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Ultrasound assisted synthesis of hybrid quinoline-imidazole derivatives: a green synthetic approach†

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A green, straightforward and efficient study for obtaining hybrid quinoline-imidazole derivatives under ultrasound (US) irradiation as well as under conventional thermal heating (TH) has been presented. The reaction pathway involves only two steps: the *N*-alkylation of imidazole ring and a Huisgen [3 + 2] dipolar cycloaddition reaction of ylides to dimethyl acetylenedicarboxylate (DMAD). For both types of reactions, a green workup procedure under US irradiation has been presented. Under US irradiation, the *N*-alkylation of nitrogen atoms from the imidazole nucleus has outstanding benefits in terms of reaction time, energy consumption and yields, and can thereby be considered an environmentally friendly method. Forty new hybrid quinoline-imidazole compounds have been synthesized: 18 salts, 8 dihydro-benzopyrrolo imidazolo quinoline, 9 benzopyrrolo-imidazolo quinoline and 5 dihydro-pyrroloquinoxaline quinoline cycloadducts.

Introduction

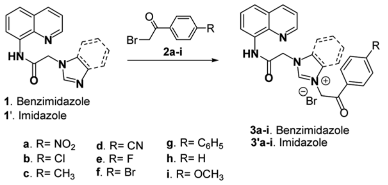
Over the past decades, ultrasound (US) assisted reactions have become a modern and successful tool in organic and medicinal chemistry. Compared with conventional thermal heating (TH), the use of US in chemical reactions has some crucial advantages, such as higher yields, better product purity, the possibility to obtain better selectivity and higher reactivity, and reduced reaction times.[1–11,31–33,36] In addition, due to milder reaction conditions, less or suppressed side reactions, energy saving nature, and the use of small amounts of solvents, the reactions become eco-friendly.[6,9–11,27,28]

Quinoline and imidazole derivatives are structural scaffolds of huge importance from pharmacological, industrial, and synthetic points of view. As for the pharmacological point of view, they are core scaffolds in medicinal chemistry, having a diverse variety of biological activities such as antiplasmodial and antimalarial, antitubercular, antibacterial, antifungal, anti-HIV, anticancer, anti-inflammatory, antidepressant, analgesic, anti-Alzheimer's, and antihypertensive activities.[12–25] The synthesis of quinoline and imidazole derivatives still remains a challenge for the scientific community because conventional synthesis is often inefficient, with low to moderate yields, the formation of by-products, and expensive and harsh reaction conditions (high temperature, long reaction time, large amount of solvents, catalysts, *etc.*).[26]

In view of our continued preoccupation with the field of US assisted reactions[27–32] and new biological entities with quinoline and imidazole skeletons,[16–18,33,34] we decided to perform a thorough study concerning the synthesis of new entities with hybrid quinoline-imidazole cores, both under US irradiation and conventional TH. In addition, we were also interested in developing an environmentally friendly method for the preparation of these hybrids using US technologies. Equally, we were also interested in the anticancer and antimicrobial potential of these compounds.

Results

In order to achieve our goal, we decided to use our expertise in cycloimmonium ylides chemistry,[35–41] with the Huisgen [3 + 2] dipolar cycloaddition reactions of ylides to dipolarophiles with triple bonds (activated alkynes) being our choice. In this regard,



Scheme 1 Synthesis of hybrid quinoline imidazolium salts **3a-i** and **3′a-i**.

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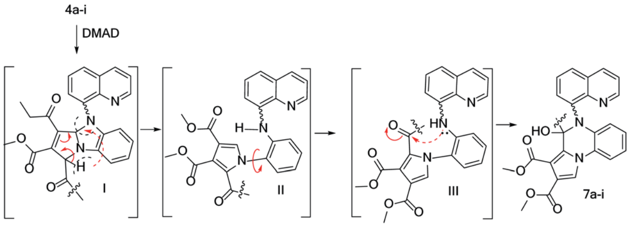
Table 1 Obtaining quinoline imidazolium salts **3a-i** and **3′a-i** using conventional TH and US irradiation

Compound		**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**
R.t. (h)	CV	48	48	48	48	48	96	48	48	48
	US	1.6	1.3	1.5	1.6	1	1.2	1.5	1.2	1.3
Compound		**3′a**	**3′b**	**3′c**	**3′d**	**3′e**	**3′f**	**3′g**	**3′h**	**3′i**
R.t. (h)	CV	48	48	48	48	48	96	96	48	48
	US	1.6	1.3	2	1.6	1.6	2.3	2.3	1.6	1.3
Compound		**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**
Yield, %	CV	90	75	56	87	82	63	74	80	88
	US	96	80	63	91	85	65	79	84	90
Compound		**3″a**	**3′b**	**3′c**	**3′d**	**3′e**	**3′f**	**3′g**	**3′h**	**3″i**
Yield, %	CV	56	84	78	86	81	51	67	75	83
	US	78	86	82	90	83	58	70	84	87



Scheme 2 Reaction mechanism for obtaining dihydro-pyrrolo-quinoxaline quinoline compounds **7a-i**.

we first obtained the corresponding hybrid quinoline imidazolium salts **3a-i** and **3′a-i** *via* *N*-alkylation with ω-halogenoacetophenones **2a-i** of the acidic nitrogen from benzimidazole **1** and imidazole **1′** (Scheme 1).

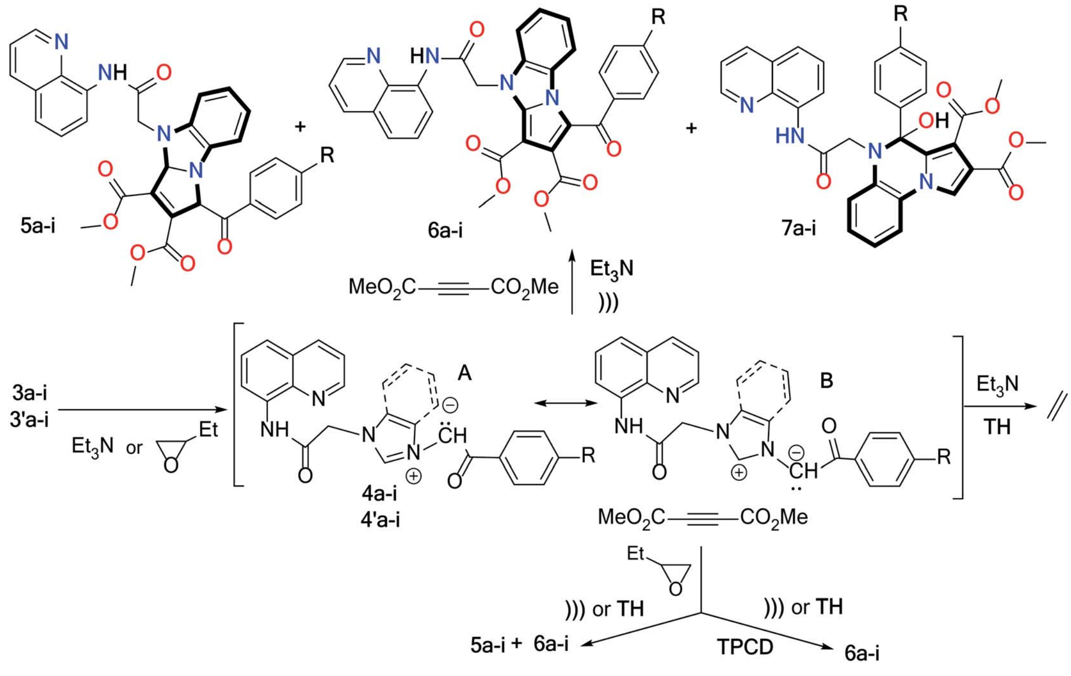
As we may notice from Table 1, the *N*-alkylation reactions of the imidazole ring under conventional TH requires long reaction times and the yields are moderate to good (around 50–90%). This is why we decided to modify the workup procedure using US irradiation (ultrasound assisted reactions were carried out using a Sonics VCX-130 reactor with titanium horn, operating in pulse mode, having a nominal power of 130 W and a frequency of 20 kHz). The data from Table 1 reveal that the use of US irradiation in the *N*-alkylation reactions of the imidazole ring have the advantages of remarkable acceleration of the reaction, substantial decrease of reaction time (from 48–96 hours to 1–2 hours) decrease of consumed energy, and slight increase of yields (by about 5–10%). As a result, this workup procedure could be considered as environmentally friendly.

As in related cases,[27] the efficiency of US irradiation in the *N*-alkylation reactions could be explained by the cavitation phenomena leading to enhanced mass transfer and better homogenization of the reaction mixture.

In the second step, benzimidazolium ylides **4a-i** and imidazolium ylides **4′a-i** (generated *in situ* from the corresponding imidazolium salts **3a-i** and **3′a-i**, using triethylamine (Et_3N) or 1,2-epoxybutane) were treated with dimethyl acetylenedicarboxylate (DMAD), a symmetrically activated alkyne, and a typical Huisgen [3 + 2] cycloaddition took place (Scheme 3).

In the case of the imidazolium ylides **4′a-i**, no matter the conditions we employed for the cycloaddition (US irradiation or conventional TH, with or without catalyst, solvents, *etc.*), the reactions did not result in any compound, and only decomposition products were obtained (probably because of the instability of the imidazole ring, as we found in a related situation[40]).

In the case of the benzimidazolium ylides **4a-i**, the cycloaddition reactions took place with the formation of the cycloadducts **6a-i** and/or **5a-i** and/or **7a-i**, according to the conditions we employed (Scheme 3 and Tables 2–4). Thus, when the Huisgen [3 + 2] cycloaddition took place using triethylamine as



Scheme 3 The Huisgen 3 + 2 cycloaddition of ylides **4a-i** and **4′a-i** with DMAD.

Table 2 Comparative study of US *versus* CV (conventional) irradiation, using Et_3N, for the cycloaddition reactions of ylides **4a-i** with DMAD

Compound		**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**
Yield, %	CV	0	0	0	0	0	0	0	0	0
	US	0	0	0	20	0	0	0	0	14
Compound		**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**
Yield, %	CV	0	0	0	0	0	0	0	0	0
	US	6	6	9	0	5	4	3	2	0
Compound		**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**
Yield, %	CV	0	0	0	0	0	0	0	0	0
	US	17	34	0	12	13	27	0	0	0

Table 3 Comparative study of US *versus* CV (conventional) irradiation, using 1,2-epoxybutane, for the cycloaddition reactions of ylides **4a-i** with DMAD

Compound		**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**
Yield, %	CV	0	14	15	15	21	13	13	12	18
	US	0	24	17	29	25	19	19	19	22
Compound		**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**
Yield, %	CV	32	7	8	10	9	10	14	10	8
	US	37	5	6	3	6	10	13	10	8
Compound		**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**
Yield, %	CV	0	0	0	0	0	0	0	0	0
	US	0	0	0	0	0	0	0	0	0

a catalyst, the reactions occurred differently according to the energy source (Table 2). When conventional TH was used, the reactions did not take place, and again only decomposition products were obtained. When US irradiation was used, the reactions took place within a very short period of time (2–4 minutes) with formation of a mixture of the cycloadducts **6a-i** and/or **5a-i** and/or **7a-i** (Table 2).

Initially, the dihydro-benzopyrrolo-imidazolo quinoline derivatives **5a-i** are formed *via* the Huisgen [3 + 2] cycloaddition of ylides **4a-i** (canonical structure B) to DMAD. As in related cases,[41–45] the initial cycloaddition is followed by an oxidative dehydrogenation of the dihydro-structure **5**, leading to more thermodynamically stable compounds: the aromatized benzopyrrolo-imidazolo quinoline compounds **6a-i**. The formation of the dihydro-pyrroloquinoxaline quinoline compounds **7a-i** could be explained *via* the following reaction mechanism (Scheme 2): after the initial Huisgen [3 + 2] cycloadditions which lead to the type I dihydro-benzopyrrolo-imidazolo derivatives, a ring opening of the imidazole cycle occurs simultaneously with a prototropic rearrangement, with the formation of a type II pyrroloaniline derivative. In the next step, rotations of the pyrrole ring around the carbon-nitrogen single bond lead to a favorable conformation of the molecule (type III) which allows cyclization to a quinoxaline cycle (*via* a nucleophilic attack of the amine electrons to the carbonyl group) with the formation of the dihydro-pyrrolo-quinoxaline quinoline compounds **7a-i**. Analogous explications have been furnished by some other authors in related cases.[41–45]

Table 4 Comparative study US *versus* CV (conventional) irradiation, using 1,2-epoxybutane and TPCD, for the cycloaddition reactions of ylides **4a-i** with DMAD

Compound		**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**
Yield, %	CV	42	25	21	39	35	31	36	30	37
	US	45	29	32	41	42	40	44	34	39

The formation of cycloadducts **5-7** could be explained *via* the substituent effect: the electron-repulsive groups favour the formation of the pyrrolo-imidazolo structure of type **5-6,** while the electron-withdrawing groups favour the formation of the pyrrolo-quinoxaline structure of type **7**.

In view of the above considerations, especially the lack of selectivity and low yields of reactions but also the toxicity of the solvent used (chloroform), we decided to modify the workup protocols by changing the solvents and using catalysts. Our next choice was to use 1,2-epoxybutane as a nontoxic solvent and as a scavenger for hydrobromic acid for the synthesis of the dihydro-benzopyrrolo-imidazolo quinoline compounds **5a-i** and the benzopyrrolo-imidazolo quinoline compounds **6a-i** (Table 3).

Our first observation is that, under these conditions, the reaction became more selective, with only two products being obtained: the dihydro- and fully aromatized cycloadducts **5a-i** and **6a-i**. No quinoxaline structures of type **7** were observed. We also noticed that under US irradiation, the global yields are slightly higher (by about 5%) and more importantly, a clear preference for obtaining the dihydro-benzopyrrolo-imidazolo quinoline structure is observed (with about 15% more compared with the aromatized one, in term of yield). We wish to also point out that under US irradiation, the reaction time decreases substantially, from 720–960 minutes under conventional TH to 150–180 minutes under US irradiation (roughly fivefold).

Since we were still not satisfied by the obtained results, we decided to perform the cycloaddition reactions in 1,2-epoxybutane using tetrakis(pyridine)cobalt(II) dichromate (TPCD) as the catalyst. The obtained results are listed in Table 4.

From Table 4 we may notice that, in these conditions, the reactions became selective, and only fully aromatized cycloadducts **6a-i** were obtained. We may also notice that under US irradiation, the yields are better, being about 5–10% higher compared with conventional TH. We also wish to point out that under US irradiation, the reaction time decreases dramatically (about twenty times), from 300–480 minutes under conventional TH to 16–20 minutes under US irradiation. Consequently, the consumed energy decreases in the same manner. As a result of all these considerations, we claim that the Huisgen [3 + 2] dipolar cycloaddition reactions of ylides **4a-i** with DMAD, in 1,2-epoxybutane and TPCD, are an environmentally friendly workup procedure.

The structures of the compounds were proven by elemental and spectral analyses (IR, ^{1}H-NMR, ^{13}C{^{1}H}-NMR, 2D-COSY, 2D-HMQC, long range 2D-HMBC) and were in accordance with the proposed structures.

Conclusions

In conclusion, a green, straightforward and efficient study for obtaining hybrid quinoline-imidazole derivatives under US irradiation as well as under conventional TH has been presented. The reaction pathway involves only two steps: the *N*-alkylation of the imidazole skeleton and a Huisgen [3 + 2] dipolar cycloaddition reaction of the ylides to DMAD. The use of US irradiation in the *N*-alkylation reactions of the imidazole ring has the advantages of remarkable acceleration of the reaction, substantial decrease of reaction time (from 48–96 hours to 1–2 hours), decrease of consumed energy, and slight increase of yields (no more than 10%). As a consequence, this workup method could be considered environmentally friendly. The Huisgen [3 + 2] dipolar cycloaddition reaction of benzimidazolium ylides to DMAD generates three types of hybrid quinoline-imidazole cycloadducts and according to the source of energy and solvent used, the reactions pathway could be conducted selectively. Thus, if the fully aromatized benzopyrrolo-imidazolo quinoline cycloadducts are to be obtained, the TPCD catalyst and 1,2-epoxybutane, have to be used both under US irradiation and conventional TH. When dihydro-pyrrolo-quinoxaline quinoline compounds are the final goal, the triethylamine catalyst and chloroform as the solvent are compulsory to be used under US irradiation. If the dihydro-benzopyrrolo-imidazolo quinoline derivatives are intended as major products, 1,2-epoxybutane and US irradiation have to be used. Taking into account the above mentioned points, alongside an obvious decrease in reaction time and energy consumption, and the fact that in the cycloaddition reactions we have used a nontoxic solvent (1,2-epoxybutane), the 1,3 dipolar cycloaddition reactions under US irradiation can be considered an environmentally friendly workup procedure. Forty new hybrid quinoline-imidazole compounds belonging to four different classes have been synthesized: 18 salts, as well as 8 dihydro-benzopyrrolo-imidazolo quinoline, 9 benzopyrrolo-imidazolo quinoline and 5 dihydro-pyrroloquinoxaline quinoline cycloadducts.

Author contributions

The manuscript was written with contributions from all authors.

Conflicts of interest

There are no conflicts to declare.

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