Microwave Assisted Reactions of Imidazole Derivatives of Potential Practical Applications

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A fast, general and facile method for preparation of 1,3-diazol salts via N-alkylation reactions under conventional heating and microwave irradiation is presented. The microwaves remarkably accelerated these N-alkylations, the reaction times decreased dramatically, the reaction conditions were milder, the consumed energy decreased considerably and the amount of solvents used was reduced substantially. Consequently, the microwave assisted alkylation of N-containing heterocycles could be considered eco-friendly. A comparative study of microwave versus classical heating (liquid solvents) has been done. Sixteen new 1,3-diazol salts of potential practical interest were obtained.

Keywords: 1,3-Diazole salts, imidazole, benzimidazole, microwave, synthesis

Imidazole and derivatives compounds are well known biologically active and medicinally potent anticancer [1, 2], anti-HIV [3, 4], antibacterial and antifungal [5, 6], cardiovascular diseases [7, 8], etc. Moreover, imidazolium salts are potent room temperature ionic liquids of current great interest in industry [9].

Recently published comprehensive books [10, 11] and papers [12-17] indicate that microwave (MW) irradiation has became an increasingly valuable tool in organic chemistry, since it offers a versatile and facile pathway in a large variety of syntheses. Thus, a large number of organic reactions can be carried out under MW irradiation in higher yields, shorter reaction time and milder conditions.

Synthesis of azaheterocyle salts by conventional heating [15-18], have some major disadvantages, including long reaction times, high energy consumption and the need for large amounts of solvents, etc. In the previous papers [19, 20] we develop a new, efficient and general method for preparation of azaheterocyle salts using MW technology.

The aim of this work was to synthetise new aza-heterocyle salts derived from 1,3-diazoles via conventional heating and MW irradiation.

Experimental part

Syntheses of imidazole salts have been done under classical heating as well as under MW irradiation. All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Advance 400 DRX spectrometer operating at 400 MHz. The IR spectra were recorded on a FTIR Shimadzu Prestige 8400s spectrophotometer. For the microwave irradiation we used a 800 W STAR SYSTEM-2 monomode reactor (CEM Corporation).

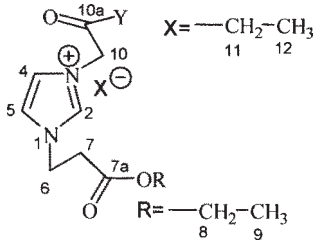
Typical procedure for synthesis of imidazolium salts 3 and 4 under classical heating

Imidazole derivatives **2** (10 mmol) were dissolved in dry acetone (30 mL). A solution of alkylbromoacetate or iodoacetamide (12 mmol) in dry acetone (10 mL) was added dropwise, under stirring. The reaction mixture was then refluxed on an oil bath for 30 to 40 h. The obtained crude salt was then processed according with the nature of reagents.

Typical procedure for syntheses of imidazolium 3 and 4 under MW irradiation

Caution! It is hazardous to rapidly heat reactions under microwave irradiation. Therefore, caution should be exercised when conducting reactions of this type.

Alkylbromoacetate or iodoacetamide (12 mmol, in 15 mL acetone) was placed in the reaction vessel (Pyrex glass or quartz; for parallel synthesis both cells of the STAR reactor could be used, in which case the irradiation power of reactor has to be double). Imidazole derivative (10 mmol) was then added. The tubes are then placed in the microwave cell and heated for the appropriate time (table 1). Stirring of the reaction mixture is desirable. If a stirring device is not available it can be replaced with nitrogen continuously bubbled into the reaction system. Once the heating cycle is complete, the tube was cooled to ambient temperature, removed from the reactor, and the cycloimmonium salts processed as indicated under classical heating, above.



Scheme 1. NMR identification of H and C atoms

1-(2-Carbamoyl-2-oxo-ethyl)-3-(2-ethoxy-carbamoyl-ethyl)-3-H-imidazol-1-ium iodide, 3d. The crude salt was filtered under vacuum, washed on the filter twice with ethanol (5 mL) and then purified by recrystallization from ethanol. ^{1}H-NMR (DMSO-D_6): 1.19-1.15 (t, J = 7.2 Hz, 3H: CH_3 (9)), 2.51-2.50 (t, J = 6.8 Hz, 2H, CH_2: H-7), 4.10-4.05 (q, J = 7.2 Hz, 2H: OCH_2 (8)), 4.46-4.43 (t, J = 6.8 Hz, 2H, CH_2: H-6), 4.96 (s, 2H, CH_2: α-C=O (10)), 7.52 (s, 1H, NH,

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Hb), 7.694-7.690 (d, J = 1.6 Hz, 1H, CH: H-4), 7.784-7.780 (d, J = 1.6 Hz, 1H, CH: H-5), 7.82 (s, 1H, NH, Ha), 9.14 (s, 1H, CH: H-2); ^{13}C-NMR (DMSO-D_6): 13.92 (C, CH_3: C-9), 33.63, (C, CH_2: C-7), 44.62 (C, CH_2: C-6), 50.44.68 (C, CH_2: X-10), 60.48 (C, CH_2: C-8), 121.76 (C-5), 123.84 (C-4), 137.58 (C-2), 166.53 (C, C=O: C-10a), 170.02 (C, C=O: C-7a).

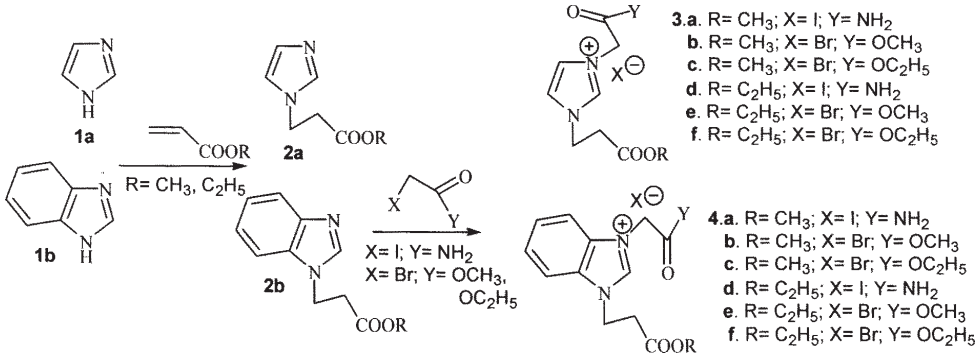
3-(2-Ethoxycarbamoyl-ethyl)-1-(2-methoxycarbamoyl-2-oxo-ethyl)-3-H-imidazol-1-ium bromide, 3e. The crude salt was triturated with diethyl ether (20 mL), filtered under vacuum and washed on the filter twice with diethyl ether (5 mL). ^{1}H-NMR (DMSO-D_6): 1.26-1.23 (t, J = 7.2 Hz, 3H: CH_3 (9)), 3.07-3.05 (t, J = 6.8 Hz, 2H, CH_2: H-7), 3.81 (s, 3H, OCH_3: H-11), 4.17-4.12 (q, J = 7.2 Hz, 2H: OCH_2 (8)), 4.70-4.67 (t, J = 6.8 Hz, 2H, CH_2: H-6), 5.53 (s, 2H, CH_2: α-C=O (10)), 7.824-7.420 (d, J = 1.6 Hz, 1H, CH: H-4), 7.898-7.894 (d, J = 1.6 Hz, 1H, CH: H-5), 9.93 (s, 1H, CH: H-2); ^{13}C-NMR (DMSO-D_6): 14.12 (C, CH_3: C-9), 34.98, (C, CH_2: C-7), 45.67 (C, CH_2: C-6), 50.37 (C, CH_2: C-10), 53.53 (C, OCH_3: C-11), 61.54 (C, CH_2: C-8), 122.63 (C-5), 123.96 (C-4), 138.10 (C-2), 166.77 (C, C=O: C-7a), 170.41 (C, C=O: C-10a).

3-(2-Ethoxycarbamoyl-ethyl)-1-(2-ethoxycarbamoyl-2-oxo-ethyl)-3-H-imidazol-1-ium bromide, 3f. The crude salt was triturated with diethyl ether (20 mL), filtered under vacuum and washed on the filter twice with diethyl ether (5 mL). ^{1}H-NMR (DMSO-D_6): 1.26-1.23 (t, J = 7.2 Hz, 3H: CH_3 (9)), 1.33-1.29 (t, J = 7.2 Hz, 3H: CH_3 (12)), 3.07-3.04 (t, J = 6.8 Hz, 2H, CH_2: H-7), 4.17-4.12 (q, J = 7.2 Hz, 2H: OCH_2 (8)), 4.29-4.24 (q, J = 7.2 Hz, 2H: OCH_2 (11)), 4.70-4.67 (t, J = 6.8 Hz, 2H, CH_2: H-6), 5.46 (s, 2H, CH_2: α-C=O (10)), 7.84 (s, 2H: H-4, H-5), 9.97 (s, 1H, CH: H-2); ^{13}C-NMR (DMSO-D_6): 14.09 (C, CH_3: C-9), 14.10 (C, CH_3: C-12), 34.93, (C, CH_2: C-7), 45.65 (C, CH_2: C-6), 50.42 (C, CH_2: C-10), 61.45 (C, CH_2: C-8), 62.90 (C, CH_2: C-11), 122.23 (C-5), 123.88 (C-4), 138.79 (C-2), 166.19 (C, C=O: C-7a), 170.59 (C, C=O: C-10a).

Results and discussion

In order to obtain the desired 1,3-diazole salts, we performed the alkylation of some five-member rings *N*-heterocyles derived from imidazole and benzimidazole, under both classical heating and MW irradiation conditions. Thus, imidazolium salts were obtained in two steps: initially we carried out the *N*-alkylation of the acidic nitrogen of imidazole derivatives (imidazole **1a** and benzimidazole **1b**) via Michael addition of ethyl or methyl acrylate; in the second step we carried out the quaternization of the second nitrogen atom with iodoacetamide and methyl- or ethyl bromoacetate, respectively scheme 2).

Under conventional heating conditions, these reactions have some major disadvantages, including long reaction times (30-40 h), high energy consumption and the need for large amounts of solvents, etc. For this reason we



Scheme 2. Reaction pathway for the synthesis of imidazolium salts

Compound	Microwaves		Conventional	
	Reaction time, min.	Yield, %	Reaction time, hours	Yield, %
3.a. R=CH_3; X=I; Y=NH_2	15	92	30	86
3.b. R=CH_3; X=Br; Y=OCH_3	15	90	30	90
3.c. R=CH_3; X=Br; Y=OC_2H_5	15	96	30	92
3.d. R= C_2H_5; X=I; Y=NH_2	15	89	30	83
3.e. R=C_2H_5; X=Br; Y=OCH_3	15	91	30	92
3.f. R= C_2H_5; X=Br; Y=OC_2H_5	15	93	30	92
4.a. R=CH_3; X=I; Y=NH_2	15	86	40	81
4.b. R=CH_3; X=Br; Y=OCH_3	15	88	40	87
3.c. R=CH_3; X=Br; Y=OC_2H_5	15	91	40	89
3.d. R= C_2H_5; X=I; Y=NH_2	15	89	40	82
3.e. R= C_2H_5; X=Br; Y=OCH_3	15	89	40	88
3.f. R= C_2H_5; X=Br; Y=OC_2H_5	15	90	40	90

Table 1
SYNTHESIS OF IMIDAZOLIUM SALTS UNDER CONVENTIONAL HEATING AND MICROWAVE IRRADIATION IN LIQUID PHASE (ACETONE)

decided to use MW technology, a nonconventional method, for the syntheses. The MW assisted reactions were carried out using a monomode reactor, under constant irradiation power and by varying the temperature (the so-called "power control"). During a cycle the temperature rise up from the room temperature closely to the boiling point of solvents, then remain almost constant no matter the time used. Initially we used for MW heating different reaction time (30, 15, 10, 5 min.), and different irradiation power of the magnetron (5, 10, 20, 25, 30%). The best results were obtained when we used 30% of the full power of the magnetron (800 W). Table 1 lists the optimized conditions we employed, under MW irradiation as well as under conventional heating.

As indicated in table 1, MW induced a remarkable acceleration for reactions, the reaction times decreasing dramatically, from 30-40 h to 15 min . Consequently, the consumed energy decreases considerably. Moreover, the amount of used solvents is 3 times less (see experimental), these type of reactions being considered as environmentally friendly. In both cases, under conventional heating and MW irradiation, the yields are high, and no substantially differences were observed between the two methods.

The structure of the new compounds was proven by elemental (C, H, N) and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). All the elemental and spectral data are in accordance with the proposed structure.

Conclusion

We report herein a comparative study of the syntheses of 1,3-diazole salts under microwave irradiation and by conventional heating in liquid solvents. A fast, general, environmentally friendly, and facile method for preparation of imidazolium salts under microwave irradiation is presented. The microwave irracdiation provided a remarkable rate of acceleration for *N*-alkylation, and the reaction times decreased dramatically, the reaction conditions were milder, the consumed energy decreased considerably and the amount of solvents used was reduced substantially, and consequently, the microwave assisted alkylation of *N*-containing heterocycles could be considered eco-friendly. Sixteen new imidazolium salts – **3a-f** and **4a-f** – of potential practical interest were obtained.

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