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Synthesis of Imidazoles via Cascade Reaction of Nitroallylic Acetates with Amidines and Studies on Their Trypanocidal Activity

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A one-pot, two step synthesis of highly substituted imidazoles has been carried out in good to excellent yield for the first time via a cascade intermolecular aza-S_N2'-intramolecular aza-Michael addition involving a variety Morita-Baylis-Hillman acetates of nitroalkenes and amidines in the presence of DABCO at room temperature. The synthetic and biological utility of the products has been demonstrated. In particular, some of the imidazoles exhibited potent activity against *T. cruzi*, the etiological agent of Chagas disease.

Imidazole is an important heterocycle which is an integral part of numerous bioactive compounds and natural products.[1] Amino acid histidine, neurotransmitter histamine, purine bases adenine and guanine and anti-ulcer agent omeprazole possess an imidazole moiety. Various biological properties of imidazoles,[2] such as antibacterial, antifungal, analgesic, antitubercular, anticancer, anti-HIV, antiarthritic and antitumor, to name a few, have been extensively investigated.[3] Imidazole containing peptides for the treatment of eye and skin diseases[4] and many imidazole based marine alkaloids[5] have been reported in the literature. The role of imidazoles as co-ordinating ligands[6] and as precursors to stable carbenes[7] and ionic liquids[8] is well-documented.

Since the early reports on the synthesis of imidazoles by Debus,[9] Radziszewski[10] and Robinson[11] via a three component reaction of 1,2-dicarbonyl compound, aldehyde and ammonia, and Bredereck synthesis using α-haloketones/diketones and formamide,[12] many multi-component reactions[13] and several new approaches involving reaction of α-haloketones with amidines,[14] and metal-mediated[15-17] reactions have offered access to functionalized and fused imidazoles.[18] The reactions of amidines with electrophiles such as α-haloketones,[14] acetylenes[16] and nitroalkenes[17] are indeed powerful methods. But, the lachrymatory nature of haloketones and the requirement of metal catalysts, often in conjunction with an oxidant, in the reaction with acetylenes and nitroalkenes as well as limited functional group diversity are obvious drawbacks.

In the last few years, synthesis and evaluation of imidazoles against *Trypanosoma cruzi*, a parasite that causes Chagas disease have been described (Figure 1).[19] Potential compounds were obtained from redox centre modification of quinones by the reaction with aromatic aldehydes in the presence of ammonium acetate.[20-21] Some of them (Figure 1) exhibited high activity against *T. cruzi*, with IC_{50}/24 h = 37.0 and 15.4 µM, respectively.[21] Studies on the mechanisms of action of these compounds demonstrated a mitochondrial swelling, abnormal chromatin condensation and kDNA disruption, as well as the presence of autophagy-related structures, suggesting the induction of this process in the parasite death. Ultrastructural, flow cytometric, and biochemical analysis suggested that these imidazoles interfere with the energetic metabolism especially in the mitochondrion and also induce DNA fragmentation.[22]

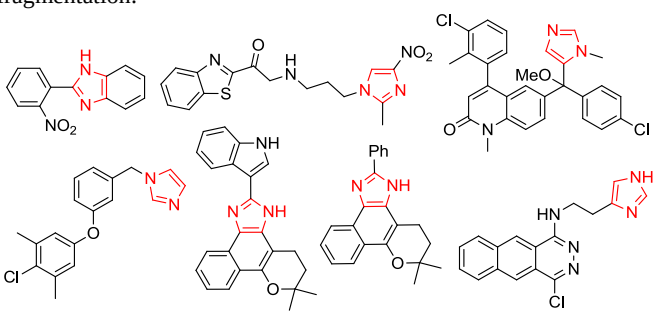

Fig. 1 Imidazoles with potent activity against *T. cruzi*

In view of the above, we envisioned a convenient entry into highly substituted and potentially bioactive imidazoles involving a one-pot reaction of Morita-Baylis-Hillman (MBH) acetates of nitroalkenes with amidines under mild conditions. The remarkable 1,2- and 1,3-bielectrophilic character of nitroallylic acetates has inspired us and others in the synthesis of several heterocycles[23] and carbocycles[24] in recent years.[25] However, construction of imidazole skeleton by exploiting the bielectrophilic reactivity of MBH acetate **1** with a 1,3-binucleophile such as amidine **2** and studies on their biological properties remain unreported hitherto.[26]

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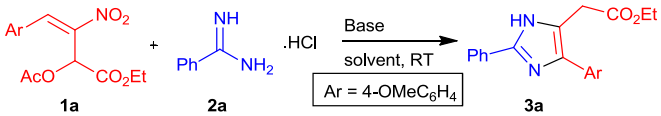
† Electronic supplementary information (ESI) available: X-ray data table, experimental procedures and complete characterization data and copies NMR and Mass spectra. CCDC reference number CCDC 1037602. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/ x0xx00000x.

We began our investigations by treating MBH acetate[27] **1a** with amidine hydrochloride **2a** in the presence of 1.5 equiv of KOH in methanol (Table 1, entry 1). Although the reaction was complete in 2 min, the reaction mixture was too complex for further analysis. Changing the solvent from methanol to THF was found beneficial as the desired product **3a** was isolated in 50% yield (entry 2). Since the role of base was primarily to neutralize amidine hydrochloride **2a**, it did not appear necessary to use a strong base such as KOH for this purpose. Therefore, we screened milder inorganic bases such as Cs_2CO_3 and K_2CO_3 (entries 3-4) and an organic base DABCO (entries 5-9). Use of 2.5 equiv of Cs_2CO_3 in THF was found suitable for the reaction which delivered imidazole **3a** in 90% yield in 7 h (entry 3). Same amount of K_2CO_3 (2.5 equiv) in THF did not improve the yield (89%) and required longer reaction time (entry 4). Subsequently, we switched to amine base DABCO (2.5 equiv) in THF which provided imidazole **3a** in 92% yield in 7 h (entry 5). Different solvents were then screened for the DABCO mediated reaction of MBH acetate **1a** with amidine hydrochloride **2a** (entries 6-8). Considerable rate acceleration was observed, though without further improvement in the yield (92%), when the reaction was conducted in acetonitrile (entry 6). Solvents such as dichloromethane and toluene were not found suitable for our reaction both in terms of the reaction time and the isolated yield (entries 7 and 8). Lower yield (79%) and longer reaction time (12 h) were encountered when the base loading was lowered from 2.5 equiv to 1.5 equiv (entry 6 vs entry 9). Finally, 2.5 equiv DABCO in acetonitrile (entry 6) was identified as the optimal reaction condition for treating various MBH acetates **1** with amidinium salts **2** for the synthesis of substituted imidazoles **3-4** (Tables 2-3).

Table 1 Optimization of reaction conditions[a]



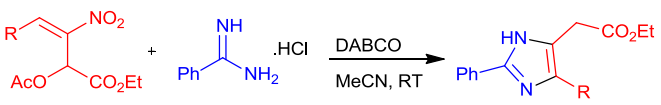
1a 2a 3a

Entry	Base (equiv)	Solvent	Time	% Yield[b]
1	KOH (1.5)	CH_3OH	2 min	-[c]
2	KOH (1.5)	THF	40 min	50
3	Cs_2CO_3 (2.5)	THF	7 h	90
4	K_2CO_3 (2.5)	THF	12 h	89
5	DABCO (2.5)	THF	7 h	92
6	DABCO (2.5)	CH_3CN	3 h	92
7	DABCO (2.5)	DCM	30 h	38
8	DABCO (2.5)	toluene	48 h	60
9	DABCO (1.5)	CH_3CN	12 h	79

[a]Reactions were carried out with 0.2 mmol of MBH acetate **1a** and 0.24 mmol of amidine **2a**. [b]After silica gel column chromatography. [c] Complex mixture.

Under the above optimized conditions, the scope of MBH acetate **1** was first investigated using amidinium salt **2a** (Table 2). MBH acetates bearing electron donating substituents at unhindered positions or no substituent in the aromatic ring **1a** and **1c-f** afforded corresponding imidazoles **3a** and **3c-f** in excellent yield (86-92%, entries 1, 3-6). On the other hand, those bearing hindered aryl groups, ortho-substituted and fused, **1b** and **1j**, respectively, delivered the imidazoles **3b** and **3j** in much lower yield (67-68%, entries 2 and 10). Similar yields were encountered for imidazoles **3g-i** which resulted from MBH acetates possessing deactivating haloaryl substituents **1g-i** (65-68%, entries 7-9). Imidazoles bearing heteroaryl substituents **3k** and **3l** could be synthesized in 74% and 62% yields, respectively, from MBH acetates **1k** and **1l** (entries 11-12). Finally, representative examples of styrenyl and alkyl substituted imidazoles **3m** and **3n** were synthesized from MBH acetates **1m** and **1n** in 58-67% yield (entries 13-14).

Table 2 Scope of MBH acetates for the synthesis of imidazoles[a]



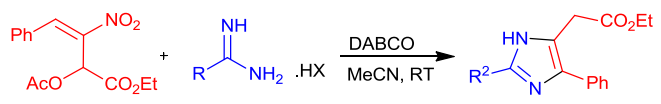
1 2a 3

Entry	1, R	Time (h)	3	% Yield[b]
1	**1a**, 4-$MeOC_6H_4$	3	**3a**	92
2	**1b**, 2,4-$(MeO)_2C_6H_3$	4	**3b**	68
3	**1c**, 3,4-$(MeO)_2C_6H_3$	3	**3c**	86
4	**1d**, 3,4-$(OCH_2O)C_6H_3$	2	**3d**	91
5	**1e**, 4-MeC_6H_4	3	**3e**	91
6	**1f**, C_6H_5	4	**3f**	89
7	**1g**, 4-FC_6H_4	2	**3g**	68
8	**1h**, 4-ClC_6H_4	0.5	**3h**	67
9	**1i**, 3-BrC_6H_4	0.5	**3i**	65
10	**1j**, 1-Naphthyl	4	**3j**	67
11	**1k**, 2-Furyl	7	**3k**	74
12	**1l**, 2-Thienyl	2	**3l**	62
13	**1m**, PhCH=CH	1.5	**3m**	58
14	**1n**, Cyclohexyl	1	**3n**	67

[a]Reactions were carried out with 0.2 mmol of MBH acetate **1**, 0.24 mmol of amidine **2a** and 0.5 mmol of DABCO. [b]Isolated yield after silica gel column chromatography.

Having investigated the scope of MBH acetates **1** in the synthesis of highly substituted imidazoles, we proceeded to demonstrate the scope of amidines **2** by treating a representative MBH acetate **1f** with various amidines **2b-h** (Table 3). Besides **2a** (Table 2), reaction of various aromatic amidines **2b-2e** with MBH acetate **1f** was first investigated. Although aromatic amidine **2c** with a strong electron withdrawing NO_2 group provided a complex mixture (entry 2), those with weakly electron donating (**2b**, entry 1) and withdrawing (**2d-2e**, entries 3-4) groups did indeed react well to give the products **4a** and **4c-d** in good to excellent yield (entries 1 and 3-4). While parent formamidine **2h** furnished a complex mixture (entry 7), other aliphatic amidines **2f-g** reacted with MBH acetate **1f** and provided imidazoles **4e-f** in good to moderate yield (entries 5-6).

Table 3 Scope of amidines[a]

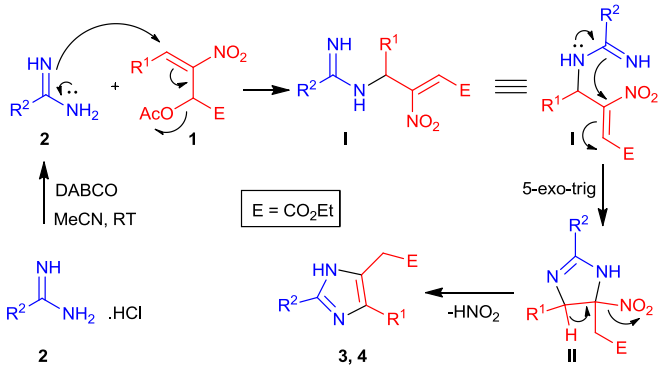


1f 2 4

Entry	2, R	Time (h)	4	% Yield[b]
1	**2b**,4-MeC_6H_4	2	**4a**	69
2	**2c**, 4-$NO_2C_6H_4$	-	**4b**	-[c]
3	**2d**, 4-ClC_6H_4	1.5	**4c**	54
4	**2e**, 3-ClC_6H_4	1	**4d**	88
5	**2f**, CH_3	1	**4e**	62
6	**2g**, CH_3S	1.5	**4f**	32
7	**2h**, H	-	**4g**	-[c]

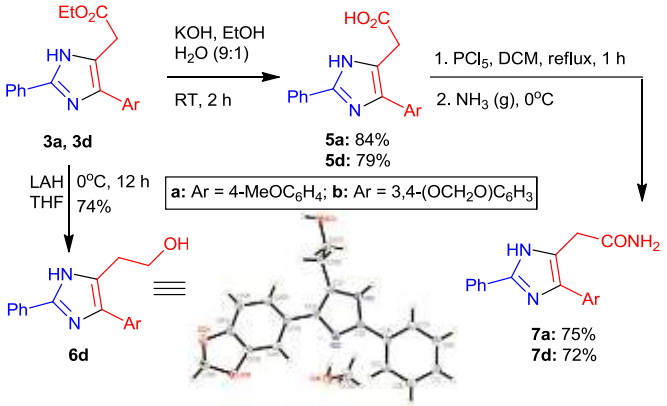
[a]Reactions were carried out with 0.2 mmol of MBH acetate **1f**, 0.24 mmol of amidine **2** and 0.5 mmol of DABCO. [b]Isolated yield after silica gel column chromatography. [c]Complex reaction mixture.

A plausible mechanism for the formation of imidazoles of type **3** or **4** is depicted in Scheme 1. Neutralization of amidinium salt **2** by DABCO and subsequent reaction of the free amidine **2** as binucleophile with MBH acetate **1** in an S_N2' fashion generates intermediate **I**, which on intramolecular aza-Michael reaction in a 5-exo-trig manner results in the initial cyclized product imidazoline **II**. A base facilitated elimination of HNO_2 from imidazoline **II** affords the imidazoles **3** or **4**. An alternative 6-endo-trig cyclization pathway leading to a dihydropyrimidine is not observed in these reactions.



Scheme 1 Proposed mechanism for the formation of imidazoles

After synthesizing a library of imidazole derivatives, a representative imidazole **3d** was subjected to LAH reduction to afford alcohol **6d** in 74% yield whose structure was confirmed by single crystal X-ray analysis (Scheme 2). Basic hydrolysis of **3a** and **3d** delivered imidazole carboxylic acids **5a** and **5d** in 84% and 79% yields, respectively. The acids **5a** and **5d** were further converted to amides **7a** and **7d** in 75% and 72% yields, respectively, by treating with PCl_5 followed by ammonia (g).

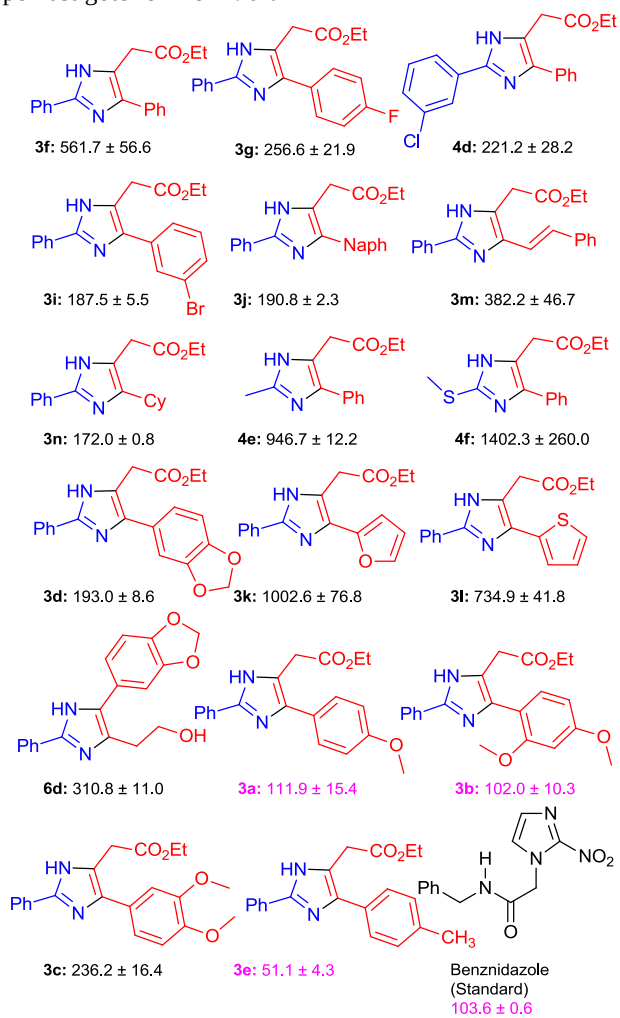


Scheme 2 Synthetic transformations of imidazole esters

Trypanocidal Activity Studies. The potential of our imidazole derivatives as trypanocidal compounds has been investigated by screening them against trypomastigote forms of *T. cruzi* (Table 4). The structures were separated into four different groups: (a) imidazoles with phenyl groups bearing electron withdrawing substituents; (b) imidazoles with R^1 or R^2 modified by alkyl, non-aromatic, naphthalene and methylthio substituents; (c) imidazoles with heterocyclic substituents such as safrole-like, furan and thiophene ring, and, finally; (d) imidazoles with phenyl groups bearing electron donating groups.

In general, imidazoles bearing electron withdrawing groups **3f-g**, **3i** and **4d** were less active than the standard drug benznidazole (IC_{50}/24 h = 103.6 ± 0.6 µM), with IC_{50}/24 h in the range of 187.5-561.7 µM. The imidazoles with modified R^1 or R^2 such as **3j**, **3m-n**, **4e-f** were also considered inactive or moderately active, e.g. **3n** with IC_{50}/24 h = 172.0 µM. The presence of heterocyclic ring was not beneficial in enhancing the trypanocidal activity and all the compounds **3d**, **3k**, **3l** and **6d** were inactive against trypomastigote forms of *T. cruzi*. Finally, we observed the relevance of the presence of electron donating groups in the phenyl ring. All the imidazoles, *viz.* methoxy- and methyl- substituted ones, exhibited significant trypanocidal activity with the exception of **3c**, which showed moderate activity. The activity of imidazoles with methoxy substituents **3a** and **3b** (IC_{50}/24 h = 111.9 and 102.0 µM, respectively) is comparable to that of benznidazole, the drug used clinically against *T. cruzi*. Compound **3e** was very active against *T. cruzi* with IC_{50}/24 h = 51.1 µM. This substance is two times more active than benznidazole which is a very significant result and we are motivated to carry out further studies against the parasite that causes Chagas disease.

Table 4 Activity (IC_{50}/24 h[a]/µM) of imidazoles against the trypomastigote form of *T. cruzi*



[a]Mean ± SD of at least three independent experiments.

Conclusions

Highly substituted imidazoles have been synthesized through a one-pot cascade reaction involving a [3+2] annulation of amidines with nitroallylic acetates. The annulation comprised an intermolecular aza-S_N2' substitution followed by an intramolecular aza-Michael addition. The imidazoles synthesized by the above methodology have been screened for their activity against parasite *Trypanosoma cruzi* that causes Chagas disease. While two of the compounds exhibited activity comparable to that of the standard (benznidazole), one of the compounds was two times more active thus prompting further studies in this area which will be reported in due course.

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