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Synthesis, crystal structure and antibacterial activity of new highly functionalized ionic compounds based on the imidazole nucleus

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ABSTRACT

Several new highly functionalized imidazolium derivatives were synthesized, via appropriate synthetic routes, using imidazole, 1-methylimidazole and 2-phenyl-1-methylimidazole as key intermediates. The antibacterial activity of the prepared compounds was evaluated against: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella thipymurium* using disk-diffusion and MIC methods. Crystal X-ray structures are reported for six compounds.

Heterocyclic compounds have so far been synthesized mainly due to the wide range of biological activities. Much attention was paid to the synthesis of heterocyclic compounds bearing nitrogen and oxygen containing ring system, like pyrazole, oxazole, coumarine, and pyrrole derivatives mainly due to their higher pharmacological activity.[1–3] At present, the role of heterocyclic compounds has become increasingly important in designing new class of structural entities of medicinal importance.[4–7]

Imidazole nucleus forms the main structure of some well-known components of human organisms, that is, histidine, Vit-B12, a component of DNA base structure and purines, histamine and biotin. It is also present in the structure of many natural or synthetic drug molecules.[8–10] For example, Lepidiline A and B exhibit significant cytotoxicity against various types of human cancer cell lines at micromolar concentrations.[11] Dacarbazine,[12] Zoledronic acid,[13] Tipifarnib[14,15] and Azathioprine[16] are also potent anticancer agents bearing an imidazole ring.

On the other hand, imidazolium salts are known for the wide-range of their biological activity. A large variety of these salts have been used as anti-inflammatory, antibacterial, antifungal and thromboxane synthetase inhibitior.[17]

Furthermore, Haloimidazoles are used as synthons for the production of various condensed heterocyclic systems[18] and some of them are known to possess remarkable and significant biological applications as drugs,[19] pharmaceuticals and agrochemicals.[20]

In the present work, a variety of functionalized imidazolium compounds were prepared (variations on C2, C4 and C5) and their antibacterial activity was studied. The structure elucidation of some prepared compounds was performed by X-ray diffraction.

First, the key intermediates **2**, **4**, **6** and **8** were prepared incorporating two bromine, iodine atoms or nitro group on the imidazole unit. Synthesis of these compounds was accomplished as outlined in Schemes 1 and 2.

According to a known procedure,[21] the hydroxymethylation of the commercially available 1-methylimidazole leads to the corresponding (1-methyl-1*H*-imidazol-2-yl)methanol **1**. Then, the resulting compound was subjected to bromination reaction using $Br_2/KHCO_3$ in DMF to give the desired (4,5-dibromo-1-methyl-1*H*-imidazol-2-yl)methanol **2**.[22]

The key intermediates 4,5-dibromo-2-methyl-1-methylimidazole **4a** and 4,5-dibromo-2-phenyl-1-methylimidazole **4b**, were obtained from the reaction of 2-methylimidazole or 2-phenylimidazole with bromine in DMF and in presence of $KHCO_3$,[22] followed by methylation reaction using Me_2SO_4.[23]

The 1-methyl-4,5-diiodoimidazole derivatives **6a** and **6b** were synthesized by reacting 2-methylimidazole and imidazole with

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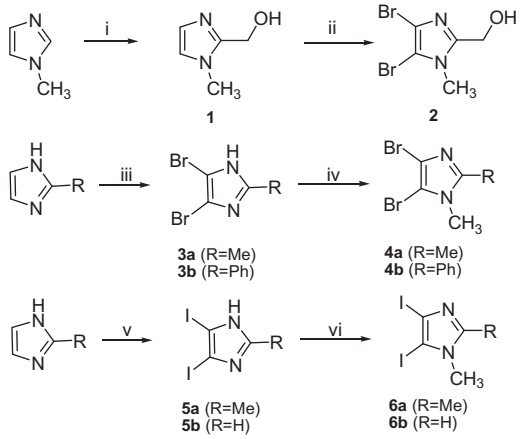
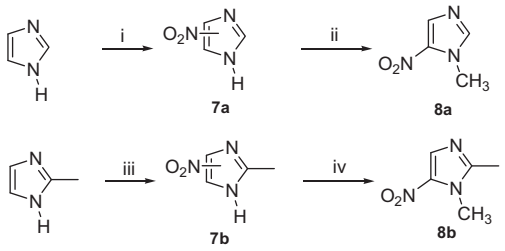
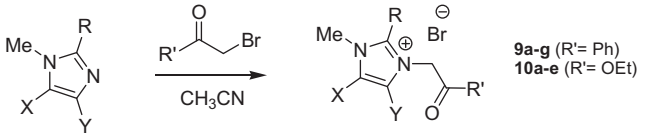


Scheme 1. Reagents and conditions: (i) CH_2O/H_2O, DMSO, 48 h (43%); (ii) Br_2, $KHCO_3$, DMF, 0–100 °C, 72 h (30%); (iii) for **3a** and **3b**: Br_2, $KHCO_3$, DMF, 0–100 °C, 72 h (36% and 61% respectively); (iv) for **4a** and **4b**: Me_2SO_4, NaOH/H_2O, 40 °C, (91% and 39%); (v) for **5a** and **5b**: I_2, NaOH, KI/H_2O, then AcOH, 24 h (60% and 70% respectively); (vi) for **6a** and **6b**: Me_2SO_4, NaOH/H_2O, 40 °C, (78% and 86% respectively).



Scheme 2. Reagents and conditions: (i) H_2SO_4, HNO_3 100%, 100 °C (85%); (ii) $MeSO_4$, 100 °C then neutralization at rt with NH_4OH, (72%); (iii) H_2SO_4, 0 °C then HNO_3 100%/Ac_2O, 140 °C (39%); (iv) Me_2SO_4, HCOOH, reflux, 4 h, (87%).



Scheme 3. Reagents and conditions: (i) $BrCH_2COR'$ (1.2 equiv R′ = Ph; 1.8 equiv R′ = OEt), CH_3CN, reflux, 48 h.

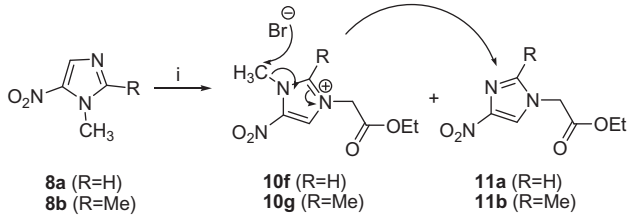
iodine in water in presence of KI and NaOH,[24] followed by treatment of the obtained 4,5-diiodo-1*H*-imidazole derivatives **5a** and **5b** with dimethylsulfate in aqueous NaOH solution.

Next, we considered the synthesis of imidazole units containing a nitro group. Some nitroimidazoles were found to be useful biological synthons and endowed with numerous important activities.[25–27] 1-Methyl-5-nitroimidazole **8a** and 1,2-dimethyl-5-nitroimidazole **8b** were obtained via a nitration/methylation sequence (Scheme 2).

Having in hand these various functionalized derivatives, we turned our attention to the synthesis of corresponding imidazolium salts using a quaternization reaction. Following the standard methodology, compounds **9a–9g** were obtained in moderate to good yields by reacting the corresponding products **2**, **4a–b**, **6a–b** and **8a–b** with 1.5 equiv of 2-bromoacetophenone at reflux of acetonitrile (Scheme 3). In similar manner, when 1.8 equivalent of ethyl bromoacetate was used as quaternization agent, the compounds **2**, **4a–b** and **6a–b** react correctly and give the imidazolium compounds **10a–e**.

Table 1
Products and yields of quaternization reactions

Products	R	X	Y	Yield (%)
9a	CH_2OH	Br	Br	27
9b	Me	Br	Br	78
9c	Ph	Br	Br	21
9d	Me	I	I	52
9e	H	I	I	66
9f	H	NO_2	H	76
9g	Me	NO_2	H	65
10a	CH_2OH	Br	Br	57
10b	Me	Br	Br	60
10c	Ph	Br	Br	83
10d	Me	I	I	82
10e	H	I	I	17



Scheme 4. Reagents and conditions: (i) 1.8 equiv $BrCH_2CO_2Et$, CH_3CN, reflux, 48 h.

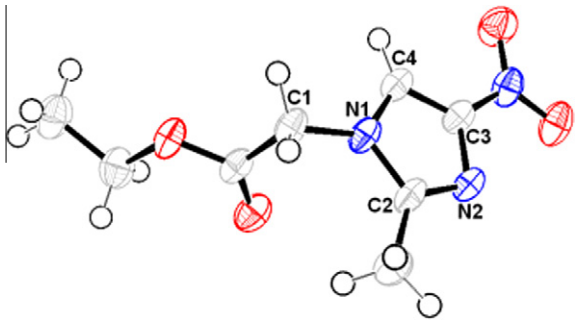


Figure 1. ORTEP plot of the X-ray crystal structure of **11b**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.379(3), C2–N2 1.317(3), N2–C3 1.370(3), N1–C1 1.450(3).[30]

Note that no purification was needed and the corresponding compounds **9a–g** and **10a–e** were isolated by simple filtration after crystallization during the reducing step of solvent volume. The prepared compounds and yields of the quaternisation reaction are shown in Scheme 3 and in Table 1 and their structures were established by spectroscopic and analytical methods.[28]

However, the reaction of compounds **8a** and **8b** (X = NO_2, Y = H) with ethyl bromoacetate afford the quaternized compounds **10f** and **10g** accompanied with unexpected products **11a** and **11b**, respectively, resulting from a demethylation reaction with bromide ion (Scheme 4). This result was previously observed by Crozet and co-workers.[29]

The structure determination of **11b** is based on an X-ray study of a suitable crystal obtained by slow evaporation at room temperature of a MeOH solution. An ORTEP representation of the crystal structure is shown in Figure 1.

On the other hand, crystallographic studies can contribute to understanding the reactivity, affinity and the binding properties of molecules.[31–33] Furthermore, numerous studies have demonstrated that the nature of substituents and substitution pattern on the imidazole unit may have a considerable impact on the pharmacological activities.[34,35] Thus it was considered of interest to