Asian Journal of Green Chemistry 2 (2018) 1-10

Contents lists available at Avicenna Publishing Corporation (APC)

Asian Journal of Green Chemistry

Journal homepage: www.ajgreenchem.com

Orginal Research Article

One-pot, clean and energy efficient synthesis of dibenzo[b,f][1,4]oxazepine derivatives promoted by ultrasound

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ARTICLE INFORMATION

Received: 18 August 2017
Received in revised: 9 September 2017
Accepted: 23 September 2017
Available online: 12 October 2017

DOI: 10.22631/ajgc.2017.95751.1018

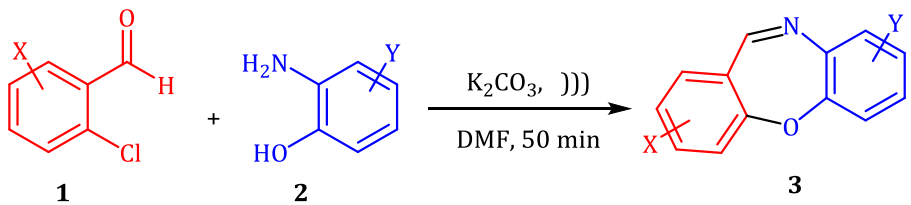
KEYWORDS

Dibenzo[b,f][1,4]oxazepine
Ultrasonic irradiation
Sonocatalytic ability
Catalyst-free reaction

ABSTRACT

In the present study, a variety of dibenzo [b,f][1,4] oxazepine derivatives was successfully synthesized in good yields under ultrasonic irradiation as an environmental friendly technique. This one-pot method is practically reliable, mild, catalyst-free, and inexpensive. Ultrasonic irradiation on the reaction mixture leads to fine emulsion between the reactants and violent collapses of a lot of cavitation bubbles in less than a microsecond releases extreme heat, leading to cross the activation energy barrier. In the absence of ultrasonic irradiation, a trace amount of the product was formed after 50 min. The superiority of the ultrasound irradiation over other methods in the synthesis of dibenzo [b,f][1,4] oxazepine derivatives is its low reaction temperature and operational simplicity in approximately same yields.

Graphical Abstract



Safe, efficient, inexpensive and clean energy method

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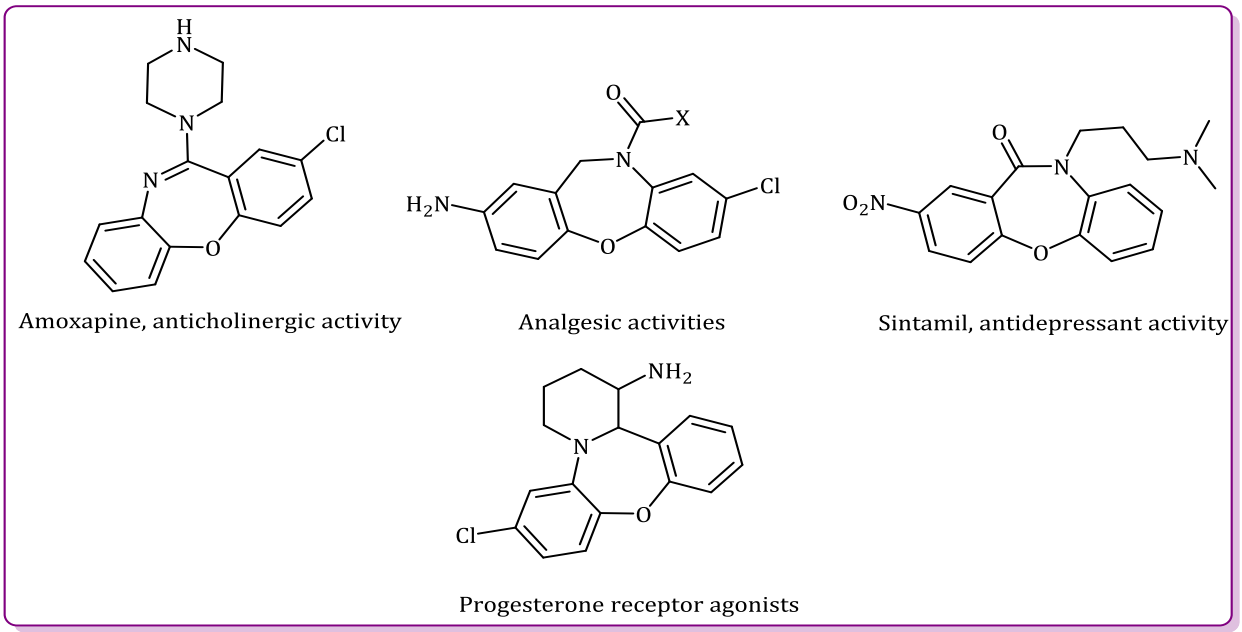
Introduction

Benzoxazepines are one of the important scaffolds of heterocycles, because of wide range of biological properties and industrial applications [1–4]. Among the family of benzoxazepines, dibenzo[b,f][1,4]oxazepine derivatives are known in many physiologically active compounds and chemical transformations [5–7]. Some important therapeutically active dibenzoxazepines are inserted in Scheme 1 [8–11].

Limited attention has been given to the synthesis of this structure including [7]: i) A two-step protocol involving etherification and reductive cyclization of 1-halo-2-nitrobenzene and salicylaldehyde (Scheme 2**a**) [12, 13], ii) A two-step method involving imination and etherification of 2-aminophenol with 2-halobenzaldehyde (Scheme 2**b**) [14, 15]. Etherification of these reactions proceed by an intramolecular nucleophilic displacement of nitro, fluoro, or chloro groups in high boiling polar solvents such as dimethyl sulfoxide at high temperature (Over 100 °C) with long reaction time.

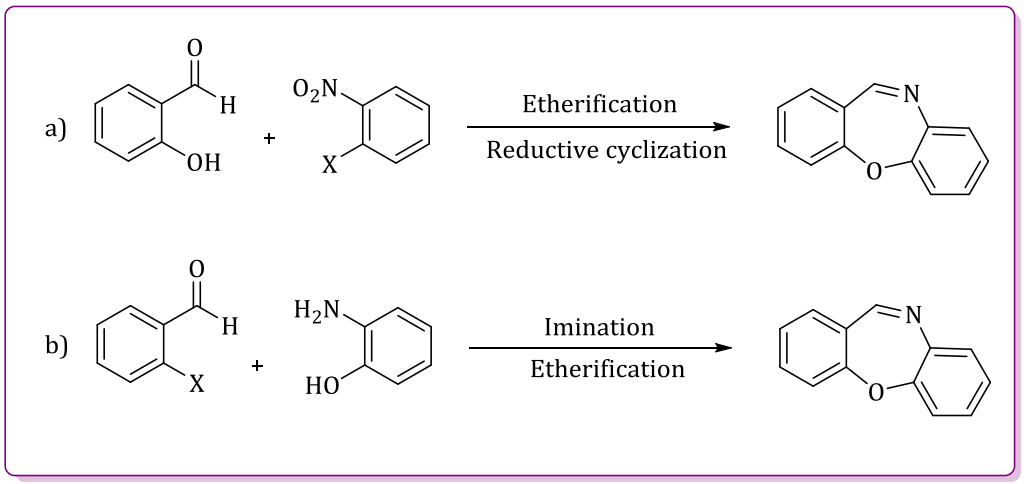
These protocols need long reaction time and harsh reaction conditions. In 2008, *Jorapur* and co-workers reported the synthesis of dibenzo [b,f][1,4] oxazepine in good yield using high molecular weight poly ethylene glycol, but it suffers from poor substituent tolerance [16]. Recently, hydrogenation and nucleophilic addition to imine dibenzo[b,f][1,4]oxazepines by using of catalysts such as iridium complex or proline were also reported [17, 18].



Scheme 1. Some important therapeutically active dibenzoxazepines

However, these methods are expensive and include unavailable starting material and catalyst. It seems, development of a clean, mild, fast, inexpensive, and versatile method for the synthesis of the dibenzo[b,f][1,4]oxazepines is necessary. Nowadays, the concept of speeding up the chemical transformations by ultrasound irradiation has created a lot of great interest in chemistry [19–28].

Ultrasonic irradiation enables the rapid and safe heating of the reaction mixture. Recently, several useful review papers summarized the latest developments on ultrasound assisted chemical reactions [29–32]. Micro-jets formation during the ultrasonic irradiation produces fine emulsion between the reactants and increases the local temperature of the reaction mixture, leading to supply the activation energy [33].



Scheme 2. General methods for synthesis of dibenzo[b,f][1,4]oxazepines

Ultrasound is also a versatile technology in different fields such as, medicine [34], nanotechnology [35–37], food [38], and energy production [39].

In this study, an efficient synthesis of a series of dibenzo[b,f][1,4]oxazepine derivatives **3** by reaction of 2-chlorobenzaldehydes **1** and 2-aminophenols **2** under ultrasound activation without any catalysts is shown in Scheme 3.

Experimental

Matreials and methodes

All chemicals required for the synthesis of dibenzo[b,f][1,4]oxazepine derivatives **3** were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluka (Neu-Ulm, Germany), and Merck (Darmstadt, Germany) companies and were used as received. The all synthesized compounds gave satisfactory spectroscopic data. A Bruker (DRX-500 Avance) NMR was used to record the ^{1}H NMR

spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Gas chromatography-MS spectrometry (GC-MS) (Agilent HP 6890, electron ionization (EI), 70 eV, HP-5 column (30 m × 0.25 mm × 0.2 μm), HP 5793 mass selective detector) was used to record the mass spectra. The reactions are monitored by thin layer chromatography (TLC) carried out on silica gel with UV light and iodine, as detecting agents. Ultrasonic irradiation was performed in an Elmasonic P ultrasonic cleaning unit (ultrasonic bath) with a frequency of 80 kHz and an output power of 80%, or using an ultrasonic homogenizer (Bandelin Sonopuls HD 3100) with probe model MS 73 and 100% power.

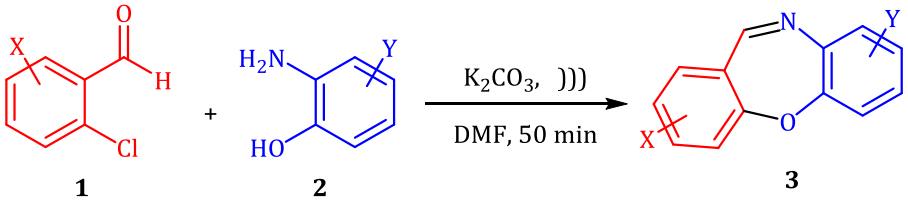
*General procedure for synthesis of dibenzo[b,f][1,4]oxazepines **3a-h***

A mixture of 2-chlorobenzaldehyde **1** (3 mmol), KOH (3.2 mmol), 2-aminophenol **2** (3 mmol), and dimethylformamide (10 mL) was charged in a 100 mL flask and was irradiated in an ultrasound bath for 50 min. After completion of the reaction, 50 mL water was added and the mixture was extracted with EtOAc (3×10 mL). The solvent was removed under vacuum and the residue was subjected to a short column chromatography (EtOAc/hexane, 1:15) on silica gel to obtain pure products. All the isolated dibenzo[b,f][1,4]oxazepines **3** successfully gave related spectral data of ^{1}H NMR, ^{13}C NMR and MS analyses in comparison with authentic samples prepared by reported methods.

*Spectra data of dibenzo[b,f][1,4]oxazepines **3a-h***

*Dibenzo[b,f][1,4]oxazepine (**3a**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 5H), 7.38 (d, J = 7.6 Hz, 1H), 7.41-7.43 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 8.57 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 121.1, 121.8, 125.5, 126.1, 127.8, 129.2, 129.6, 130.5, 133.7, 140.9, 153.1, 160.8, 161.0. MS (EI) (70 eV): m/z (%) 195 (100) [M+], 167 (42), 139 (35), 89 (28), 63 (78).



Scheme 3. Efficient synthesis process of dibenzo[b,f][1,4]oxazepine derivatives **3** using ultrasonic irradiation

*8-Methyl dibenzo[b,f][1,4]oxazepine (**3b**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 3H,), 7.00-7.18 (m, 5H), 7.29 (dd, J_1 = 7.6, J_2 = 1.6 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 8.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.0, 121.0, 121.4, 125.3, 126.3, 127.8, 129.7, 129.9, 130.5, 133.7, 135.8, 140.4, 150.9, 161.0. MS (EI) (70 eV): *m/z* (%) 209 (100) [M^+], 180 (50), 77 (30), 39 (43).

*4-Chloro dibenzo[b,f][1,4]oxazepine (**3c**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.39 (dd, J_1 = 8.0, J_2 = 2.0 Hz, 1H), 7.52 (dd, J_1 = 8.0, J_2 = 2.0 Hz, 1H), 8.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 122.4, 125.9, 126.5, 126.7, 128.6, 129.2, 129.4, 129.5, 133.7, 140.5, 152.5, 155.5, 159.8. MS (EI) (70 eV): *m/z* (%) 232 (34)[M+2], 229 (100) [M^+], 201 (25), 166 (45), 139 (20), 63 (12).

*4-Chloro-8-methyl dibenzo[b,f][1,4]oxazepine (**3d**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 7.15 (m, 5H), 7.51 (dd, J_1 = 8.0, J_2 = 2.0 Hz, 1H), 8.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.1, 121.9, 125.8, 126.6, 128.5, 129.2, 129.7, 130.0, 133.5, 136.2, 140.1, 150.3, 155.5, 159.7. MS (EI) (70 eV): *m/z* (%) 245 (33)[M+2], 243 (100) [M^+], 214 (25), 180 (12), 75 (10).

*4,8-Dichloro dibenzo[b,f][1,4]oxazepine (**3e**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (m, 4H), 7.36 (d, J = 2.0 Hz, 1H), 7.53-7.56 (dd, J_1 = 8.0, J_2 = 2.0 Hz, 1H), 8.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 123.3, 126.2, 126.7, 128.7, 128.9, 129.0, 129.1, 131.5, 134.0, 141.4, 151.1, 155.3, 160.9. MS (EI) (70 eV): *m/z* (%) 267 (10)[M+4], 265 (67)[M+2], 263 (100) [M^+], 235 (10), 200 (50), 164 (80).

*3-Chloro dibenzo[b,f][1,4]oxazepine (**3f**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (m, 6H), 7.36 (d, J = 7.2 Hz, 1H), 8.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 121.8, 121.8, 125.9, 126.2, 126.5, 129.5, 129.7, 131.3, 139.5, 140.5, 152.6, 159.8, 161.1. MS (EI) (70 eV): *m/z* (%) 231 (34)[M+2], 229 (100) [M^+], 201 (25), 166 (28), 139 (12), 63 (10).

*3-Chloro-8-methyl dibenzo[b,f][1,4]oxazepine (**3g**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 7.12 (m, 6H), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.0, 121.3, 121.7, 125.7, 126.2, 130.0, 130.1, 131.2, 136.2, 139.3, 140.1, 150.5, 159.7, 161.2. MS (EI) (70 eV): *m/z* (%) 245 (34)[M+2], 243 (100) [M^+], 214 (45), 180 (12), 152 (10), 77 (8).

*3,8-Dichloro dibenzo[b,f][1,4]oxazepine (**3h**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05-7.25 (m, 5H), 7.34 (d, J = 2.0 Hz, 1H), 8.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 121.7, 122.8, 126.0, 126.1, 129.0, 129.4, 131.4, 131.5, 139.9, 141.5, 151.2, 160.9, 160.9. MS (EI) (70 eV): *m/z* (%) 267 (11)[M+4], 265 (67)[M+2], 263 (100) [M^+], 235 (8), 200 (7), 165 (5).

Results and discussion

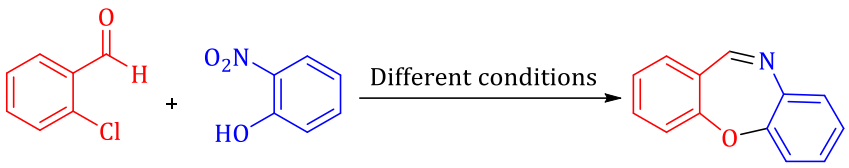
The effect of various conditions was studied on the synthesis of dibenzo [b,f][1,4] oxazepine **3a** using the reaction of 2-chlorobenzaldehyde and 2-minophenol as a model reaction (Table 1). In the absence of any base, even after 2 h, no desired product was obtained, while good results were demonstrated in the presence of the base.

Various base were applied in *N,N*-dimethylformamide (DMF) under ultrasonic irradiation. Base has two vital roles in the reaction, including deprotonation of the phenol for nucleophilic displacement of chloro group on 2-chlorobenzaldehyde and increasing the rate of imine formation (Scheme 4). The reaction in the presence of KOH provided the desired product **3a** with a high yield (Table 1, entry 6). The model reaction was also carried out in various solvents (Table 1, entries 6–10). The best yield was achieved by using DMF as a polar aprotic solvent (Table 1, entry 6). It should be noted that, prolonging the reaction is necessary in order to achieve a desired product **3a** with a high yield (Table 1, entry 11).

Analysis of the mixture by GC-MS revealed that, at the beginning of the reaction, formation of imine **I** is favor than dibenzo[b,f][1,4] oxazepine **3a** (Scheme 4). It noteworthy that, using ultrasonic irradiation on the reaction mixture leads to fine emulsion between the reactants and violent collapses of a lot of cavitation bubbles in less than a microsecond releases extreme heat which leads to cross the activation energy barrier. In the absence of ultrasonic irradiation, trace amount of the product was formed after 50 min (Table 1, entry 12). Thus, the optimal reaction conditions were determined to be KOH as the base, DMF as the solvent at room temperature under ultrasound irradiation for 50 min.

With the optimal reaction conditions in hand, attention turned to explore the scope of the reaction. Various 2-chlorobenzaldehydes **1** and 2-aminophenols **2** were employed and corresponding substituted dibenzo [b,f][1,4] oxazepine derivatives were obtained in high yields (Scheme 5). The superiority of the ultrasound irradiation over microwave irradiation [15] in the synthesis of dibenzo [b,f][1,4] oxazepine derivatives is low reaction temperature and operational simplicity of the ultrasound irradiation technique.

Table 1. The optimization experiments for synthesis of dibenzo[b,f][1,4]oxazepine **3a** under ultrasonic irradiation[a]



1 **2** **3a**

Entry	Solvent	Base	Time (min)	Yield (%)[b]
1	DMF	-	120	-
2	DMF	NaH	50	76
3	DMF	NaOH	50	71
4	DMF	K_2CO_3	50	49
5	DMF	Cs_2CO_3	50	56
6	DMF	KOH	50	87
7	H_2O	KOH	50	Trace
8	DMSO	KOH	50	78
9	EtOH	KOH	50	70
10	xylene	KOH	50	68
11	DMF	KOH	30	53
12	DMF	KOH	50	Trace

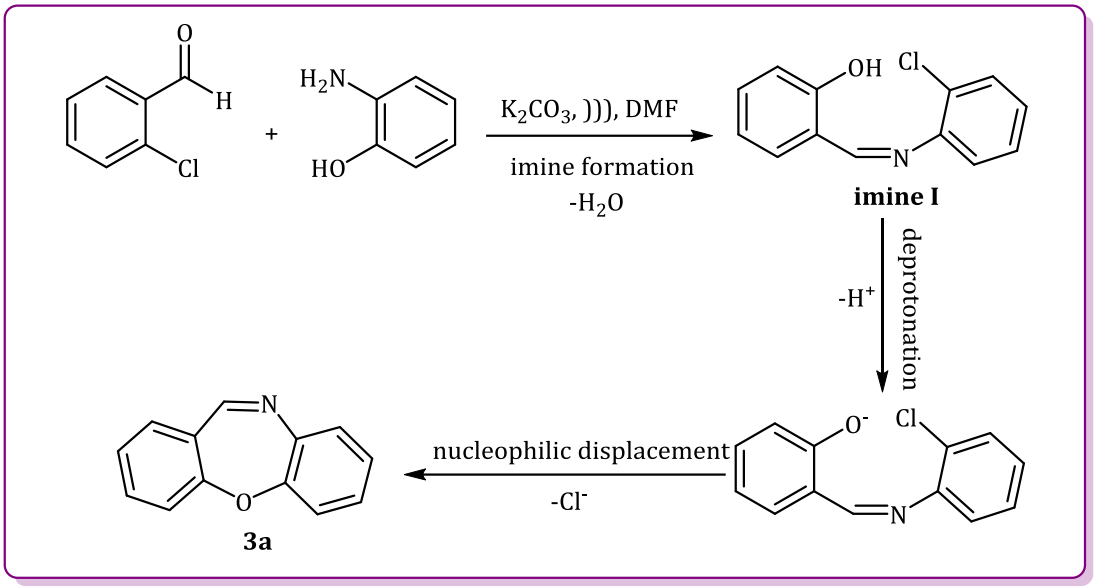
[a] Reaction conditions: solvent (5 mL), 2-chlorobenzaldehyde (3 mmol), 2-minophenol (3 mmol), base (3 mmol)

[b] Determined by GC

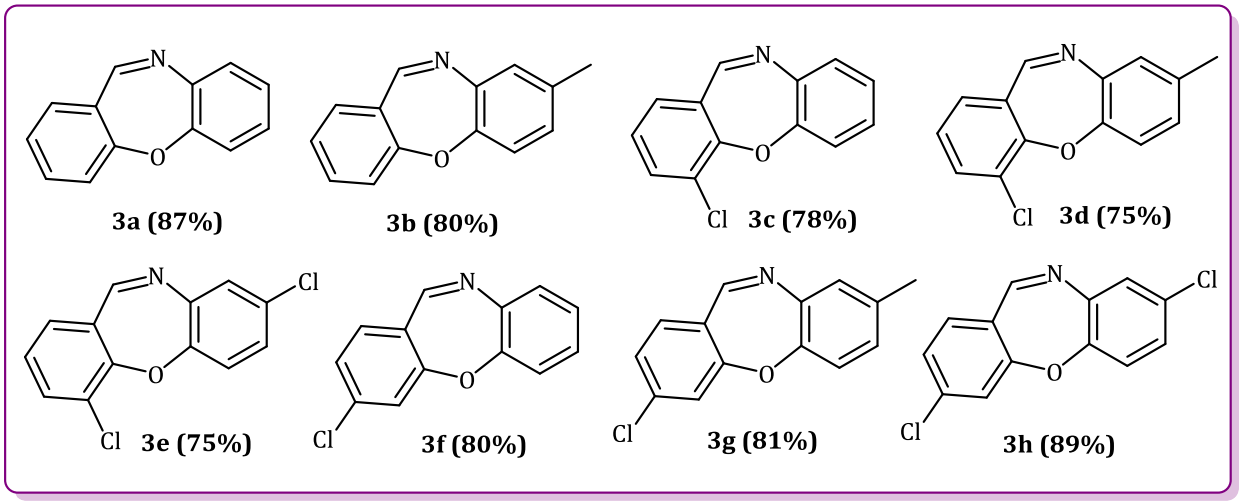
[c] Without ultrasound irradiation

The structure of the products was investigated by ^{1}H NMR, ^{13}C NMR, and EI-MS analyses. The ^{1}H NMR spectrum of the product **3a** consisted of a multiplet line at δ = 7.22-7.26 ppm (5H), two doublet resonances (2H) at δ = 7.38 and 7.42 and a triplet line (1H) at δ = 7.48 ppm for the aromatic protons. The presence of characteristic sharp signal for proton of imine at δ = 8.57 ppm is a good indication of the formation of desired product **3a**.

The ^{1}H-decoupled ^{13}C NMR spectrum of the product **3a** indicated 13 resonances in agreement with the proposed structure, at δ = 161.04 ppm a sharp resonance for carbon of imine and 12 distinct resonances for aromatic carbons between δ = 121.15-160.89 ppm. The MS (EI) mass spectrum of **3a** clearly showed the presence of the molecular ion (195) [$M^{+\bullet}$] with elimination of CH_2N radical from $M^{+\bullet}$ to give m/z = 167 as a characteristic cation in its spectrum.



Scheme 4. The proposed mechanism for the formation of dibenzo[b,f][1,4]oxazepine by using ultrasonic irradiation



Scheme 5. Structure of the synthesized dibenzo[b,f][1,4]oxazepines **3a-h** by using ultrasonic irradiation

Conclusion

In conclusion, efficiency of the ultrasound as an environmental remediation technique for synthesis of dibenzo[b,f][1,4]oxazepine derivatives was reported. Desired products were prepared in high yields under the mild conditions and catalyst-free. Compared to other methodologies used for the same chemical transformation, ultrasound displays several advantages including a safe, inexpensive and clean energy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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How to cite this manuscript: Hossein Paghandeh, Hamid Saeidian*, Ebrahim Saeedian Moghadam, Zohreh Mirjafary, Mohammad Ghaffarzadeh*. One-pot, clean and energy efficient synthesis of dibenzo[b,f][1,4]oxazepine derivatives promoted by ultrasound. *Asian Journal of Green Chemistry*, 2018, 2, 1-10. DOI: 10.22631/ajgc.2017.95751.1018