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Rapid and Efficient Synthesis of Imidazolines and Bisimidazolines Under Microwave and Ultrasonic Irradiation

Majid Moghadam[1,*], **Iraj Mohammadpoor-Baltork**[2], **Valiollah Mirkhani**[2], **Shahram Tangestaninejad**[2], **Mohammad Abdollahi-Alibeik**[3], **Behrooz H. Yousefi**[4], and **Hadi Kargar**[2]

[1] Department of Chemistry, Yasouj University, Yasouj, Iran
[2] Catalysis Division, Department of Chemistry, Isfahan University, Isfahan, Iran
[3] Department of Chemistry, Yazd University, Yazd, Iran
[4] Institute of Applied Synthetic Chemistry, Vienna University of Technology, Vienna, Austria

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Summary. Small assemblies of 2-imidazolines and bisimidazolines from appropriate nitriles and ethylenediamine with catalytic amounts of P_2S_5 employing a microwave assisted protocol were prepared. Sonication of this system also led to successful synthesis of 2-imidazolines and bisimidazolines. Another advantage of these systems is the ability to carry out large scale reactions.

Keywords. Imidazolines; Nitriles; P_2S_5; Microwave-assisted organic synthesis; Ultrasonic irradiation.

Introduction

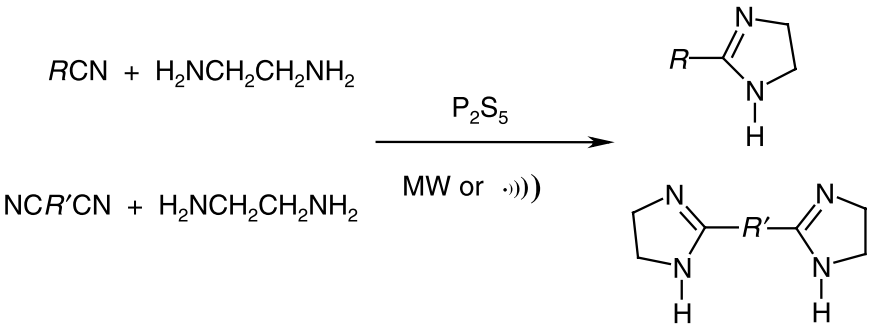
Many naturally occurring and synthetic compounds containing an imidazoline scaffold possess interesting biological activities as *e.g.* antihypercholesterolemic [1], anti-inflammatory [2], antihyperglycemic [3–7], and antihypertensive [8, 9]. Moreover, these compounds are used as intermediates [10], auxiliaries [11], and catalysts [12] for different organic syntheses.

Several preparation approaches to 2-imidazolines from carboxylic acids [13], esters [14], nitriles [15], orthoesters [16], hydroximoyl chlorides [17], hydroxyl amides [18], iminoester hydrochlorides [16–19], and mono- or di-substituted chlorodicyanovinylbenzene [20] have been reported. Some of these methods suffer from limitations, such as long reaction times, low yields of the products, difficulty in preparation of starting materials, and tedious workup procedures. However, preparation of bisimidazolines from the reaction of dinitriles with ethylenediamine (*EDA*) is of practical importance [13, 20, 21].

The rapid development of combinatorial and parallel synthesis has led to a growing demand for fast reactions and efficient purification procedures. Moreover, high speed parallel synthesis is proving to be a powerful tool and valuable strategy for drug discovery. Since the first reports using domestic multimode cavities [22], microwave-assisted organic synthesis (*MAOS*) has created new possibilities in performing chemical transformations. Microwaves heat reactants much more quickly than conventional means. Therefore, it has been frequently observed that instead of a long time, synthesis usually occurs just in a few minutes. The salient reported features of the MAOS approach are the enhanced selectivity, improved reaction rates, milder and solvent-free reaction conditions, formation of cleaner products, and associated ease of manipulation [23]. Another important issue for a chemist is the scalability of microwave reactions and the possibility of direct translation from small to large scale reactions [24].

In continuation of our interest in the synthesis of imidazolines [25] we aimed to develop a MAOS procedure for preparation of assemblies of 2-imid-

* Corresponding author. E-mail: moghadamm@mail.yu.ac.ir



Scheme 1

azolines and bisimidazolines, from appropriate nitriles and *EDA* in the presence of catalytic amounts of P_2S_5, which could be applied to a high-throughput format. We also report the rapid and efficient synthesis of 2-imidazolines and bisimidazolines by the reaction of nitriles and *EDA* under ultrasonic irradiation (Scheme 1).

Results and Discussion

Synthesis of 2-Imidazolines and Bisimidazolines under Microwave Irradiation

Initially, benzonitrile (**1a**) was chosen as a model substrate for the synthesis of 2-imidazoline. A mixture of **1a**, *EDA*, and P_2S_5 was subjected to microwave irradiation. After completion of the reaction, the mixture was cooled to room temperature. Next, cold water was added and the mixture was extracted with chloroform. Removal of the solvent and recrystallization of the crude product from cyclohexane gave the corresponding 2-imidazoline (**2a**) in 93% yield. Similarly, the substituted benzonitriles **1b**–**1e** were reacted with *EDA*, which afforded the corresponding 2-imidazolines **2b**–**2e** in 91–98% yields with excellent purities. The heterocyclic nitrile compounds **1f**–**1i** were converted to the corresponding 2-imidazolines **2f**–**2i** in 86–95% yields with an HPLC purity >98%. Surprisingly, dinitriles **1j** and **1k** also reacted with *EDA* and thus furnished the corresponding bisimidazolines **2j** and **2k** in excellent yields (90–98%) and the same purities (Table 1).

Table 1. Preparation of 2-imidazolines and bisimidazolines **2** from nitriles and dinitriles **1** under microwave and ultrasonic irradiation[a]

Entry	Nitrile **1**	Imidazoline **2**[b]	MW Irradiation		US irradiation		Refs. for known compounds
			Time/min	Yield/%[c]	Time/min	Yield/%[c]	
a	*Ph*-CN	*Ph-Im*	5.50	93	10	90	[14, 15]
b	4-*Me-Ph*-CN	4-*Me-Ph-Im*	6.50	96	20	85	[14]
c	4-Cl-*Ph*-CN	4-Cl-*Ph-Im*	3.75	94	10	90	[15, 16]
d	3-Cl-*Ph*-CN	3-Cl-*Ph-Im*	2.50	98	10	91	[32a]
e	4-*Me*O-*Ph*-CN	4-*Me*O-*Ph-Im*	8.00	91	25	85	[4, 15]
f	4-*Py*-CN	4-*Py-Im*	1.75	95	10	95	[13, 32b]
g	3-*Py*-CN	3-*Py-Im*	1.65	86	10	90	[13, 32b]
h	2-*Py*-CN	2-*Py-Im*	1.25	92	10	95	[32c]
i	Thien-2-yl-CN	Thien-2-yl-*Im*	2.50	94	15	90	[13]
j	3-CN-*Ph*-CN	3-*Im-Ph-Im*	1.5	95	10	85	[14, 15]
k	4-CN-*Ph*-CN	4-*Im-Ph-Im*	2	98	10	86	[14, 15]
l	4-Cl-*Ph*-CN	4-Cl-*Ph*-(*N-Me-Im*)	5	93[d]	10	91[d]	[27]

[a] Reaction conditions: nitrile **1** (4 mmol), *EDA* (16 mmol), P_2S_5 (0.14 mmol) under MW irradiation, and nitrile **1** (10 mmol), *EDA* (40 mmol), P_2S_5 (0.35 mmol) under ultrasonic irradiation

[b] The identities of products were confirmed by m.p., IR, and ^{1}H NMR spectroscopic data

[c] Isolated yields

[d] *N*-Methylethylenediamine was used instead of *EDA*

In order to confirm the scalability of our fast MAOS protocol, the reaction of benzonitrile was directly translated to a 100 mmole scale and performed under the same irradiation condition. The result (90% yield) was comparable to that obtained by the small scale experiment. In addition, using a combinatorial parallel approach one ensemble was performed with 5 min irradiation time in the same cavity and the results were comparable to the sequential reaction conditions (yields 81–98% and excellent purities).

Blank experiments in the absence of P_2S_5 showed that the reactions did not proceed at all, and the starting materials remained unchanged in the reaction mixture.

For this purpose, the model reaction with benzonitrile was performed using the sealed vessel capabilities of a dedicated single-mode microwave reactor, CEM Explorer^{TM} [26]. Therefore, the synthesis reported in our study was successful under a monomode environment with careful optimization. It has been frequently observed that a large variety of the chemistry accelerated under microwave heating do not at all times claim a specific microwave effect (non-thermal). However, this is still not a generally accepted idea for microwave heating and the actual nature of the effect of microwaves is still discussed to augment the understanding in other cases. In our approach to synthesize assemblies of imidazolines, we do not wish to express our interest in the ongoing argument for the existence of a microwave effect (non-thermal). However, we observed that the syntheses became significantly accelerated using microwave irradiation.

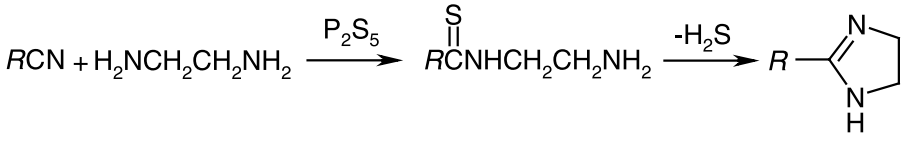
Synthesis of 2-Imidazolines and Bisimidazolines Under Ultrasonic Irradiation

The application of ultrasonic irradiation in reactions using heterogeneous catalysts is a promising technique. The advantages of ultrasound procedures, such as good yields, short reaction times, and mild reaction conditions, are well documented [27–30]. Ultrasonic irradiation can also be used to influence selectivity and yields of reactions.

Typically, **1a**, *EDA*, and P_2S_5 were mixed and exposed to ultrasonic irradiation for 10 min. Cold water was added and the mixture was extracted with chloroform. Removal of the solvent and recrystallization of the crude product from cyclohexane gave the corresponding 2-imidazoline **2a** in 90% yield. The effect of ultrasonic irradiation intensity on this reaction was also investigated. The results show that the highest yield of **2a** was obtained at 100% intensity. Under the same reaction conditions, a variety of nitriles and dinitriles were cleanly and rapidly converted to their corresponding 2-imidazolines and bisimidazolines in 85–95% yields within 10–25 min. When *N*-methylethylenediamine was used instead of *EDA* in the reaction with 4-chlorobenzonitrile under the same reaction conditions, both under microwave irradiation and under ultrasonic irradiation, the corresponding *N*-substituted 2-imidazoline **2l** was obtained in high yield (Table 1, entry **l**).

The presence of P_2S_5 was shown to be necessary by blank experiments in the absence of P_2S_5, but with ultrasonic irradiation, which showed that the reaction did not proceed at all.

To the best of our knowledge, the mechanism of this reaction is not completely clear. However, a plausible explanation is that P_2S_5 reacts with the nitrile **1** to produce the thioamide. The latter reacts with *EDA*, which upon elimination of hydrogen sulfide and ammonia produces 2-imidazoline **2**. Evolution of H_2S is a good indication of the above statement (Scheme 2). The produced H_2S, which is dissolved in the reaction mixture, can then catalyze the conversion of nitriles to imidazolines [14]. Thus, a catalytic amount of P_2S_5 is able to catalyze the reaction. Reaction of **1a** with *e.g. n*-butylamine gave the corresponding thiobenzamide. On the other hand, it has been reported that thioamides could be converted to the corresponding nitriles in the presence of *EDA* [31]. All these observations provide good evidence for the suggested mechanism.



Scheme 2

In conclusion, we have demonstrated that assemblies of different 2-imidazolines and bisimidazolines can be rapidly prepared by microwave-assisted protocols. The isolated yields in the both parallel and sequential synthesis were comparable (81–98%) and provided the desired compounds in high purity after a simple workup. We have demonstrated that the syntheses reported herein could equally be successfully executed under a monomode environment with careful optimizations. Also, feasibility of a direct scale-up has been confirmed. In comparison with the reported procedure for the synthesis of 2-imidazolines catalyzed by P_2S_5, the workup of this method is easier and extraction of the reaction mixture gives almost pure products. The application of ultrasonic irradiation also led to the synthesis of 2-imidazolines and bisimidazolines in high yield in short reaction times.

Experimental

All chemicals were commercial products. *EDA* was distilled over KOH before use. All melting points were obtained using a Stuart Scientific apparatus. TLC monitoring for all reactions, and all yields refer to isolated products. For reaction monitoring and quality (purity) control of the product a Waters 996 HPLC system, that included Waters 600-MS pumps, an autosampler (Waters 712 WISP), and Waters 996 photodiode array UV detector was used. The separations were carried out using a Chromolith Performance reversed phase analytical column (E. Merck, 100×4.6 mm) at 25°C and a mobile phase from (A) 0.1% *TFA* in 97/3 $H_2O/MeCN$ and (B) 0.1% *TFA* in *MeCN* (all solvents were HPLC grade, Fisher and Merck; *TFA* was analytical reagent grade, Roth). The following gradients were applied at a flow rate of 3 cm^3/min: linear increase from 3 to 60% solution B in 8 min, hold at 60% solution B for 2 min. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker AC 80 spectrometer. Infrared spectra were recorded on a Shimadzu IR-435 spectrophotometer in KBr with absorption in cm^{-1}.

The reactions, under MW irradiation, were performed using the sealed vessel capabilities of a dedicated single-mode microwave reactor, CEM Explorer^{TM} (a single mode automated microwave instrument). The reactions, under ultrasonic irradiation, were carried out at room temperature in a 40 cm^3 glass reactor. A UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture, was used for sonication.

General Procedure for the Synthesis of 2-Imidazolines and Bisimidazolines Under MW Irradiation

A mixture of 4 mmol nitrile **1**, 16 mmol *EDA*, and 0.14 mmol P_2S_5 was irradiated with microwave (720 W) for 1.25–20 min by pulsed irradiation (30 s with 20 s interval). The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was cooled to room temperature, cold H_2O was added, and then extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4). Evaporation of the solvent gave an almost pure product. Further purification was achieved by recrystallization of the product (**2a** was recrystallized from cyclohexane, **2b**–**2i** were recrystallized from *n*-hexane, and **2j** and **2k** were recrystallized from methanol) and gave the pure 2-imidzolines and bisimidazolines **2** in 84–98% yields (Table 1). The identities of products were confirmed by mp, IR, and ^{1}H NMR spectroscopic data.

General Procedure for the Synthesis of 2-Imidazolines and Bisimidazolines Under Ultrasonic Irradiation

A mixture of 10 mmol nitrile **1**, 40 mmol *EDA*, and 0.35 mmol P_2S_5 was irradiated with ultrasonic waves for appropriate time (Table 1). After completion of the reaction as indicated by TLC (eluent: $EtOAc/MeOH = 4/1$), cold H_2O was added and the product was extracted with 2×10 cm^3 $CHCl_3$. Evaporation of the solvent under reduced pressure and purification by a silica gel column (eluent: $EtOAc/MeOH = 4/1$) gave the imidazoline **2**. Recrystallization of product (**2a** was recrystallized from cyclohexane, **2b**–**2i** were recrystallized from *n*-hexane, and **2j** and **2k** were recrystallized from methanol) gave the pure product in good to excellent yields based on the starting nitrile (Table 1). The identities of products were confirmed by mp, IR, and ^{1}H NMR spectral data.

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