and infrared spectra) is available free of charge at <http://jbcs.sbq.org.br> as PDF file.

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