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Ultrasound Promoted Synthesis and Antimicrobial Evaluation of Novel Seven and Eight-Membered 1,3-Disubstituted Cyclic Amidinium Salts

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Abstract

Series of 1,3-dibenzyl-1*H*-4,5,6,7-tetrahydro-1,3-diazepinium and 1,4,5,6,7,8-hexahydro-1,3-diazocinium salts derivatives were efficiently synthesized in excellent yields by dehydrogenation of the corresponding *N*,*N*′-dibenzyl aminals employing *N*-bromosuccinimide (NBS) as dehydrogenating agent under ultrasound irradiation. The present methodology has proven to be simple, efficient and environmentally benign. All novel compounds were identified and characterized by ^{1}H and ^{13}C NMR spectra. The synthesized compounds were screened for their antimicrobial activities.

Keywords

Medium Ring Amidinium Salts, Ultrasonic Assisted Synthesis, Antimicrobial, Green Chemistry

1. Introduction

Cyclic amidinium salts (CAS) with a fully saturated backbone (**I**) have attracted a great deal of interest in recent years. Most CAS (**I**) investigated so far are five- or six-membered rings derived from imidazole (1*H*-4,5-dihydroimidazolium salts) or pyrimidine (1,4,5,6-tetrahydropyrimidinium salts) (**I**, n = 0 and 1 respectively) [1]-[5]. However, higher homologues, such as 1*H*-4,5,6,7-tetrahydro-1,3-diazepinium and 1,4,5,6,7,8-hexahydro-1,3-diazocinium salts (**I**, n = 2 and 3) have been less studied [6]. It is known that medium-size rings are generally

more difficult to synthesize than their lower counterparts [7] [8] [9] [10] since the synthetic strategies employed have to overcome unfavorable transannular interactions leading to large enthalpies of activation [11] [12] (**Figure 1**).

CAS **I** possess soft Lewis acidic character due to the contribution of the fully saturated mesomeric structure **Ib** and they have also found applications on their own as organocatalysts [13] [14] [15] [16].

2-Unsubstituted salts (**I**, R^2 = H), are conventional synthetic precursors, of NHCs (*N*-heterocyclic carbenes) [1] [17] [18] [19]. These compounds are of special interest due to their electron richness. Consequently, they have been widely applied as ligands in transition-metal catalysis and organometallic chemistry [20]-[28] and as organocatalysts in their own right [29] [30]. In particular, tetrahydrodiazepinium salts (**I**, n = 2) have been synthesized to be employed as precursor of ring expanded NHCs (RE-NHCs), which are stronger σ-donating ligands [24] [25] [26] [27] [31] [32] [33] [34]. A few years ago was reported the synthesis of the first eight-membered ring 8-NHC through the reaction of the corresponding cyclic amidinium salt (**I**, n = 3) with KHMDS (potassium hexamethyldisilylamide) [35].

Green chemistry focuses on research that attempts to reduce or eliminate the negative environmental impacts [36]. In accordance with green chemistry requirements, ultrasound irradiation has emerged as an efficient technique for reagent activation in organic reactions and has been considered as a clean and useful methodology in organic synthesis for the last years [37] [38]. In this context, many organic reactions can be carried out under ultrasound irradiation and compared with classical synthetic procedures [39]-[44].

On the other hand, the search for compounds with antibacterial activity has gained increasing importance in recent time, due to growing worldwide concern over the increase in the rate of infection by antibiotic-resistant microorganisms [45]. One of the groups with good antimicrobial activity is cationic nitrogen containing molecules as acyclic [46] and cyclic [47] [48] quaternary ammonium compounds (QACs). In this line, cyclic amidinium salts as pyrimidinium [49] and imidazolium [50] and their silver complex were investigated as antibacterial agents [51].

The synthetic methods for cyclic amidinium salts of medium size ring, are in general extensions of the methods employed for lower homologues as imidazolinium and tetrahydropirimidinium salts. The literature describes general strategies that involve cyclic and acyclic compounds as precursors [6]. In line with our ongoing work in the use of green chemistry tools [52]-[56] for heterocyclic chemistry,

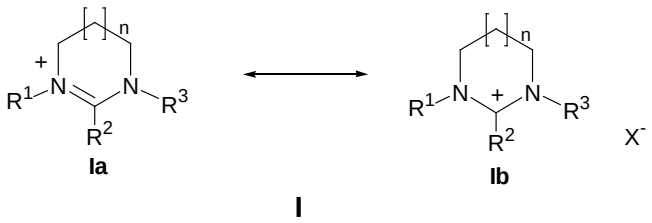

Figure 1. Cyclic amidinium salts (CAS).

we report herein an eco-friendly approach for the synthesis of 1,3-dibenzyl tetrahydro-1,3-diazepinium (**1**, n = 2) and hexaydro-1,3-diazocinium salts (**1**, n = 3) with potential microbiological activity, under ultrasound irradiation.

2. Experimental

2.1. Materials and Methods

2.1.1. Chemistry. General Data

Melting points were taken on a Büchi capillary apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured in $DCCl_3$ solutions on a Bruker Avance II 500 MHz spectrometer at room temperature in 5 mm tubes. Standard concentration of the samples was 2 and 10 mg/mL for ^{1}H and ^{13}C respectively. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Coupling constant (J) values are given in Hz. Splitting multiplicities are reported as singlet (s), broad signal (bs), doublet (d), triplet (t), broad triplet (bt), multiplet (m), double doublet (dd), double triplet (dt) and pentuplet (p). High resolution mass spectra (HMRS), were acquired with a model GCT (Waters, Milford, MA, USA), operating at 8000 resolving power (50% valley definition) using heptacose (m/z 219) as the reference compound. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer.

Ultrasonic irradiation experiments were performed using a VCX 750 Vibra-Cell high intensity ultrasonic processor (Sonics & Materials, USA) equipped with an immersion ultrasonic probe, which was made of titanium alloy T1-6AL-4V, and with the tip diameter of 13 mm. The frequency is 20 KHz and the net power output is 750 W. The variable power output control allows the ultrasonic vibrations at the probe tip to be set to any desired amplitude. With the amplitude control set at 100%, the amplitude at the tip with diameter of 13 mm is 124 μm. In our work, the amplitude control was set at 35%.

2.1.2. Antimicrobial Activity

Antimicrobial activity was tested by the disk diffusion method, with Antibiotic Medium number 1 (pH 6.5) and 11 (pH 7.9). The assayed microorganisms were *B. subtilis* ATCC 6633 CCM-A-10, *S. aureus* ATCC 6538P CCM-A-424, *E. coli* ATCC 11105 CCM-A-424 and *A. niger* ATCC 16404. MIC determination was performed following the agar dilution method recommendations as proposed by CLSI (MO7-A10) [57].

2.2. Synthesis and Characterization of Cyclic Amidinium Salts 1

Aminals **2** were synthesized by reaction of *N*,*N*'-disubstituted alkylenediamines with formaldehyde under microwave irradiation [52]. Compounds **2a** [58] **b,c,e,g-l** were previously described [58]. Aminals **2d,f** were obtained in the same way and were used as precursors of the salts **1d,f** without previous purification.

2.2.1. Conventional Synthesis

To a stirred solution of corresponding aminal **2** (0.01 mol) in ethyl ether (5 mL)

at room temperature, the dehydrogenating agent (0.02 mol) was added in portions while the reaction was monitored by TLC. After complete disappearance of the starting material, salts **1** precipitate in variable times. The solid products were collected and recrystallized from anhydrous methanol and the oils were purified by column chromatography (*n*-hexane-ethyl acetate 1:1). Required times and yields are indicated in Table 1.

2.2.2. Reaction under Ultrasound Irradiation

A mixture of the corresponding aminal **2** (0.01 mol) in ethyl ether (5 mL) and the dehydrogenating agent (NBS, 0.02 mol) was taken in a flask. The reaction mixture was sonicated by an ultrasonic probe in ice bath for the specified period until complete consumption of starting materials (monitored by TLC). Compounds 1 were isolated and purified as was indicated in conventional synthesis. Required times and yields are indicated in Table 1.

2.2.3. Data of the New Compounds

- 1,3-*Dibenzyl*-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1*a***).

This compound was obtained as oil. ^{1}H NMR δ ppm: 9.52 (s, 1H, NC*H*N), 7.43 - 7.42 (m, 4H$_{arom.}$) 7.38 - 7.31 (m, 6H$_{arom.}$), 4.94 (s, 4H, NCH_2Ar), 3.62 (bs, 4H, NCH_2), 1.83 (p, 4H, CH_2CH_2, J = 2.9 Hz). ^{13}C NMR δ ppm: 159.7, 134.6, 130.1, 129.9, 127.1, 62.1, 50.4, 25.7. IR (film) ν: 3030, 2940, 1674, 1455, 1090, 748, 705 cm^{-1}. MS: *m*/*z* 278 (M-1-Br). HRMS: 278.17821. Calcd. for $C_{19}H_{22}N_2$: 278.17830.

- 1,3-*Di*-(4-*methylbenzyl*)-1*H*.4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1*b***).

Table 1. Synthesis of cyclic amidinium salts 1a-l under sonication and conventional conditions.

Comp. **1**	Ar	n	Conventional (ethyl ether)		Ultrasonic irradiation Sonicator (HIU)	
			Time (min)	Yield (%)	Time (min)	Yield (%)
a	C_6H_5	2	25	34	2	85
b	4-$CH_3C_6H_4$	2	30	36	1	87
c	4-ClC_6H_4	2	29	32	1	91
d	2-ClC_6H_4	2	25	25	2	94
e	3-ClC_6H_4	2	30	42	1	88
f	4-$NO_2C_6H_4$	2	20	35	1	95
g	2,3-$Cl_2C_6H_3$	2	25	30	3	89
h	3,4-$Cl_2C_6H_3$	2	35	51	3	98
i	C_6H_5	3	25	50	2	87
j	3-ClC_6H_4	3	30	51	2	80
k	2,3-$Cl_2C_6H_3$	3	25	52	4	85
l	3,4-$Cl_2C_6H_3$	3	30	55	5	80

MP: 122˚C - 124˚C. ^{1}H NMR δ ppm: 9.90 (s, 1H, NC*H*N), 7.30 (d, 4H$_{arom.}$, J = 7.7 Hz), 7.15 (d, 4H$_{arom.}$ J = 7.7 Hz), 4.89 (s, 4H, NCH_2Ar), 3.54 (bt, 4H, NCH_2), 2.32 (s, 6H, CH_3), 1.79 (bp, 4H, CH_2CH_2). ^{13}C NMR δ ppm: 159.6, 139.7, 131.6, 130.7, 129.7, 61.6, 30.1, 25.6, 22.1. IR (film) ν: 3022, 2936, 1609, 1489, 1030, 919, 757 cm^{-1}. MS: m/z 306 (M-1-Br). HRMS: 306.20895. Calcd. for $C_{21}H_{26}N_2$: 306.20960.

- 1,3-*Di*(4-*chlorobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1c**).

MP: 200˚C - 202˚C. ^{1}H NMR δ ppm: 10.04 (s, 1H, NC*H*N), 7.43 (d, 4H, 4H$_{arom.}$, J = 8.5 Hz), 7.32 (d, 4H$_{arom.}$, J = 8.5 Hz), 4.94 (s, 4H, NCH_2Ar), 3.54 (bt, 4H, NCH_2), 1.83 (p, 4H, CH_2CH_2, J = 2.9 Hz). ^{13}C NMR δ ppm: 160.3, 136.0, 133.1, 131.3, 130.3, 61.1, 50.4, 25.7. IR (film) ν: 2941, 2870, 1668, 1492, 815, 801 cm^{-1}. MS: m/z 346 (M-1-Br). HRMS: 346.10049. Calcd. for $C_{19}H_{20}Cl_2N_2$: 346.10035.

- 1,3-*Di*(2-*chlorobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1d**).

This compound was obtained as oil. ^{1}H NMR δ ppm: 9.26 (s, 1H, NC*H*N), 7.70 - 7.68 (m, 2H$_{arom.}$), 7.43 - 7041 (m, 2H$_{arom.}$), 7.36 - 7.34 (m, 4H$_{arom.}$), 5.05 (s, 4H, NCH_2Ar), 3.69 (bt, 4H, NCH_2), 1.90 (p, 4H, CH_2CH_2, J = 2.8 Hz). ^{13}C NMR δ ppm: 160.0, 134.5, 132.3, 131.3, 130.7, 130.1, 127.8, 58.4, 49.4, 24.6. IR (film) ν: 2932, 2864, 1615, 1586, 1443, 766, 700 cm^{-1}. MS: m/z 346 (M-1-Br$^-$). HRMS: 346.10120. Calcd. for $C_{19}H_{20}Cl_2N_2$: 346.10035.

- 1,3-*Di*(3-*chlorobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1e**).

This compound was obtained as oil. ^{1}H NMR δ ppm: 9.06 (s, 1H, NC*H*N), 7.36 (bs, 2H$_{arom.}$), 7.32 (bs, 6H$_{arom.}$), 4.76 (s, 4H, NCH_2Ar), 3.61 (bs, 4H, NCH_2), 1.85 (p, 4H, CH_2CH_2, J = 2.9 Hz). ^{13}C NMR δ ppm: 158.9, 135.5, 134.9, 130.6, 129.2, 128.5, 126.7, 60.5, 49.5, 24.5. IR (film) ν: 2930, 1673, 1431, 785, 682 cm^{-1}. MS: m/z 346 (M-1-Br$^-$). HRMS: 346.10087. Calcd. for $C_{19}H_{20}Cl_2N_2$: 346.10035.

- 1,3-*Di*(4-*nitrobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1f**).

This compound was obtained as oil. ^{1}H NMR δ ppm: 9.78 (s, 1H, NC*H*N), 7.45 (d, 4H$_{arom}$ J = 7.2 Hz), 7.37 (dd, 4H$_{arom}$ J = 7.2 Hz), 4.93 (s, 4H, CH_2Ar), 3.58 (bt, 4H, NCH_2N), 1.79 (bt, 4H, CH_2N). ^{13}C NMR δ ppm: 158.7, 133.6, 129.2, 128.9, 128.8, 60.0, 49.3, 24.4. IR (film) ν: 3109, 2853, 1607, 1539, 1345, 835 cm^{-1}. MS: m/z 368 (M-1-Br$^-$). HRMS: 368.14722. Calcd. for $C_{19}H_{20}N_4O_4$: 368.14845.

- 1,3-*Di*(2,3-*dichlorobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1g**).

MP: 182˚C - 184˚C. ^{1}H NMR δ ppm: 9.42 (s, 1H, NC*H*N), 7.69 (dd, 2H$_{arom.}$, J = 7.6, 1.5 Hz), 7.47 (dd, 2H$_{arom.}$, J = 8.1, 1.5 Hz), 7.28 (dd, 2H$_{arom.}$, J = 8.1, 7.6 Hz Hz), 5.10 (s, 4H, NCH_2Ar), 3.67 (bt, 4H, NCH_2), 1.90 (p, 4H, CH_2CH_2, J = 2.9 Hz). ^{13}C NMR δ ppm: 161.3, 134.9, 134.3, 133.6, 132.4, 131.3, 129.2, 59.8, 50.8, 25.5. IR (film) ν: 2930, 1674, 1424, 788, 737 cm^{-1}. MS: m/z 414 (M-1-Br$^-$). HRMS: 414.02358. Calcd. for $C_{19}H_{18}Cl_4N_2$: 414.02241.

- 1,3-*Di*(3,4-*dichlorobenzyl*)-1*H*-4,5,6,7-*tetrahydro*-1,3-*diazepinium bromide* (**1h**).

MP: 163˚C - 165˚C. ^{1}H NMR δ ppm: 9.87 (s, 1H, NC*H*N), 7.53 (bs, 2H$_{arom.}$), 7.44 - 7.43 (bs, 4H$_{arom.}$), 4.93 (s, 4H, NCH_2Ar), 3.57 (bt, 4H, NCH_2), 1.90 (p, 4H,

CH_2CH_2, J = 2.8 Hz). ^{13}C NMR δ ppm: 160.7, 134.7, 134.4, 134.2, 132.6, 131.6, 129.3, 60.9, 50.7, 25.7. IR (film) ν: 2934, 2859, 1611, 1470, 837, 732 cm^{-1}. MS: m/z 414 (M-1-Br$^-$). HRMS: 414.02310. Calcd. for $C_{19}H_{18}Cl_4N_2$: 414.02241.

- 1,3-*Dibenzyl*-1,4,5,6,7,8-*hexahydro*-1,3-*diazocinium bromide* (**1*i***).

MP: 187˚C - 189˚C. ^{1}H NMR δ ppm: 10.32 (s, 1H, NC*H*N), 7.50 - 7.36 (m, 10H$_{arom.}$), 5.02 (s, 4H, NCH_2Ar), 3.70 (bs, 4H, NCH_2), 1.54 (bs, 4H, CH_2CH$_2$N), 1.45 (bs, 2H, CH$_2$CH_2CH$_2$). ^{13}C NMR δ ppm: 154.9, 134.9, 130.2, 130.1, 130.0, 62.7, 48.6, 29.1, 20.1. IR (film) ν: 3055, 2938, 1618, 1585, 778, 700 cm^{-1}. MS: m/z 292 (M-1-Br$^-$). HRMS: 292.19421. Calcd. for $C_{20}H_{24}N_2$: 292.19395.

- 1,3-*Di*(3-*chlorobenzyl*)-1,4,5,6,7,8-*hexahydro*-1,3-*diazocinium bromide* (**1*j***).

MP: 273˚C - 275˚C. ^{1}H NMR δ ppm: 10.48 (s, 1H, NC*H*N), 7.52 (bs, 2H$_{arom.}$), 7.42 (s, 2H$_{arom.}$), 7.34 - 7.33 (4H$_{arom.}$), 5.07 (s, 4H, NCH_2Ar), 3.72 (bs, 4H, NCH_2), 1.66 (p, 4H, CH_2CH$_2$N, J = 6.2 Hz), 1.53 (p, 2H, CH$_2$CH_2CH$_2$, J = 6.2 Hz). ^{13}C NMR δ ppm: 159.5, 135.6, 134.7, 130.6, 129.5, 129.0, 127.4, 60.6, 47.9, 27.9, 19.7. IR (film) ν: 2930, 1674, 1471, 820, 733. MS: m/z 360 (M-1-Br$^-$). HRMS: 360.11655 Calcd. for $C_{20}H_{22}Cl_2N_2$: 360.11600.

- 1,3-*Di*(2,3-*dichlorobenzyl*)-1,4,5,6,7,8-*hexahydro*-1,3-*diazocinium bromide* (**1*k***).

This compound was obtained as oil. ^{1}H NMR δ ppm: 9.30 (s, 1H, NC*H*N), 7.62 (dd, 2H$_{arom.}$, J = 7.7, 1.3 Hz), 7.44 (dd, 2H$_{arom.}$, J = 8.1, 1.3 Hz), 7.27(dd, 2H$_{arom.}$, J = 8.1, 7.7 Hz), 5.04 (s, 4H, NCH_2Ar), 3.80 (bs, 4H, NCH_2), 1.54 (bs, 4H, CH_2CH$_2$N), 1.47 (bs, 2H, CH$_2$CH_2CH$_2$). ^{13}C NMR δ ppm: 159.8, 134.6, 134.2, 133.6, 132.2, 131.4., 129.0, 60.8, 48.7, 29.1, 21.0. IR (film) ν: 2933, 1671, 1422, 1049, 782, 753 cm^{-1}. MS: m/z 428 (M-1-Br$^-$). HRMS: 428.03872. Calcd. for $C_{20}H_{20}Cl_4N_2$: 428.03806.

- 1,3-*Di*(3,4-*dichlorobenzyl*)-1,4,5,6,7,8-*hexahydro*-1,3-*diazocinium bromide* (**1*l***).

MP: 228˚C - 230˚C. ^{1}H NMR δ ppm: 10.40 (s, 1H, NC*H*N), 7.57 (d, 2H$_{arom.}$, J = 2.0 Hz), 7.54 (dd, 2H$_{arom}$, J = 8.2, 2.0 Hz), 7.43(d, 2H$_{arom.}$ J = 8.2 Hz), 5.01 (s, 4H, NCH_2Ar), 3.67 (bs, 4H, NCH_2), 1.63 (p, 4H, CH_2CH$_2$N, J = 6.2 Hz), 1.51 (p, 2H, CH$_2$CH_2CH$_2$, J = 6.2 Hz). ^{13}C NMR δ ppm: 159.7, 134.8, 134.5, 134.1, 132.2, 131.8, 129.7, 61.3, 48.8, 29.0, 20.8. IR (film) ν: 2936, 1611, 1469, 838, cm^{-1}. MS: m/z 428 (M-1-Br$^-$). HRMS: 428.03791. Calcd. for $C_{20}H_{20}Cl_4N_2$: 428.03806.

3. Results and Discussion

3.1. Preparation of Cyclic Amidinium Salts (1)

The compounds synthesized in this work were obtained by dehydrogenation of the corresponding aminals **2** (n = 2,3, hexahydro-1,3-diazepines and octahydro-1,3-diazocines respectively). The required aminals **2** were synthesized by our improved method involving the reaction of *N*,*N*′-disubstituted alkylenediamines with formaldehyde under microwave irradiation [52].

In order to set dehydrogenation conditions we used the diazepine derivative **2c** and test several dehydrogenating agents and solvents following the method

described for the synthesis of five membered cyclic amidinium salts [59]. Dehydrogenations with NBA, NBS, and DBDMH (1,3-dibromo-5,5-dimethylhydantoin) were carried out at room temperature (20˚C) by stirring a mixture of the aminal and the reagent. Conversions were achieved in as few minutes. Ether solvents (ethyl ether, dimethoxyethane, and THF) were preferred due to the insolubility of products in such media. NBS in ethyl ether afforded the best results, with higher yields and purer reaction products (**Figure 2**).

Having set up the conditions, compounds **2a-n** were dehydrogenated at room temperature by stirring a mixture with NBS in anhydrous ethyl ether (**Figure 2**). In this medium, salts generally precipitate as long as they were formed. Under those conditions the reactions proceeded with different yields (**Table 1**). Diazepinium salts **1a-h** were obtained with low yields (25% - 51%) and required 20 - 35 min for complete consumption of the starting material. On the other hand, diazocinium salts **1i-l** were obtained with moderate yields (50% - 55%) and required 25 - 30 min.

In order to optimize the dehydrogenation reaction of aminals described above, we explored the use of ultrasound irradiation as promoting agent. The reactions were carried out in ice bath with high intensity ultrasonic (HIU) probe system. In all cases, the experimental results show that yields of compounds 1a-l improved under sonication (80% - 94%) and the reaction times decreased (1 - 5 min) if compared to conventional heating (**Table 1**).

Unlike other medium size cyclic amidinium salts [53] the compounds were generally isolated as hygroscopic solids, melting above 100˚ and, therefore, they are not ionic liquids. This would be related with the structural symmetry of salts **1**.

The analysis of the NMR and IR spectra of compounds **1** confirmed their identity. The most valuable spectroscopic feature for assessing the success of the dehydrogenation was the appearance of the a strongly deshielded H-2 signal at ca. 9 - 10 ppm, results from the electron deficiency of the heterocyclic ring, caused by the cationic character of the amidinium system **Ib**. On the other hand, infrared spectra confirmed their ionic structure, as it can be seen from the amidinium band at *ca.* 1600 - 1620 cm^{-1}. The ^{13}C-NMR spectra characteristically show the C-2 signal at approximately 160 ppm. The ^{1}H and ^{13}C NMR and IR spectra of a representative compound are shown in **Figures 3-5**.

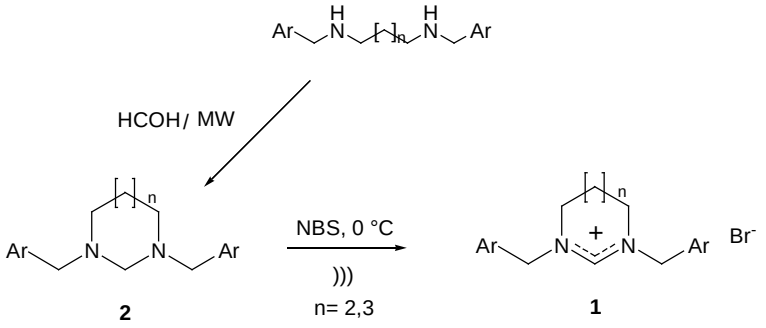

Figure 2. Synthesis of cyclic amidinium salts **1** from aminals **2**.

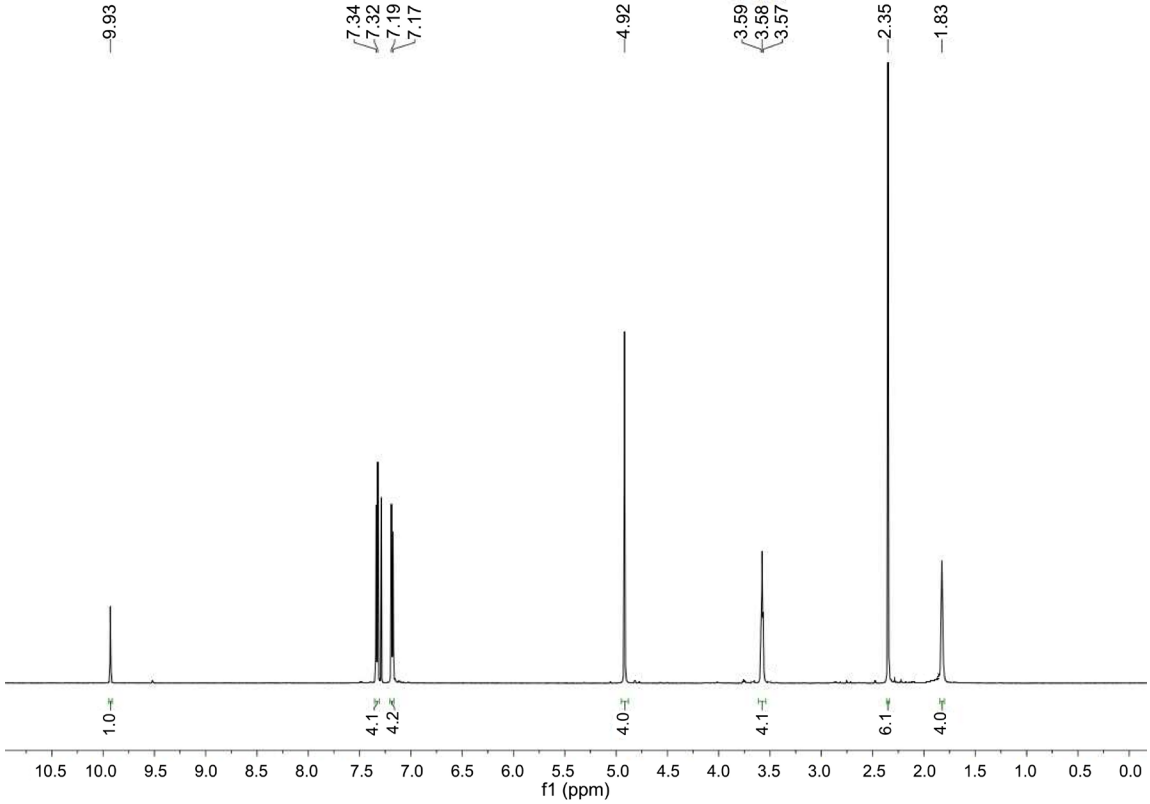

Figure 3. [1]H-NMR spectrum of compound **1b**.

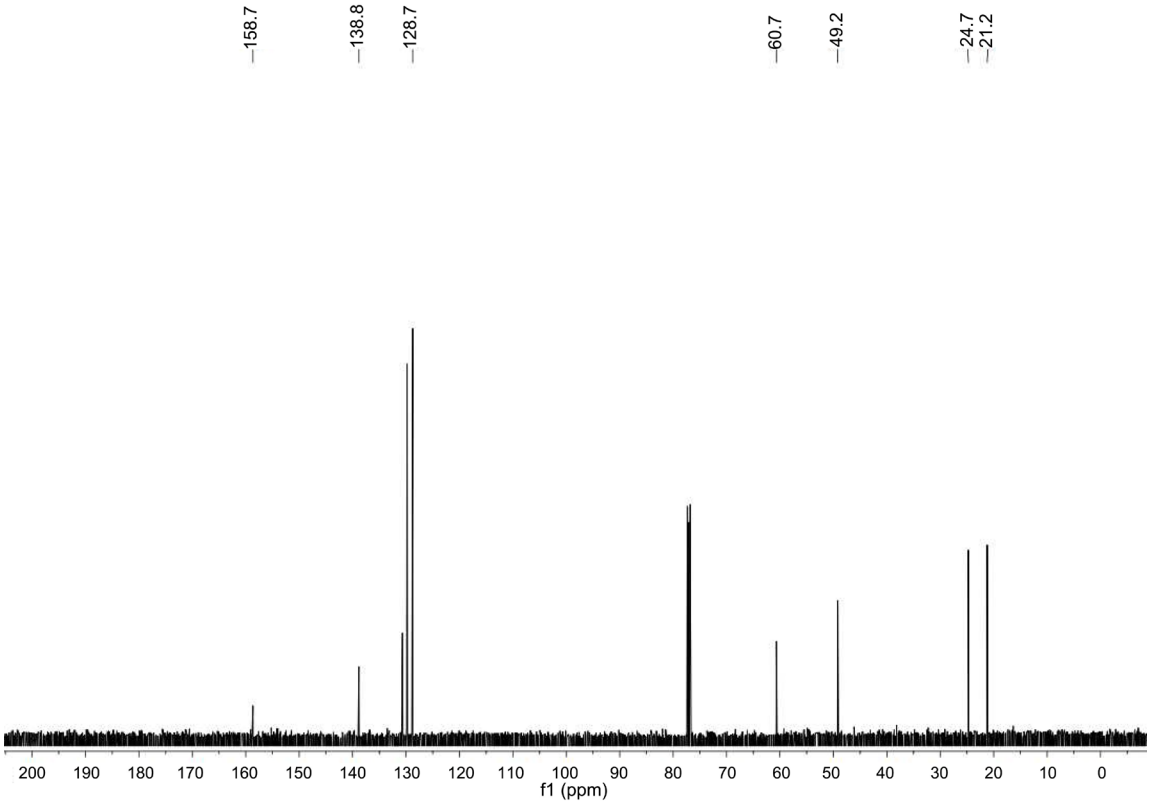

Figure 4. [13]C-NMR spectrum of compound **1b**.

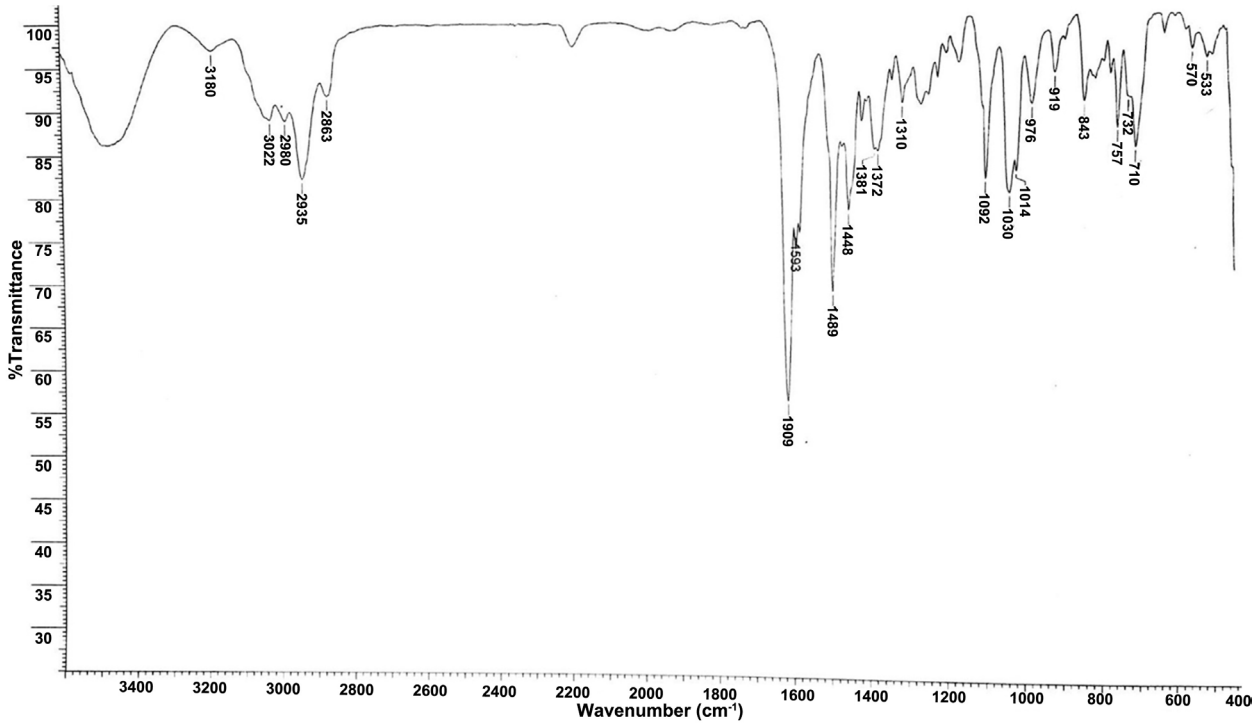

Figure 5. IR spectrum of compound **1b**.

3.2. Biological Evaluation

The synthesized salts were screened for their *in vitro* antimicrobial activity using the disk diffusion method employing Gram positive (*Staphylococcus aureus*, *Bacilus subtilis*) and Gram-negative bacteria (*Escherichia coli*) and funji (*Aspergillus niger*). Those compounds which presented any inhibition zone were evaluated by their minimal inhibitory concentration (MIC). Results are shown in Table 2.

According to the antimicrobial activity results, the derivatives without substitution in the aromatic nucleus (**1a,i**) and the nitroderivative **1f** do not present antimicrobial activity with any of the microorganisms tested. The N-monosubstituted aryl compounds (**1b-e,j**) have low antimicrobial activity against *Staphylococcus aureus*, *Bacilus subtilis* and *Escherichia coli.* Compounds with two chloro atoms in the aryl groups (**1g,h,k,l)** were those with the highest antibacterial activity showing also antifungal activity against *Aspergillus niger*.

4. Conclusions

In conclusion, we have developed a simple and efficient procedure for the synthesis of 1,3-dibenzyl-tetrahydro-1,3-diazepinium (**1**, n = 2) and hexahydro-1,3-diazocinium (**1**, n = 3) salts, a new family of medium ring nitrogen heterocyclic salts. The method involves the dehydrogenation of aminals employing a cheap commercially available reagent under ultrasound irradiation as promoting agent. This approach has several and important advantages including methodologically easy reactions, milder conditions, shorter reaction times and

Table 2. Synthesis of cyclic amidinium salts 1a-l under sonication and conventional conditions.

Comp. 1	*E. coli*	*S. aureus*	*B. subtilis*	*A. niger*
a	-	-	-	-
b	>256	256	>256	-
c	>256	>256	>256	-
d	-	-	-	-
e	-	>256	-	-
f	-	-	-	-
g	128	32	128	>256
h	256	32	64	128
i	-	-	-	-
j	>256	>256	>256	-
k	128	16	16	>256
l	>256	32	32	128

higher yields, and provides biologically interesting nitrogen containing heterocycles in good yields.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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