Ultrasonics Sonochemistry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method

Pedro De-la-Torre [a,b,*], Edison Osorio [b], Jans H. Alzate-Morales [b], Julio Caballero [b], Jorge Trilleras [c], Luis Astudillo-Saavedra [a], Iván Brito [d], Alejandro Cárdenas [e], Jairo Quiroga [f], Margarita Gutiérrez [a,*]

[a] Organic Synthesis Laboratory and Biological Activity (LSO-Act-Bio), Institute of Chemistry of Natural Resources, Universidad de Talca, Casilla 747, Talca, Chile
[b] Center for Bioinformatics and Molecular Simulation, Universidad de Talca, 2 Norte 685, Casilla 721, Talca, Chile
[c] Research Group Heterocyclic Compounds, Chemistry Program, Universidad del Atlántico, Km 7 vía Puerto Colombia, Barranquilla, Colombia
[d] Department of Chemistry, Universidad de Antofagasta, Av. Angamos 601, Casilla 170, Antofagasta, Chile
[e] Department of Physics, Universidad de Antofagasta, Av. Angamos 601, Casilla 170, Antofagasta, Chile
[f] Heterocyclic Compounds Research Group, Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia

ARTICLE INFO

Article history:
Received 26 November 2013
Accepted 20 February 2014
Available online xxxx

Dedicated to the memory of Professor Luis Astudillo Saavedra for his scientific career, support and fraternity.

Keywords:
Knoevenagel reactions
Phase-transfer catalysis
Microwave
Ultrasound
Density functional theory
X-ray crystallography

ABSTRACT

Given the broad spectrum of uses of acrylonitrile derivatives as fluorescent probes, AChE inhibitors, and others, it is necessary to find easy, efficient and simple methods to synthesize and diversify these compounds. We report the results of a comparative study of the effects of three techniques on the reactions between heterocyclic aldehydes and 2-(benzo[*d*]thiazol-2-yl)acetonitrile: stirring; ultrasound coupled to PTC conditions (US-PTC); and MW irradiation (MWI) under solvent and catalyst-free conditions. The effects of conditions on reaction parameters were evaluated and compared in terms of reaction time, yield, purity and outcomes. The US-PTC method is more efficient than the MWI and conventional methods. The reaction times were considerably shorter, with high yields (>90%) and good levels of purity. In addition, X-ray diffraction analysis and quantum mechanical calculations, at the level of density functional theory (DFT), ratify obtaining acrylonitrile isomers with *E* configurations. The crystal structure of **3c** is stabilized by weak C–$H_o\cdots$N intermolecular interactions ($H_o\cdots$NC = 2.45 Å, $C_o\cdots$NC = 3.348(3) Å, $H_o\cdots$NC = 162°), forming centrosymmetric ring R_2^2 (20) along the crystallographic *a* axis.

1. Introduction

Knoevenagel condensation has been extensively studied and used for the preparation of a broad spectrum of substituted alkenes [1], including the antimalarial drug lumefrantine [2], and some acrilonitrile derivatives [3]. The 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1** (Fig. 1) is a heterocyclic system used in the synthesis of libraries of compounds by Knoevenagel condensation [3,4].

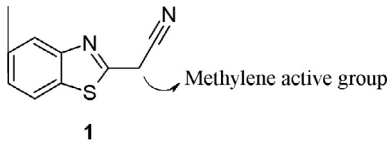
Some derivatives and analogs have interesting biological properties, including antifungal, antitumor, and antibacterial activities [5–9]. In addition, they have been used as β-glucuronidase inhibitors [10], as scaffolds for the design of dendrimers [11], and as acetylcholinesterase (AChE) inhibitors [4]. They have also been reported in the literature as versatile precursors for building molecules with potential biological or pharmaceutical applications [2,12–17].

Several methodologies have been developed to carry out Knoevenagel condensation, including the use of strong bases [18], micro reactors using zeolite catalysts [19,20], ionic liquids [21,22], inorganic and organic supports [23–25], reactions in aqueous medium [26], ultrasound [27], and microwave-assisted irradiation [3]. However, many of these methodologies involve the use of organic solvents and costly reagents, the formation of reaction byproducts, and toxicity, as well as presenting the problem of disposal.

* Corresponding authors at: Organic Synthesis Laboratory and Biological Activity (LSO-Act-Bio), Institute of Chemistry of Natural Resources, Universidad de Talca, Casilla 747, Talca, Chile. Tel.: +56 71 200 389 (P. De-la-Torre). Tel.: +56 71 200 389; fax: +56 71 200 448 (M. Gutiérrez).

E-mail addresses: pdelatorre@utalca.cl (P. De-la-Torre), eosorio@utalca.cl (E. Osorio), jalzate@utalca.cl (J.H. Alzate-Morales), jcaballero@utalca.cl (J. Caballero), jorgetrilleras@mail.uniatlantico.edu.co (J. Trilleras), lastudi@utalca.cl (L. Astudillo-Saavedra), ibrito@uantof.cl (I. Brito), acardenas@uantof.cl (A. Cárdenas), jairo.quiroga@correounivalle.edu.co (J. Quiroga), mgutierrez@utalca.cl (M. Gutiérrez).

http://dx.doi.org/10.1016/j.ultsonch.2014.02.021
1350-4177/



1

Fig. 1. 2-(benzo[*d*]thiazol-2-yl)acetonitrile structure.

The use of ultrasound irradiation (USI) to promote reactions in organic chemistry has had a major impact in recent years, [28–33] because it offers versatility, rapidity and high reaction yields, while being eco-friendly by employing water as a solvent [34]. Some investigations have coupled USI with other synthetic methods in order to promote organic reactions more efficiently, such as ultrasound coupled with phase transfer catalysis (PTC) [35].

Reactions using PTC conditions are among the most attractive synthetic methods from the environmental point of view because they make minimal use of toxic organic solvents and reagents, coupled with higher yields and reduced reaction times. However, classical PTC conditions often require strong basic conditions with NaOH as a catalyst and the presence of quaternary ammonium salts (Quats) or crown ethers as nucleophile stabilizers [36]. Thus, the search for facile protocols to produce Knoevenagel adducts by eco-friendly synthetic methods, with high yields, short reaction times and high levels of purity, is of interest in synthetic and medicinal chemistry.

In this work, we compared stirring at room temperature (rt), ultrasound (USI), and MWI-assisted (MWI) and USI-PTC techniques to promote the Knoevenagel reaction for the synthesis of (*E*)-2-(benzo[*d*]thiazol-2-yl)-3-heteroaryl-acrylonitriles **3** in order to ascertain the most useful methodology in general terms. We conducted X-ray diffraction analysis and made quantum mechanical calculations to gain a better understanding of the minimum energy conformation for acrylonitriles.

2. Experimental

2.1. Materials and methods

Three methods (A, B and C) were used for the reactions, which were monitored by thin layer chromatography (TLC), with visualization of the spots by UV light. TLC was done on plates pre-coated with silica gel (Merck). Solvents employed for the reactions and recrystallization were of analytical grade. Nuclear magnetic resonance spectra were recorded in diluted solutions of $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 instrument. Melting points were recorded on a Buchi apparatus and are uncorrected, IR spectra, KBr pellets, 500–4000 cm^{-1} were recorded on a Thermo Nicolet NEXUS 670 FT-IR spectrophotometer. High-resolution mass spectrometry ESI-MS and ESI-MS/MS analyses were conducted in a high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) mass spectrometer (Waters/Micromass Q-TOF micro, Manchester, UK) with a constant nebulizer temperature of 100 °C. The experiments were carried out in positive ion mode, and the cone and extractor potentials were set at 10 and 3.0 V, respectively, with a scan range of *m*/*z* 100–600. MS/MS experiments were carried out by mass selection of a specific ion in Q1, which was then submitted to collision-induced dissociation (CID) with helium in the collision chamber. The MS product ions were analyzed with a high-resolution orthogonal TOF analyzer. The samples were infused directly into the ESI source via a syringe pump at flow rates of 5 μL min^{-1}, via the instrument's injection valve.

2.2. General procedure for the synthesis of acrylonitriles 3

2.2.1. Method A (rt)

Compounds were synthesized as described in recent publications [4], using ethanol (10 mL) as a solvent, catalytic amounts of trietylamine (0.2 mL) and stirring at rt (19 °C). The solid products were isolated by simple filtration of the reaction mixture and crystallization from ethanol.

2.2.2. Method B (US)

(a) Ultrasonic irradiation was performed using a ultransonic reactor (Elma transsonic 460, Elma, Singen, Germany), with a mechanical timer (60 min with continuous hold) and heater switch, frequency of 35 kHz using ethanol (10 mL), and triethylamine (0.2 mL). (b) US-PTC, TEA (0.2 mL), 5 mL of ethanol:H_2O (50%), tetrabutylammonium bromide (TBAB) 20 mol%, 35 kHz. The solid products were collected by filtration and washed with ethanol:H_2O (50%) to remove the TBAB and TEA to yield compounds **3**.

2.2.3. Method C (MW)

Reactions were performed in a focused microwave reactor (CEM Discover TM), with power of 105 W and a temperature of 373 K. The solid products were isolated by crystallization of the reaction mixture from ethanol and washed with a mixture of hexane/ethanol (7:3) to give the corresponding compounds. The solid products obtained were purified by flash column chromatography using ethyl acetate–ether (3:7) or dichloromethane as an eluent to obtain pure compounds.

The spectral data and melting point of compound **3a–l** were consistent with values in the literature [3,4]. The authenticity of the **3m–v** products was established by their ^{1}H NMR, IR, and MS data. The yields obtained and times are summarized in Tables 1 and 2.

Data for (*E*)-2-(benzo[*d*]thiazol-2-yl)-3-[5-(4-nitrophenyl)furan-2-yl]acrylonitrile (**3m**): red solid, yield by US 70%, mp 239–242 °C. IR (KBr) cm^{-1}: 3120, 3052, 29176, 2213 (CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.33 (d, 2H, J = 8.81 Hz, H_o), 8.08 (s, 1H, H—C═), 8.06 (d, 1H, J = 8.07 Hz H4′$_{BT}$), 8.01 (d, 2H, J = 8.80 Hz, H_m), 7.91 (d, 1H, J = 8.07 Hz, H7′$_{BT}$), 7.53 (t, 1H, H6′$_{BT}$), 7.43 (t, 1H, H5′$_{BT}$), 7.27 (d, 1H, H3$_{furanyl}$), 7.10 (d, 1H, J = 3.91 Hz, H4$_{furanyl}$); EI-MSMS (*m*/*z*): 373.0313 (M$^+$, 100.00), 372.0096 (33.69), 326.0505 (7.57), 298.0530 (7.11), 251.0288 (14.68), 222.0257 (7.86), 198.0231 (8.28), 76.0310 (2.28).

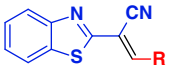
(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-[5-(methylacetate)furan-2-yl]acrylonitrile (**3n**): Yellow solid, yield by US 42%, mp 116–118 °C. IR (KBr) cm^{-1}: 3118, 3054, 2923, 2201 (CN), 1588, 1741 (C═O), 1229. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.05 (d, 1H, H4′$_{BT}$), 8.03 (s, 1H, H—C═), 7.90 (d, 1H, J = 8.07 Hz, H7′$_{BT}$), 7.51 (t, 1H, H6′$_{BT}$), 7.41 (t, 1H, H5′$_{BT}$), 7.32 (d, 1H, J = 3.43 Hz, H3$_{furanyl}$), 6.63 (d, 1H, J = 3.42 Hz, H4$_{furanyl}$), 5.15 (s, 2H, CH_2–O), 2.13 (s, 1H, CO–CH_3); EI-MSMS (*m*/*z*): 324.0538 (M$^+$, 34.39), 281.9926 (11.70), 251.0176 (100.00), 222.0245 (8.18), 198.0252 (3.23).

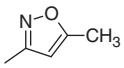
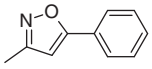
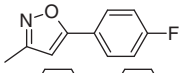
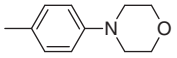
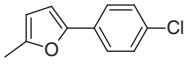
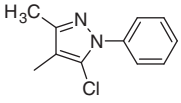
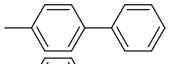
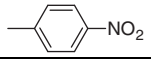
(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-[2-(chloroquinolin)-3-yl]acrylonitrile (**3o**): Yellow solid, yield by US 58%, mp 198–201 °C. IR (KBr) cm^{-1}: 3081, 3056, 2218 (CN), 1571, 1479. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.07 (s, 1H, H4$_{quinoline}$), 8.66 (s, 1H, H—C═), 8.16 (d, 1H, J = 8.32 Hz, H8$_{quinoline}$), 8.00 (d, 1H, J = 8.07 Hz, H4′$_{BT}$), 7.94 (d, 1H, J = 8.07 Hz, H7′$_{BT}$), 7.85 (t, 1H, H6$_{quinoline}$), 7.66 (t, 1H, H7$_{quinoline}$), 7.57 (t, 1H, H6′$_{BT}$), 7.48 (t, 1H, H5′$_{BT}$). EI-MSMS (*m*/*z*): 346.9782 (M$^+$, 100), 312.8994 (57.32), 179.7984 (38.57),

(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(6-chloro[1,3]dioxolo[4,5-*g*]quinoline-7-yl)acrylonitrile (**3p**): Yellow solid, yield by US 57%, mp 288–290 °C. IR (KBr) cm^{-1}: 3041, 2996, 2220 (CN), 1574, 1485, 1251. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.90 (s, 1H, H4$_{quinoline}$), 8.62 (s, 1H, H—C═), 8.15 (d, 1H, J = 8.31 Hz, H4′$_{BT}$), 7.94 (d, 1H, J = 8.07 Hz, H7′$_{BT}$), 7.58 (t, 1H, H6′$_{BT}$), 7.49 (t, 1H, H5′$_{BT}$), 7.33 (s, 1H,

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

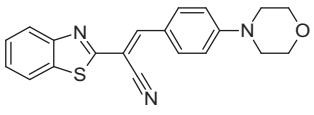
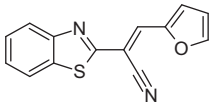
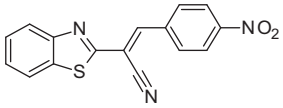
Table 1
Products of Knoevenagel condensation and comparisons of methods A [4], B and C.



Compound	R	mp (°C)[4]	Yield (%)			Time reaction min		
			rt[a][4]	USI[b]	MWI[c]	rt[a]	USI[b]	MWI[c]
3a[4]		209–211	84	87	88	18	10	9
3b[4]		241–243	87	90	89	15	8	7
3c[4]		228–230	85	88	90	17	9	8
3d[4]		244–246	40	46	47	21	13	9
3e[4]		190–192	80	83	85	40	12	11
3f[4]		155–157	66	70	75	18	5	4
3g[4]		185–187	59	82	68	25	7	10
3h[4]		188–190	59	61	67	26	7	7
3i[4]		138–140	51	60	62	22	8	8
3j[4]		191–193	84	84	85	20	7	10
3k[4]		158–160	83	86	87	14	6	4
3l[3]		170–172[3]	25	48	50[3]	42	19	20[3]

Conditions.
[a] Method A: Ethanol/Trietylamine/Stirring/rt: 19 °C.
[b] Method B: Ethanol/Trietylamine/Ultrasound, 35 kHz/rt: 19 °C.
[c] Method C: Catalyst/Solvent Free/MW/100 °C/105 W.

Table 2
Conditions and results of ultrasound-assisted phase-transfer catalysis in aqueous medium to promote the Knoevenagel reaction.

Compound	Enty	Conditions*		Method A (conventional)*	Method B (US-35 kHz)*	Method C (105 W/100 °C)[c]
		Solvent	Catalyst	Time (min)/Yield (%)	Time (min)/Yield (%)	Time (min)/Yield (%)
 3d	1	None	Catalyst free	–[d]	–	12/47
	2[4]	Ethanol	TEA	21/40	13/46	13/44
	3[a]	H_2O	$NaOH_{(aq)}$:TBAB	8/13	4/10	–
	4[b]	Ethanol:H_2O	TEA:TBAB	20/41	9/88	–
 3i	1a	None	Catalyst free	–	–	8/62
	2a[4]	Ethanol	TEA	22/51	8/60	8/61
	3a[a]	H_2O	$NaOH_{(aq)}$:TBAB	6/15	3/17	–
	4a[b]	Ethanol:H_2O	TEA:TBAB	20/53	1.5/79	–
 3l	1b[3]	None	Catalyst free	–	–	20/50[3].
	2b	Ethanol	TEA	25/42	19/48	19/52
	3b[a]	H_2O	$NaOH_{(aq)}$:TBAB	5/9	5/14	–
	4b[b]	Ethanol:H_2O	TEA:TBAB	7/55	8/75	–

Entry 1a is also empty to highlight the conditions of the entries 2–4.
[a] Ratios: NaOH 50%: TBAB 20 mol%.
[b] Ratios: EtOH:H_2O (50%), TEA: 0.2 mL, TBAB 20 mol%.
[c] Method A and B at ambient temperature 19 °C; MWI at 100 °C.
[d] Entries 1 and 1b are empty with the rt and USI methods because the aldehydes used as precursors are in the solid-state and could not react under conditions of stirring at rt or USI.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

$H5_{quinoline}$), 7.20 (s, 1H, $H8_{quinoline}$), 6.19 (s, 1H, O–CH_2–O); EI-MSMS (*m*/*z*): 391.9835 (M^+, 0.91), 390.9780 (3.54), 356.9911 (23.53), 355.9853 (100.00), 298.0354 (10.06), 177.7071 (14.42).

(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(1-methyl-1*H*-imidazol-2-yl)acrylonitrile (**3q**): Yellow solid, yield by US 61%, mp 235–237 °C. IR (KBr) cm^{-1}: 3045, 2211 (CN), 1596, 1478, 1416. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.17 (s, 1H, H—C=), 8.03 (d, 1H, J = 8.31 Hz, $H4'_{BT}$), 7.93 (d, 1H, J = 8.07 Hz, $H7'_{BT}$), 7.53 (t, 1H, $H6'_{BT}$), 7.46 (s, 1H, $H4_{imidazole}$), 7.42 (t, 1H, $H5'_{BT}$), 7.11 (s, 1H, $H5_{imidazole}$), 3.90 (s, 1H, N–CH_3); EI-MSMS (*m*/*z*): 266.0629 (M^+, 100.00), 265.0554 (45.55), 240.0594 (10.12), 233.0829 (10.27), 198.0238 (19.07), 132.0571 (12.58).

(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(6-isopropyl-4-oxo-4*H*-chromen-3-yl)acrylonitrile (**3r**): Yellow solid, yield by US 36%, mp 198–199 °C. IR (KBr) cm^{-1}: 2958, 2915, 2859, 2195 (CN), 1663, 1612 (C=O). ^1H NMR (400 MHz, DMSO-d_6): δ ppm 8.06 (d, 1H, J = 7.82 Hz, $H4'_{BT}$), 7.77–7.76 (m, 2H, $H7'_{BT}$ and H—C=), 7.69 (s, 1H, $H_{\beta C}$=O), 7.62–7.56 (m, 2H, $H6'_{BT}$ and $C8_{chromone}$) 7.47 (t, 1H, $H5'_{BT}$), 7.33 (s, 1H, $C5_{chromone}$), 7.06 (d, 1H, J = 8.56 Hz, $C7_{chromone}$), 2.95 (m, 1H, $CH_{isopropyl}$), 1.21 (d, 6H, $CH_{3\text{-isopropyl}}$); EI-MSMS (*m*/*z*): 372.0662 (M^+, 100.00), 356.9871 (99.69), 343.0783 (46.47), 328.9936 (20.46), 301.0415 (6.63), 210.0246 (8.00), 164.1818 (16.16), 91.0540 (5.9).

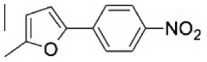
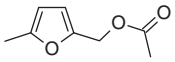
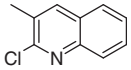
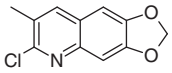
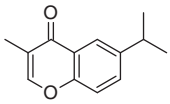
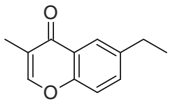
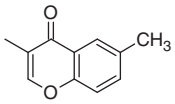
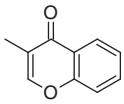
(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(6-ethyl-4-oxo-4*H*-chromen-3-yl)acrylonitrile (**3s**): Yellow solid, yield by US 34%, mp 229–230 °C. IR (KBr) cm^{-1}: 3187, 2963, 2196 (CN), 1655, 1610 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.85 (s, 1H, H—C=), 7.70 (d, 1H, J = 8.07 Hz, $H7'_{BT}$), 7.61 (d, 1H, J = 8.31 Hz, $H4'_{BT}$), 7.53 (t, 1H, $H6'_{BT}$), 744–7.4 (m, 4H, $H_{\beta C}$=O, $H5'_{BT}$, $C8_{chromone}$ and $C5_{chromone}$), 6.97 (d, 1H, J = 8.32 Hz, $C7_{chromone}$), 2.66 (q, 2H, CH_2), 1.24 (t, 3H, CH_3); EI-MSMS (*m*/*z*): 358.0247 (M^+, 100.00), 342.9775 (36.21), 329.9837 (30.64) 328.9803 (96.79), 315.0053 (17.90), 210.0213 (9.44), 157.1292 (10.37).

(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(6-methyl-4-oxo-4*H*-chromen-3-yl)acrylonitrile (**3t**): Yellow solid, yield by US 59%, mp 257–259 °C. IR (KBr) cm^{-1}: 3087, 2201 (CN), 1668, 1611 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.82 (s, 1H, H—C=), 7.70 (d, 1H, J = 8.07 Hz, $H7'_{BT}$), 7.61 (d, 1H, J = 8.32 Hz, $H4'_{BT}$), 7.53 (t, 1H, $H6'_{BT}$), 744–7.4 (m, 4H, $H_{\beta C}$=O, $H5'_{BT}$, $C8_{chromone}$ and $C5_{chromone}$), 6.94 (d, 1H, J = 8.31 Hz, $C7_{chromone}$), 2.66 (s, 3H, CH_3); EI-MSMS (*m*/*z*): 343.9991 (M^+, 60.10), 315.0551 (100.00), 290.0611 (7.89), 210.0269 (5.97).

(*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-(4-oxo-4*H*-chromen-3-yl)acrylonitrile (**3u**): Yellow solid, yield by US 51%, mp 205–207 °C. IR (KBr) cm^{-1}: 3085, 2201 (CN), 1668, 1611 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.08 (d, 1H, J = 7.83 Hz, $H4'_{BT}$), 7.88 (d, 1H, $C8_{chromone}$), 7.82 (s, 1H, H—C=), 7.79 (d, 1H, 7.82 Hz, $H7'_{BT}$), 7.68 (t, 1H, $H5'_{BT}$), 764 (m, 1H, $C6_{chromone}$), 7.49 (t, 1H, $H7'_{BT}$), 7.37 (s, 1H, $H_{\beta C}$=O), 7.23 (t, 1H, $C7_{chromone}$), 7.12 (d, 1H, J = 8.31 Hz, $C5_{chromone}$); EI-MSMS (*m*/*z*): 330.9170 (M^+, 12.45), 329.9822 (49.50), 301.0385 (100.00), 276.0476 (3.26), 210.0185 (5.23), 108.0035 (4.58).

(*E*)-2-(benzo[*d*]thiazol-2-yl)-3-pyridin-4-ylacrylonitrile (**3v**): Yellow solid, yield by US 61%, mp 252–254 °C. IR (KBr) cm^{-1}: 3170, 2212 (CN), 1588. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 8.82 (d, 2H, J = 5.87 Hz, $H_{2\text{-pyridine}}$), 8.20 (s, 1H, H—C=), 8.13 (d, 1H, J = 8.07 Hz, $H4'_{BT}$), 7.95 (d, 1H, 8.07 Hz, $H7'_{BT}$), 7.81 (d, 2H,

Table 3
Results of ultrasound-assisted phase-transfer catalysis to obtain heteroaryl-acrylonitrile derivatives.

Compound	*R*	mp (°C)	USI/TEA/Ethanol[b]		USI/TEA:TBAB/Ethanol[b]	
			Time (min)	Yield (%)	Time (min)	Yield (%)
3m		239–242	10	70	4	81
3n		116–118	30	42	9	56
3o		198–201[a]	20	58	3	92
3p		288–290[a]	9	57	6	80
3q		235–237	7	61	2	78
3r		198–199	25	36	4	50
3s		229–230	5	34	4	49
3t		257–259	6	59	3	62
3u		205–207	20	51	5	60
3v		252–254	15	61	8	94

[a] The compounds exhibit a narrow range of fusion with evidence of decomposition (darkening).
[b] Ratios: Ethanol (10 mL), TEA (0.2 mL), TBAB (20 mol%) US 35 kHz.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

Table 4
X-ray crystallographic data and structural refinement for (*E*)-2-(Benzo[*d*]thiazol-2-yl)-3-[5-(4-fluorophenyl)isoxazol-3-yl]acrylonitrile **3c**.

Empirical formula	$C_{19}H_{10}FN_3OS$
Formula weight	347.36
Temperature	293(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P−1
Unit cell dimensions	a = 5.8784(8) Å α = 88.145(8)° b = 7.5099(8) Å β = 87.031(10)° c = 17.9799(13) Å γ = 82.230(11)°
Volume	785.14(15) Å^3
Z	2
Calculated density	1.469 Mg/m^3
Absorption coefficient	2.039 mm^{-1}
F(000)	356
Crystal size	0.300 × 0.120 × 0.090 mm
Theta range for data collection	2.462–73.250°
Limiting indices	$-6 \leqslant h \leqslant 7$, $-9 \leqslant k \leqslant 9$, $-22 \leqslant l \leqslant 21$
Reflections collected/unique	5044/3021 [$R_{(int)}$ = 0.0341]
Completeness to theta	67.684° 99.4%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3021/0/226
Goodness-of-fit on F^2	1.080
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0465, wR_2 = 0.1262
R indices (all data)	R_1 = 0.0546, wR_2 = 0.1437
Extinction coefficient	n/a
Largest diff. peak and hole	0.214 and −0.342 e Å^{-3}

J = 5.62 Hz, $H_{3\text{-pyridine}}$), 7.57 (t, 1H, H5′$_{BT}$), 7.48 (t, 1H, H6′$_{BT}$); EI-MSMS (m/z): 263.0457 (M$^+$, 91.01), 262.0394 (100.00), 235.0326 (14.86), 210.0256 (14.58), 118.0699 (5.55).

2.3. X-ray crystallography

A 0.300 × 0.120 × 0.090-mm yellow needle crystal of **3c** was mounted on a goniometer head for X-ray measurements [37]. Cell unit parameters were determined on the setting angles of 5044 centered reflections in the range $2.46 \leqslant \theta \leqslant 73.25°$. The intensities of 3021 reflections were collected from $\omega/2\ \theta$ scans in the range $2.46 \leqslant \theta \leqslant 73.25°$. The collected reflections were corrected for Lorentz and polarization effects [38]. The structure was solved by direct methods with SHELXS-97 [39] and refined by a full-matrix least-squares procedure based on F^2 with SHELXL-97 [39]. The molecular structure was drawn with the aid of the OLEX2 program [40] and is presented in this article. All non-hydrogen atoms were refined anisotropically. H atoms were placed at idealized positions, with C–H distances of 0.93 Å and U_{iso} = 1.2 U_{eq}(C). The complete crystallographic data is presented in Table 4.

Table 5
Relative energies for hypothetical conformations, calculated for the products **3e**, **3f** and **3i** at three DFT levels of theory. The values are given in kcal/mol. All calculations were performed at the 6-311++G** basis set.

Products	B3LYP	TPSS	MO6-2X
3e*E*a	0.0	0.0	0.0
3e*E*b	3.0	2.8	3.2
3e*Z*b	4.2	3.7	4.4
3e*Z*a	5.8	6.2	5.3
3f*E*a	0.0	0.0	0.0
3f*E*b	1.6	1.6	1.9
3f*Z*b	6.8	7.0	5.4
3f*Z*a	5.8	5.2	6.5
3i*E*a	0.0	0.0	0.0
3i*E*b	1.6	1.6	1.8
3i*Z*b	5.8	6.7	7.7
3i*Z*a	6.4	6.1	6.5

2.4. Computational details

Conformational energy for all structures was assessed at three levels of theory: B3LYP [41,42]/6-311++G** [43,44], TPSS [45]/6-311++G** and MO6-2X [46]/6-311++G**. The imaginary frequencies were absent in all the evaluated models, which ensures that the structures correspond to a true minimum in the potential energy surface (PES) at these levels of theory. All the calculations were made with the Gaussian 03 program [47] (see Table 5).

3. Results and discussion

In the pursuit of a facile protocol to obtain heteroaryl-acrylonitrile derivatives by Knoevenagel condensation, a series of (*E*)-2-(benzo[*d*]thiazole-2-yl)-3-heteroaryl-acrylonitriles **3a–l** [3,4] were synthesized by reaction between 2-(benzo[*d*]thiazol-2-yl)acetonitrile **1** (1.0 mmol) and different substituted heteroaryl-aldehydes **2a–l** (1.0 mmol). Catalytic amounts of triethylamine (TEA) (0.2 mL) were used to promote these reactions by stirring at room temperature with ethanol (10 mL) as a solvent (Method A) [4]. Previous reports have shown that this solvent is advantageous to promote the Knoevenagel reaction [27]. To find the specific effect of ultrasound on this reaction with respect to parameters like reaction times and improved yields, we carried out the same reactions with Method B (US), using the same amount of reagents and solvent, and evaluating the effects of the microwave on solvent-free and catalyst-free conditions (MWI). The results of the different reaction setup conditions on the interaction between **1** and the aldehydes **2a–l** (rt, USI and MWI) are summarized in Scheme 1 and Table 1. The products were obtained in high purity, low to high yields and at varying reaction times.

The reactions by USI were performed in an ultrasonic reactor (Elma transsonic 460, Elma, Singen, Germany), at 19 °C (rt) and 35 kHz. The use of different frequencies from 45 to 100 kHz did not significantly affect yields. The reactions by MWI were performed in a focused microwave reactor (CEM Discover TM). The reaction mixture of **1** and **2** was irradiated at 105 watts (the same output power of 35 kHz was used in order to maintain similar conditions [27]) for 4–20 min at 373 K. The increases in irradiation periods did not significantly affect yields.

Generally, USI and MWI methods gave superior yields with shorter reaction times than did the rt method. The shorter processing time could be due to the physical phenomenon of acoustic cavitation [30–33] and, because of purely thermal/kinetic effects of the MWI method [48]. There were no significant improvements in terms of the yields of compounds **3a**–**3e**, **3j**, **3k** and **3l**. However, improvements were observed with the USI and MWI methods.

In the series of compounds, **3d** gave low yields with rt, USI and MWI, although, there was a slight improvement in yield with USI and MWI, combined with a more significant reduction in reaction time. The yield for the compound **3g** significantly improved with USI, while the yields for compounds **3f**, **3h**, **3i** and **3l** were significantly higher with MWI than with the rt method. They were also higher with the USI than with the rt method, although the difference was not as pronounced as with MWI. This analysis does not definitively demonstrate which technique is the most effective in terms of decreasing reaction times while increasing yields at the same time.

The improved yields under catalyst and solvent-free conditions could lead to the conclusion that MWI is more advantageous than the USI and rt methods. However, considering the previous results, it is not clear if the MWI method is particularly better than USI. MWI requires high temperatures (100 °C) to promote Knoevenagel condensation and organic solvents to purify products (use 30 mL of ethanol by compounds), and in some cases, it requires purification

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

by column chromatography. In comparison to the room temperature (rt of 19 °C), USI only requires filtering and washing products (30 mL of ethanol:H_2O 50%). Thus, weighing the benefits of MWI against the energy costs and the use of recrystallization with solvents and chromatography to purify derivatives, it can be argued that USI is more advantageous.

Moreover, regardless of the method of synthesis, it is worth noting as can be seen in Table 1, that the electronic effects of the electron-withdrawing and electron-releasing substituents at position 3 of *R* of the acrylonitrile derivatives had a slight effect on reaction times and yields of the products. We observed that compounds obtained from aldehydes with five member substituents, such as furanyl had lower yields, while products containing isoxazole substituents had higher yields. However, reductions in reaction times due to the influence of the furan and isoxazole nuclei were very diverse; whereby, it was not observed the same behavior.

Compounds **3d**, **3i**, and **3l** had low yields with all three methods. To improve yields, we carried out a study of the influence of different catalysts and solvents in synthesizing these compounds. Once again, we evaluated the same methods (rt, USI and MWI), but this time an ultrasound-assisted phase-transfer catalysis in aqueous medium (USI-PTC, entries 3 and 4 in Table 2) was performed.

As shown in Table 2, a slight improvement in the reaction yields is evident in the MW-reaction (entries 1, 1a and 1b) between **1** and 4-(morpholin-4-yl)benzaldehyde, furfuraldehyde and 4-NO_2-benzaldehyde to obtain **3d**, **3i** and **3l**, respectively, but not in the reaction time using MWI at 100 °C and 105 W, compared to the rt method and USI at room temperature and with 35 kHz (entries 2, 2a and 2b).

The results are striking when US is coupled with PTC conditions (entries 3–4, 3a–4a and 3b–4b). Using classical PTC conditions in the presence of aqueous sodium hydroxide and tetrabutylammonium bromide (TBAB) with the rt and USI methods, time and yields decreased for **3d** (8 min/13%, rt) and (4 min/10%, US). The same behavior was observed for **3i** and **3l** using rt and USI, respectively. This behavior could be due to the strong base conditions used, which caused the formation of reaction by-products that could not be isolated [49]. We expect that the MWI technique at high temperatures would yield poorer results. Finally, the results with USI, catalyst and solvent reaction conditions (ethanol and TEA) in the presence of TBAB in an aqueous medium (entries 4, 4a and 4b) are better than those with the solvent and catalyst-free MWI method (entry 1). Under mild USI-PTC conditions with TEA as a weak base in ethanol:H_2O (50%), the formation of reaction by-products is avoided and an efficient Knoevenagel reaction obtains **3d**, **3i** and **3l** in only 9, 1.5 and 8 min with PTC yields of 88%, 79% and 75%, respectively. These results indicate that the conditions are optimal to obtain acrylonitrile derivatives, which confirms that USI-PTC conditions in the presence of TBAB and water efficiently catalyze Knoevenagel condensation, activating the reagents with increased reaction rates and yields. In this sense, the use of USI-PTC conditions surpasses the rt and solvent and catalyst-free MWI methods.

The main advantages of the US-PTC procedure are shorter reaction times, room temperature, lower reaction temperatures, higher yields, green chemistry protocols with water instead of organic solvents and simple purification procedures. The miscibility of TBAB and TEA with water allows the development of clean reactions, as the catalyst can be removed from the product simply by washing the product with 50% aqueous alcohol.

We tested the catalysis with TEA/ethanol under USI-PTC conditions freeing the synthesis of novel acrylonitrile derivatives. Acrylonitriles **3m–v** were synthesized with the optimum frequency of 35 kHz for effective Knoevenagel condensation. The compounds were obtained in short reaction times, with good yields at room temperature (Table 3).

As shown in Table 3, the compounds were obtained in 5–30 min using USI/TEA:ethanol, with yields of 42–70%. The results were better with the USI-PTC method for both process time (2–9 min) and yield (50–94%). The majority of compounds were obtained with moderate to high yields, **3m** (81%), **3o** (92%), **3p** (80%), **3q** (78%), **3v** (94%), representing increases of 11%, 34%, 23%, 17% and 33%, respectively over the yields with the USI/TEA/ethanol methods. Yields of compounds **3n** and **3r–u** were moderate (the lowest yields of the series) 56%, 50%, 49%, 62% and 60% respectively, but the reaction times were short in all cases. We believe that the low yields of compounds **3n** and **3r–u** were due to complex mixtures of products related possibly to Michael addition adducts or hydrolysis and aperture products because of having added water to the acetate group of **3n** and in the α,β-unsaturated system of the chromone ring, respectively; which were not isolated [49–52].

The compounds **3a–l** reported in this work were characterized by comparing their spectroscopic data and melting points against previously reported data [4]. The new compounds **3m–v** were characterized by ^{1}H NMR spectra, IR and ESI-MS. ^{1}H NMR analysis for all the derivatives revealed a single olefinic proton, which was consistent with the formation of a single isomer, which was considered as the thermodynamically more stable *E* configuration [4]. However, ^{1}H NMR analysis does not effectively clarify the double-bond configuration in heteroaryl-acrylonitriles.

Since these acrylonitriles are potential candidates for biological activity tests, and in order to gain better understanding of the minimum energy conformation, we conducted an analysis of their structure and the possible conformations. Since only **3c** gave the suitable crystals for X-ray diffraction analysis, crystallographic data of this compound were collected (Fig. 2). The X-ray diffraction analysis and the quantum mechanic calculations identified the

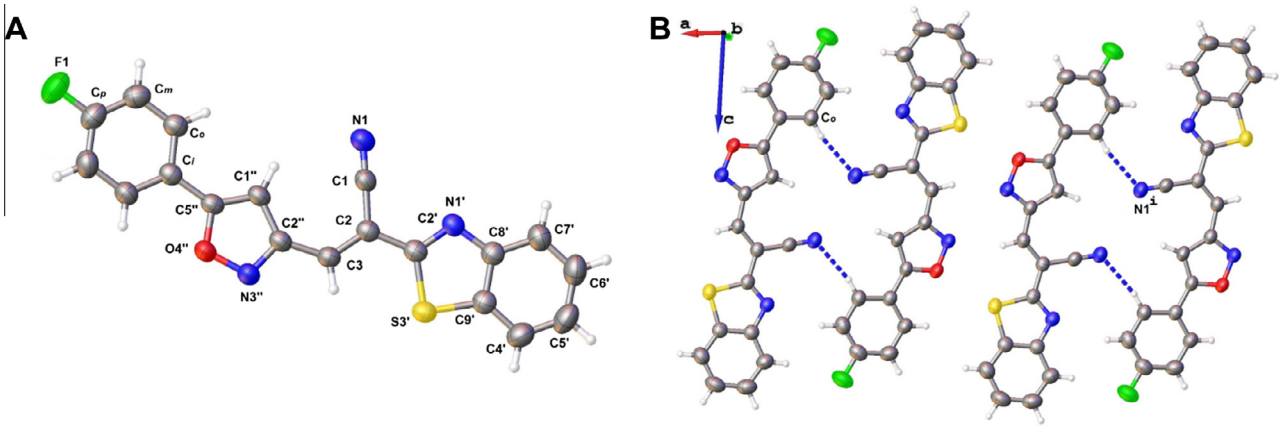


Fig. 2. X-ray crystallography data for compound **3c**.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

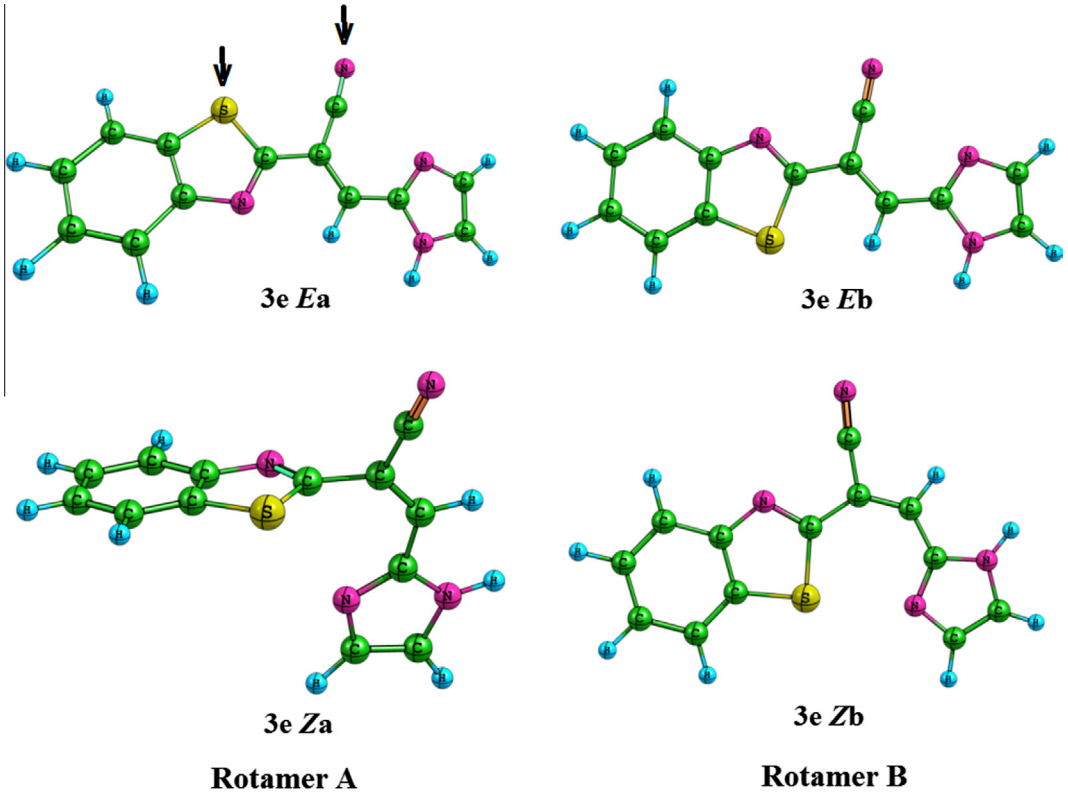


Fig. 3. The hypothetical structural conformations for product **3e**. DFT methods were able to identify that the *E* isomers **a**–**b** are more stable than the *Z* isomers **c**–**d**.

most stable energy conformations for the acrylonitriles, namely the *E* configurations.

Fig. 2A shows the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability for non-H atoms. The essentially planar benzothiazole system [maximum deviation = −0.013(1) Å for the C2′ atom] is oriented at a dihedral angle of 3.74 (11)° with respect to the isoxazole ring, whereas in the fluorophenyl moiety the dihedral twist is 3.03 (11)°. The packing of the molecules in the unit cell contains a hydrogen bond network (Fig. 2B). The crystal structure is stabilized by weak C–H···N intermolecular interaction ($H_o\cdots N2$ = 2.45 Å, $C_o\cdots N1$ = 3.348(3) Å, C_o–$H_o\cdots N2$ = 162°), forming a centrosymmetric ring $R_2^2(20)$ [53] along the crystallographic *a* axis, (see Fig. 2B). Crystallographic data is presented in Table 4.

We did a conformational energy study to determine by medium level quantum mechanic calculations which configuration (*E* or *Z* with respect to R group and the benzothiazole scaffold) is more stable (see Figs. 3 and 4). For simplicity, and in order to reduce

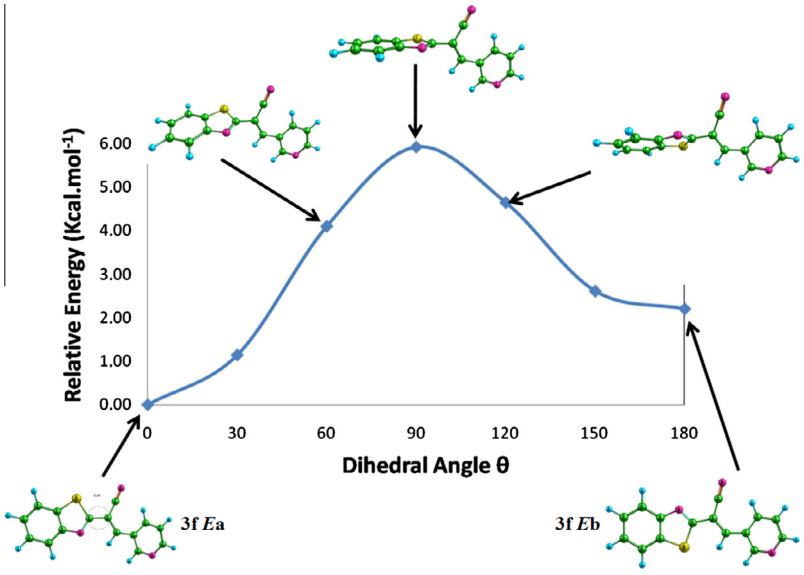
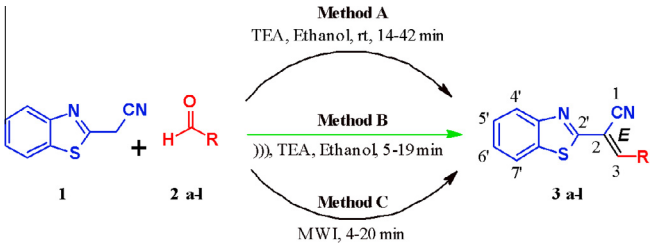


Fig. 4. The rotamers conversion energy represented as a scan profile between the **3f*Ea*** and **3f*Eb*** conformations. The low energy barrier of 5 kcal mol^{-1} allows interconversion between the two *E* isomer conformations.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021



Scheme 1. Synthesis of heteroaryl-acrylonitriles. Experimental data of the Knoevenagel reaction using stirring at room temperature, microwave or ultrasound irradiation.

computational costs, the relative energy and structural conformations of three heteroaryl-acrylonitrile products were determined (**3e**, **3f**, and **3i**). We assumed that *E* and *Z* isomers have two possible rotational isomers respect to the dihedral C2–C2′ bond. **3e*E*a** and **3e*Z*a** are considered as rotamer A where the S atom of the benzothiazole framework and the CN group are eclipsed, and **3e*E*b** and **3e*Z*b** are rotamer B where the N atom of the benzothiazole framework and the CN group are eclipsed. Density functional theory (DFT) methods were used to determine the conformations and relative energies with respect to the global minimal structure. Fig. 3 and Table 5 show that the energy difference between the *E* (**3e*E*a**) and *Z* (**3e*Z*a**) conformations is about 6 kcal/mol.

The energy difference between the **3e*E*a** and **3e*E*b** isomers, could be due to rotation of the dihedral C2–C2′ bond. In this sense, we evaluated a rotational energy profile around the dihedral angle of **3f**, as presented in Fig. 4.

The energy profile has an energy barrier close to 5 kcal/mol for conversion from **3e*E*a** to **3e*E*b** isomers, which is easily broken. This suggests that the global minimum structure is a combination of these conformations. Hence, the DFT study predicts the possible conformations of the derivatives quite well and these results nicely match with the X-ray diffraction analysis because the *E* isomer is the global minimum energy structure in both experiments.

4. Conclusions

The US-PTC method is most efficient of the three methods to promote the Knoevenagel reaction in the synthesis of acrylonitrile derivatives. High yields of (*E*)-2-(benzo[*d*]thiazole-2-yl)-3-heteroaryl-acrylonitriles were obtained in short times and under eco-friendly conditions. The results demonstrate that the TBAB and TEA under USI and PTC conditions can efficiently promote the synthesis of novel acrylonitrile derivatives (compounds **3m–v**). The present theoretical and experimental results suggest that *E* conformations are the most stable for synthesized heteroaryl-acrylonitrile derivatives.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PDM carried out the synthesis and spectroscopic characterization of synthesized compounds and monitored the experimental setup. EO implemented and carried out the computer studies. JC, JAM, LAS, MG, JT and JQ contributed with technical support and data analysis and interpretation. IB and AC carried out the X-ray diffraction analysis. All authors participated in drafting the manuscript, as well as reading and approving the final version of the manuscript.

Acknowledgements

PDM thanks the Doctoral Program of Applied Sciences of the Universidad de Talca, as well as the Chilean International Cooperation Agency (AGCI) and CONICYT-Chile for a doctoral fellowship. The authors thank 'Becas Universidad de Talca', FONDECYT project 1100481, Universidad del Atlántico and Universidad del Valle. The authors also thank the Centro de Bioinformática y Simulación Molecular (CBSM) for allowing computer time, and Horacio Poblete and Ariela Vergara for their valuable scientific comments and discussions.

References

[1] F. Freeman, Properties and reactions of ylidenemalononitriles, Chem. Rev. 80 (1980) 329–350.
[2] U. Beutler, P.C. Fuenfschilling, A. Steinkemper, An improved manufacturing process for the antimalaria drug coartem. Part II, Org. Process Res. Dev. 11 (2007) 341–345.
[3] J.E. Trilleras, K.J. Velasquez, D. Pacheco, J. Quiroga, A. Ortíz, Microwave-assisted synthesis under solvent-free conditions of (*E*)-2-(benzo[*d*]thiazol-2-yl)-3-arylacrylonitriles, J. Braz. Chem. Soc. 22 (2011) 2396–2402.
[4] P. De la Torre, L. Astudillo-Saavedra, J. Caballero, J. Quiroga, J.H. Alzate Morales, M. Gutiérrez-Cabrera, et al., A Novel class of selective acetylcholinesterase inhibitors synthesis and evaluation of (*E*)-2-(benzo[*d*]thiazol-2-yl)-3-heteroarylacrylonitriles, Molecules 17 (2) (2012) 12072–12085.
[5] J. Quiroga, D. Cobo, B. Insuasty, R. Abonía, M. Nogueras, J. Cobo, et al., Synthesis and evaluation of novel E-2-(2-thienyl)- and Z-2-(3-thienyl)-3-arylacrylonitriles as antifungal and anticancer agents, Arch. Pharm. 340 (2007) 603–606.
[6] M. Hranjec, G. Pavlović, M. Marjanović, M. Kralj, G. Karminski-Zamola, Benzimidazole derivatives related to 2,3-acrylonitriles, benzimidazo[1,2-a]quinolines and fluorenes: synthesis, antitumor evaluation in vitro and crystal structure determination, Eur. J. Med. Chem. 45 (2010) 2405–2417.
[7] H.M. Refaat, Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives, Eur. J. Med. Chem. 45 (2010) 2949–2956.
[8] A.R. Shaikh, M. Ismael, C.A. Del Carpio, H. Tsuboi, M. Koyama, A. Endou, et al., Three-dimensional quantitative structure-activity relationship (3 D-QSAR) and docking studies on (benzothiazole-2-yl) acetonitrile derivatives as c-Jun N-terminal kinase-3 (JNK3) inhibitors, Bioorg. Med. Chem. Lett. 16 (2006) 5917–5925.
[9] F. Saczewski, A. Stencel, A.M. Bieńczak, K.A. Langowska, M. Michaelis, W. Werel, et al., Structure-activity relationships of novel heteroaryl-acrylonitriles as cytotoxic and antibacterial agents, Eur. J. Med. Chem. 43 (2008) 1847–1857.
[10] K.M. Khan, F. Rahim, S.A. Halim, M. Taha, M. Khan, S. Perveen, et al., Synthesis of novel inhibitors of β-glucuronidase based on benzothiazole skeleton and study of their binding affinity by molecular docking, Bioorg. Med. Chem. 19 (2011) 4286–4294.
[11] P. Rajakumar, V. Kalpana, S. Ganesan, P. Maruthamuthu, Synthesis and DSSC application of novel dendrimers with benzothiazole and triazole units, Tetrahedron Lett. 52 (2011) 5812–5816.
[12] J. Quiroga, J. Trilleras, D. Pantoja, R. Abonía, B. Insuasty, M. Nogueras, et al., Microwave-assisted synthesis of pyrazolo[3,4-b]pyridine-spirocycloalkanediones by three-component reaction of 5-aminopyrazole derivatives, paraformaldehyde and cyclic β-diketones, Tetrahedron Lett. 51 (2010) 4717–4719.
[13] J. Quiroga, S. Cruz, B. Insuasty, R. Abonía, M. Nogueras, J. Cobo, Three-component synthesis of hexahydropyridopyrimidine–spirocyclohexanetriones induced by microwave, Tetrahedron Lett. 47 (2006) 27–30.
[14] T.-S. Jin, J.-S. Zhang, A.-Q. Wang, T.-S. Li, Ultrasound-assisted synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by p-dodecylbenzenesulfonic acid in aqueous media, Ultrason. Sonochem. 13 (2006) 220–224.
[15] J. Quiroga, J. Trilleras, J. Gálvez, B. Insuasty, R. Abonía, M. Nogueras, et al., 5-Cyanoacetylpyrimidines as intermediates for 7-aryl-6-cyanopyrido[2,3-d]pyrimidin-5-ones, Tetrahedron Lett. 50 (2009) 6404–6406.
[16] J. Quiroga, C. Cisneros, B. Insuasty, R. Abonia, M. Nogueras, A. Sánchez, A regiospecific three-component one-step cyclocondensation to 6-cyano-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-ones. Using microwaves under solvent-free conditions, Tetrahedron Lett. 42 (2001) 5625–5627.
[17] J. Quiroga, J. Trilleras, B. Insuasty, R. Abonía, M. Nogueras, A. Marchal, et al., A straightforward synthesis of pyrimido[4,5-b]quinoline derivatives assisted by microwave irradiation, Tetrahedron Lett. 51 (2010) 1107–1109.
[18] H.M. Refaat, Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives, E. J. Med. Chem. 45 (2010) 2949–2956.
[19] E.S. Xiongfu Zhang, An investigation of Knoevenagel condensation reaction in microreactors using a new zeolite catalyst, Appl. Catal. A 261 (2004) 109–118.
[20] W.N. Lau, K.L. Yeung, R. Martin-Aranda, Knoevenagel condensation reaction between benzaldehyde and ethyl acetoacetate in microreactor and membrane microreactor, Microporous Mesoporous Mater. 115 (2008) 156–163.
[21] F. Santamarta, P. Verdía, E. Tojo, A simple, efficient and green procedure for Knoevenagel reaction in [MMIm][MSO_4] ionic liquid, Catal. Commun. 9 (2008) 1779–1781.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021

[22] C. Yue, A. Mao, Y. Wei, M. Lü, Knoevenagel condensation reaction catalyzed by task-specific ionic liquid under solvent-free conditions, Catal. Commun. 9 (2008) 1571–1574.
[23] D. Jain, C. Khatri, A. Rani, Fly ash supported calcium oxide as recyclable solid base catalyst for Knoevenagel condensation reaction, Fuel Process. Technol. 91 (2010) 1015–1021.
[24] M.B. Ansari, H. Jin, M.N. Parvin, S.-E. Park, Mesoporous carbon nitride as a metal-free base catalyst in the microwave assisted Knoevenagel condensation of ethylcyanoacetate with aromatic aldehydes, Catal. Today 185 (2012) 211–216.
[25] A. Vass, A. Földesi, T. Lóránd, Reactions of 3-isochromanone with aromatic aldehydes–microwave assisted condensations performed on solid basic inorganic supports, J. Biochem. Biophys. Methods 69 (2006) 179–187.
[26] M.L. Deb, P.J. Bhuyan, Uncatalysed Knoevenagel condensation in aqueous medium at room temperature, Tetrahedron Lett. 46 (2005) 6453–6456.
[27] Q. Liu, H. Ai, Z. Li, Potassium sorbate as an efficient and green catalyst for Knoevenagel condensation, Ultrason. Sonochem. 18 (2011) 477–479.
[28] D.J. Pacheco, L. Prent, J. Trilleras, J. Quiroga, Facile sonochemical synthesis of novel pyrazolyne derivates at ambient conditions, Ultrason. Sonochem. 20 (2013) 1033–1036.
[29] G. Cravotto, P. Cintas, Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications, Chem. Soc. Rev. 35 (2006) 180–196.
[30] A. Ziarati, J. Safaei-Ghomi, S. Rohani, Sonochemically synthesis of pyrazolones using reusable catalyst CuI nanoparticles that was prepared by sonication, Ultrason. Sonochem. 20 (2013) 1069–1075.
[31] T.J. Mason, Sonochemistry and sonoprocessing: the link, the trends and (probably) the future, Ultrason. Sonochem. 10 (2003) 175–179.
[32] J. Trilleras, E. Polo, J. Quiroga, J. Cobo, M. Nogueras, Ultrasonics promoted synthesis of 5-(pyrazol-4-yl)-4,5-dihydropyrazoles derivatives, Appl. Sci. 3 (2013) 457–468.
[33] M. Shekouhy, A. Hasaninejad, Ultrasound-promoted catalyst-free one-pot four component synthesis of 2H-indazolo[2,1-b]phthalazine-triones in neutral ionic liquid 1-butyl-3-methylimidazolium bromide, Ultrason. Sonochem. 19 (2012) 307–313.
[34] V. Selvaraj, V. Rajendran, Preparation of 1,3-bis(allyloxy)benzene under a new multi-site phase-transfer catalyst combined with ultrasonication-A kinetic study, Ultrason. Sonochem. 20 (2013) 1236–1244.
[35] F. Zhang, J. Sun, D. Gao, Y. Li, Y. Zhang, T. Zhao, et al., An efficient and convenient procedure for the synthesis of 2-alkyl-2-alkoxy-1,2-di(furan-2-yl)ethanone under ultrasound in the presence of solid–liquid phase transfer catalysis conditions, Ultrason. Sonochem. 14 (2007) 493–496.
[36] V. Dryanska, C. Ivanov, Reaction of 2-methylbenzoxazole with aromatic aldehydes in aqueous medium, Tetrahedron Lett. 16 (1975) 3519–3520.
[37] Crystallographic data for **3c** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 954445. Copies of these data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223336 033; or e-mail: deposit@ccdc.cam.ac.uk), (n.d.).
[38] L.J. Farrugia, WinGX suite for small-molecule single-crystal crystallography, J. Appl. Crystallogr. 32 (1999) 837–838.
[39] G.M. Sheldrick, A short history of SHELX, Acta Crystallogr. 64 (2007) 112–122.
[40] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program, J. Appl. Cryst. 42 (2009) 339–341.
[41] A.D. Becke, Density-functional thermochemistry. III. The role of exact exchange, J. Chem. Phys. 98 (1993) 5648–5652.
[42] C. Lee, W. Yang, R.G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, Phys. Rev. B. 37 (1988) 785–789.
[43] R. Krishnan, J.S. Binkley, R. Seeger, J.A. Pople, Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions, J. Chem. Phys. 72 (1980) 650–654.
[44] A.D. McLean, G.S. Chandler, Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, $Z = 11–18$, J. Chem. Phys. 72 (1980) 5639–5648.
[45] J. Tao, J.P. Perdew, V.N. Staroverov, G.E. Scuseria, Climbing the density functional ladder: nonempirical meta-generalized gradient approximation designed for molecules and solids, Phys. Rev. Lett. 91 (2003) 146401.
[46] Y. Zhao, D.G. Truhlar, The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, Theor. Chem. Acc. 120 (2008) 215–241.
[47] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision B03, Gaussian Inc., Wallingford CT, 2004 (n.d.).
[48] C.O. Kappe, Controlled microwave heating in modern organic synthesis, Angew. Chem., Int. Ed. Engl. 43 (2004) 6250–6284.
[49] P. Lignier, J. Estager, N. Kardos, L. Gravouil, J. Gazza, E. Naffrechoux, et al., Swift and efficient sono-hydrolysis of nitriles to carboxylic acids under basic condition: role of the oxide anion radical in the hydrolysis mechanism, Ultrason. Sonochem. 18 (2011) 28–31.
[50] S. Shimizu, S. Shirakawa, T. Suzuki, Y. Sasaki, Water-soluble calixarenes as new inverse phase-transfer catalysts. Their application to aldol-type condensation and Michael addition reactions in water, Tetrahedron 57 (2001) 6169–6173.
[51] J. Isaad, A.E. Achari, Biosourced 3-formyl chromenyl-azo dye as Michael acceptor type of chemodosimeter for cyanide in aqueous environment, Tetrahedron 67 (2011) 5678–5685.
[52] J. Quiroga, A. Rengifo, B. Insuasty, R. Abonía, M. Nogueras, A. Sánchez, A novel product from the reaction of 6-aminopyrimidines and 3-formylchromone, Tetrahedron Lett. 43 (2002) 9061–9063.
[53] J. Bernstein, R.E. Davis, L. Shimoni, N.-L. Chang, Patterns in hydrogen bonding: functionality and graph set analysis in crystals, Angew. Chem., Int. Ed. Engl. 34 (1995) 1555–1573.

Please cite this article in press as: P. De-la-Torre et al., Ultrasound-assisted phase-transfer catalysis method in an aqueous medium to promote the Knoevenagel reaction: Advantages over the conventional and microwave-assisted solvent-free/catalyst-free method, Ultrason. Sonochem. (2014), http://dx.doi.org/10.1016/j.ultsonch.2014.02.021