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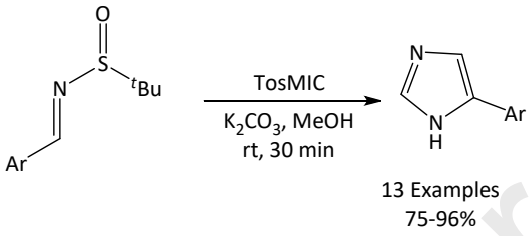

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Novel synthesis of *N*-unsubstituted imidazoles *via* the cycloaddition of *N*-(*tert*-butylsulfinyl)imines and TosMIC

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ABSTRACT

A facile and efficient method was developed for the synthesis of *N*-unsubstituted imidazoles *via* the cycloaddition of *N*-sulfinyl imines and *p*-toluenesulfonylmethyl isocyanide (TosMIC). This methodology is operationally simple and useful for the preparation of various aromatic and heteroaromatic imidazoles in good to excellent yields.

Introduction

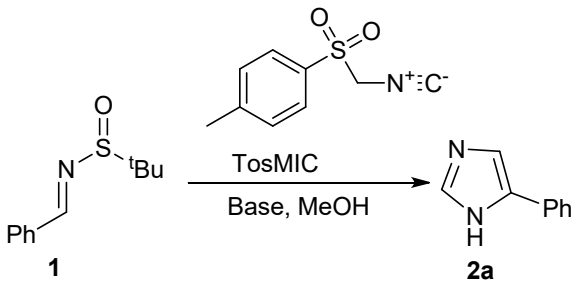
Imidazoles and their derivatives are valuable scaffolds which have attracted the attention of organic chemists due to their significant biological and pharmacological properties [1-5]. With their unique structural features, imidazoles represent an important class of compounds, forming the core of many natural products, such as vitamin B12, histidine, histamine, nucleic acid [6-8] bases, alkaloids [9], biotin and many other bioactive molecules. Their biological properties include, antifungal, antibacterial, antimalarial [10-11], antinociceptive, anti-inflammatory [12], anti-hypertensive [13], hypoxic cell therapy, imaging agents [14], anticancer [15], and antiplasmodium [16]. They have a wide range of applications in materials and polymer sciences [17-18] and are also exploited as anion sensors, optical materials, electronic and ionic liquids [19]. Consequently, significant efforts have been invested in the synthesis of different substituted imidazoles [20-25]. In this regard, several strategies have been reported for the synthesis of *N*-unsubstituted imidazoles using *p*-toluenesulfonylmethyl isocyanide (TosMIC) derivatives and imines [26-28]. However these protocols suffer from drawbacks such as high temperatures, long reaction times, multi-step reaction sequences, moderate yields, limited substrate scope and difficulty in accessing the starting materials. Therefore, there is still scope for the development of mild and efficient methods to address the drawbacks in the existing protocols. To the best of our knowledge, the synthesis of 4(5)-aryl-1*H*-imidazoles using *N*-(*tert*-butylsulfinyl) imines and TosMIC in the presence of potassium carbonate has not been reported.

Our methodology reports an alternate approach for the synthesis of 4(5)-aryl-1*H*-imidazoles *via* a [2+3] cycloaddition protocol at ambient temperature. This facile and highly efficient method offers advantages such as operational simplicity, short reaction times, high yields, simple work-up and mild reaction conditions.

Results and Discussion

Recently, we reported the synthesis of *N*-(*tert*-butylsulfinyl) imines from aldehydes and *tert*-butanesulfinamides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [29]. In continuation of our efforts regarding the development of novel methodologies in organic synthesis, we discovered the formation of *N*-unsubstituted imidazoles using *N*-benzylidene-2-methylpropane-2-sulfinamide (**1**) and *p*-toluenesulfonylmethyl isocyanide (TosMIC) as starting materials. In our preliminary experiments, we examined the reactivity of *N*-benzylidene-2-methylpropane-2-sulfinamide (**1**) and TosMIC in the presence of different bases such as triethylamine (TEA), *N,N*-diisopropylethylamine (DIPEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), sodium carbonate (Na_2CO_3), cesium carbonate (Cs_2CO_3), potassium phosphate tribasic (K_3PO_4) and potassium carbonate (K_2CO_3) in methanol. After 60 minutes, the desired product was not formed in the presence of TEA, DIPEA, DBU and Na_2CO_3. On the other hand, formation of the desired product 4(5)-phenyl-1*H*-imidazole (**2a**) was observed with Cs_2CO_3, K_3PO_4 and K_2CO_3 which was confirmed by TLC and LC-MS. To determine the optimum reaction conditions, we further investigated the influence of time, temperature, stoichiometry and various solvents such as ethanol (EtOH), isopropanol (IPA) and tetrahydrofuran (THF) (Table 1). The reaction was best performed with **1** (1.0 mmol) and TosMIC (1.1 mmol) in the presence of K_2CO_3 (2.5 mmol) and protic solvents (MeOH, EtOH, IPA) at room temperature for 0.5 h (Table 1, entry 10).

Tab *H*-imidazoles were previously reported by ten Have and co-workers [28].

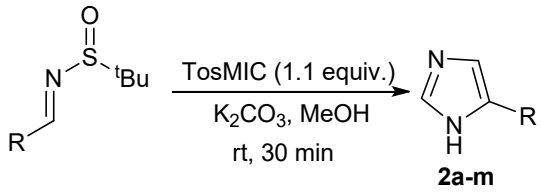


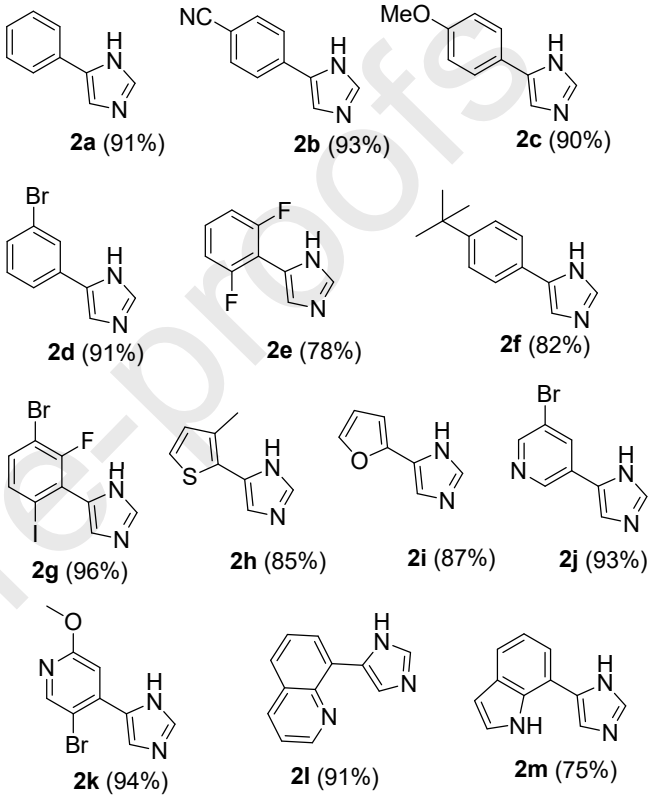
Entry	Base (equiv.)	T (°C)	Solvent	Time (min)	Yield **2a** (%)[a]
1	TEA (1.5)	25	MeOH	60	0
2	DIPEA (1.5)	25	MeOH	60	0
3	DBU (1.5)	25	MeOH	60	0
4	Na_2CO_3 (1.5)	25	MeOH	60	0
5	Cs_2CO_3 (1.5)	25	MeOH	60	61
6	K_3PO_4 (1.5)	25	MeOH	60	52
7	K_2CO_3 (1.5)	25	MeOH	60	62
8	K_2CO_3 (1.5)	25	MeOH	30	64
9	K_2CO_3 (2.0)	25	MeOH	30	75
10	**K_2CO_3 (2.5)**	**25**	**MeOH**	**30**	**91**
11	K_2CO_3 (3.0)	25	MeOH	30	90
12	K_2CO_3 (2.5)	25	MeOH	15	68
13	K_2CO_3 (2.5)	50	MeOH	30	82
14	K_2CO_3 (2.5)	50	MeOH	15	78
15	K_2CO_3 (2.5)	25	EtOH	30	85
16	K_2CO_3 (2.5)	25	IPA	30	50
17	K_2CO_3 (2.5)	25	THF	30	0

[a] Isolated yield after chromatographic purification.

With the optimized conditions in hand, we then explored the scope of this method. Diversified *N*-sulfinyl imines having different substitutions at various positions on the aromatic ring were reacted with TosMIC. Initially, *N*-benzylidene-2-methylpropane-2-sulfinamide (Table 2, entry 1) was reacted with TosMIC in the presence of K_2CO_3 in methanol at room temperature. The cycloaddition between electron-withdrawing and electron-donating sulfinyl imines (Table 2, entries 2 and 3) provided the corresponding imidazoles **2b** and **2c** in excellent yields. The reaction was explored with substrates bearing *para* and *meta* substituents (Table 2, entries 4 and 6) which gave the corresponding imidazoles in high yields. Sterically hindered *N*-sulfinyl imines (Table 2, entries 5 and 7) provided **2e** and **2g** in 78% and 96% yield, respectively. The reaction scope was further examined with a variety of five- and six-membered heteroaromatic *N*-sulfinyl imines (Table 2, entries 8-11). Upon cycloaddition with TosMIC the corresponding imidazoles **2h, 2i, 2j** and **2k** were obtained in high yields. Bicyclic *N*-sulfinyl imines proceeded smoothly to furnish the desired compounds (**2l** and **2m**) in 91% and 75% yield, respectively. To further demonstrate the scope of this method, the optimized conditions were applied to aliphatic *N*-sulfinyl imines with *tert*-butyl, cyclopropyl and cyclohexyl groups, but no product formation was observed by TLC and LCMS and the starting materials were unreacted.

Table 2. Synthesis of *N*-unsubstituted imidazoles.[a]





[a] Reagents and conditions: *N*-sulfinyl imines (1.0 mmol), TosMIC (1.1 mmol), MeOH (3 mL), K_2CO_3 (2.5 mmol), rt, 0.5 h. [b] Isolated yield after chromatographic purification.

Conclusion

In conclusion, we have developed a new methodology for the synthesis of 4(5)-aryl-1*H*-imidazoles *via* the cycloaddition of *p*-toluenesulfonylmethyl isocyanide (TosMIC) and *N*-(*tert*-butylsulfinyl)imines in the presence of potassium carbonate at room temperature. This methodology provides easy access to *N*-unsubstituted imidazoles, with advantages such as short reaction times, high yields, mild reaction conditions and simple work-up. This method was shown to be appropriate for a broad range of sulfinyl imines containing aromatic, heteroaromatic, sterically hindered, electron-rich, electron-deficient and bicyclic substituents. Unfortunately this method was not suitable for aliphatic *N*-sulfinyl imines.

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Experimental details, ^{1}H, ^{13}C NMR and HRMS spectra of compounds **2a-m** are available in the supporting information.

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Declaration of interests

✓ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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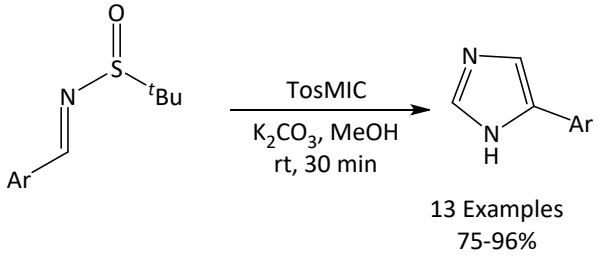

Highlights

- Facile and efficient approach for the synthesis of 4(5)-aryl-1*H*-imidazoles.
- Transition-metal-free, mild reaction conditions with operational simplicity.
- Short reaction times with higher yields.