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An easy, safe and simple method for the iodination of heterocyclic compounds in water

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Abstract: Iodination of heteroarenes was carried out by reacting arene substrate with iodine generated from $HIO_4/SiO_2/H_2SO_4$ in the presence of sodium chloride. All reactions conducted in water and good yields of iodinated products obtained.

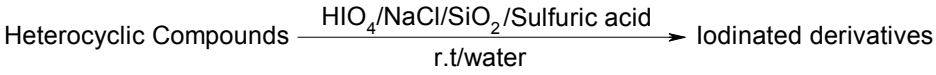
Keywords: Iodination; HIO_4; Silica gel; Sulfuric acid; Aqueous media.

Introduction

Iodo-Substituted Heterocycles are valuable precursors in pharmaceutical chemistry and natural product synthesis.[1] Due to the low reactivity of iodine toward electrophilic addition a versatile reaction media have been employed in order to find efficient and applicable methods for direct iodination of organic compounds. Numerous reagents and procedures have been developed for iodination of aromatic compounds, for example, $NaClO_2/NaI/HCl$ [2a], Py·ICl [2b], $BTMAICl_2$ [2c], $NaNO_2/HA/I_2$/air [2d], Benzyltriethylammonium Dichloroiodate/Sodium Bicarbonate [2e], $Pd(OAc)_2$/NIS [2f], HI/H_2O_2 [2g], H_5IO_6/I_2 [2h], BuLi/I_2 [2i], $Ph(CH_3)_3N^+ICl_2^-$/[bmim]PF_6 [2k], HNO_3/H_2SO_4 [3], HIO_3 or HIO_4/H_2SO_4 [4]. However, there are some limitation on the use of above procedures such as long reaction times, low yields, tedious work up procedure, use of toxic heavy metals and organic solvents. In the last decade, the increasingly importance of green chemistry to conducting organic reactions in aqueous media obligates academic and industries to find efficient alternatives for organic reactions.

On the other hand, organic reactions on solid surface have many synthetically advantages and often going faster, generating higher yields than via the solution followed by easy product isolation.

Herein we wish to report a new, efficient and simple method for the preparation of iodoheteroaromatic compounds using $HIO_4/NaCl/SiO_2/H_2SO_4$ (Scheme 1).



Scheme 1

Results and Discussion

Initially, 3,5-dimethylpyrazole was chosen as a model substrate for iodination in order to find the optimal conditions. Preliminary experiments have been carried out using HIO_4, sulfuric acid and silica gel or alumina in water at room temperature (Scheme 1). Under these conditions, the iodination reaction afforded low yields of the products. Raising the reaction temperature had no obvious effect on the reaction yield. In the next step, according to a plausible mechanism [5] in which the active iodine was generated in situ, we added sodium chloride to reaction mixture in order to examine the activity strength of the reagent.

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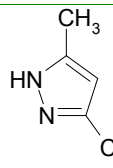
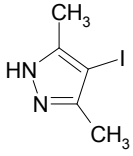
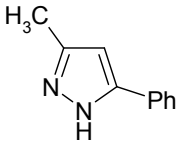
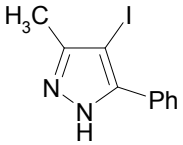
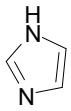
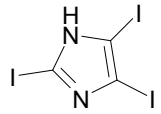
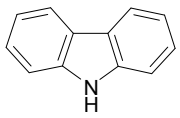
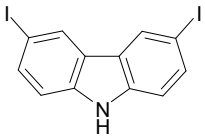
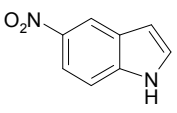
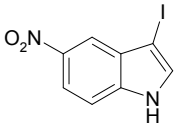
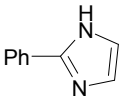
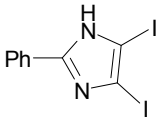
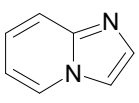
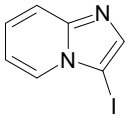
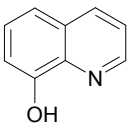
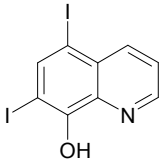
Surprisingly, the same reaction in the presence of sodium chloride furnished the product with 82% yield at room temperature (Table 1).

Although, the rate of reaction was increased at higher temperature however, all reactions were conducted at room temperature in order to provide better control on substitution. To prove the generality of the method, a variety of other heterocycles were subjected to this method under similar reaction conditions, and our results are summarized in Table 1. Iodination of pyrazole derivative afforded good yields of desired product in short reaction time. Imidazole was iodinated mostly at all positions (Table 1, entry 3), however, our attempts failed to obtain mono or diiodo derivatives. As expected, all the substrates underwent iodination reactions and delivered good yields of corresponding iodo products (Table 1, entries 4-8).

In conclusion, we report an efficient new method for the iodination of heteroaromatic compounds using HIO_4/SiO_2 as an iodine generation source in the presence of sodium chloride and sulfuric acid.

Table 1. iodination of heterocyclic compounds using $HIO_4/NaCl/SiO_2/H_2SO_4$ in water

Entry	Substrate	Product	Time (min)	Yield (%)	mp°C	Lit. mp°C
1			15	82	134-135	134–136[6a]
2			30	82	114-116	113-115[6a]
3			12	82	191-192	192[6b]
4			40	75	195-196	195-196[6c]
5			30	70	167-170	167-170[2a]
۶			20	84	200 dec.	200[6d] dec.
7			20	78	۱۶۷	165-166[6e]
8			35	85	196-199	198-200[6f]

General procedure for the iodination of 3,5-dimethylpyrazole:

To a mixture of silica gel (0.5 gr), sulfuric acid (0.1 gr, 1 mmol), NaCl (0.35 gr, 6 mmol) and HIO_4 (3 mmol) dissolved in water (5 mL), heteroaromatic substrate (3 mmol) dissolved in minimum dioxane (in the case of insoluble water compounds) was added with stirring over 5 min. Reactions were monitored by TLC and/or GC. Reaction times are specified in Table 2. The mixtures were then treated with aqueous sodium thiosulfate, extracted with dichloromethane, washed with water, and dried over anhydrous sodium sulphate. Solvents were removed at reduced pressure. The crude product was crystallized or subjected to column chromatography. The products were characterized from their physical constants and NMR spectra.

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