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An efficient strategy for *N*-alkylation of benzimidazoles/imidazoles in SDS-aqueous basic medium and *N*-alkylation induced ring opening of benzimidazoles

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ABSTRACT

A sustainable route for the *N*-1 alkylation of imidazole and benzimidazole derivatives has been developed under volatile organic solvent free condition in alkaline water-SDS system. Incorporation of SDS in the reaction medium enhances the reaction rate by suppressing the solubility issue that arises for different substrates. This method provides high yield of the alkylated product in a shorter reaction time. For reactive alkyl halides reaction proceeds at ambient temperature whereas in the cases of less reactive alkyl halides require 55–60 °C to complete alkylation process. *N*-alkylation induced ring opening of the heterocyclic ring in benzimidazole derivatives to multifunctional aromatic compounds were noticed at 60 °C when more than two equivalents of alkyl halide was used.

1. Introduction

The development of novel synthetic methodologies that are efficient and more compatible with the environment is an intense area of research to facilitate the synthesis of target molecules of specific interest. One of the most desirable approaches to address this challenge is a search for surrogates for commonly employed organic solvents those are used in large quantity due to various health and environmental reasons associated with them. In this regard water would be the perfect solvent to carry out chemical operations due to the fact that it is safe, most non-toxic, and inexpensive. However, often the poor solubility of organic compounds in aqueous medium becomes detrimental and therefore improving the solubility of organic compounds in water has been drastically investigated [1–7]. One of such approach is the incorporation of surface-active agents (surfactants) [8,9] in aqueous media that not only enhance the solubility of organic substrates but also increase the reactivity via the formation of micelles or vesicular cavities [10–13]. In recent years micelle-mediated organic reactions become an area of rapidly growing interest [14–17]. On the other hand, imidazoles/benzimidazoles are the most abundant and integral scaffolds that occur ubiquitously in a large number of bioactive natural products, synthetic drugs, pharmaceuticals and agro-chemicals [18,19]. Amongst many derivatives of benzimidazoles, an *N*-1 substituted derivative represents an important branch of this family due to their wide spectrum of biological and pharmacological activity [20]. *N*-1 Alkylated benzimidazoles and imidazoles are also important intermediates in the preparation of various ionic liquids [21–29]. Thus, synthesis of *N*-1 alkylated benzimidazole/imidazole derivatives depending on the biological importance or application in the development of new methodologies have become a challenge in organic synthesis and moreover the reaction in aqueous medium is of further importance. Although Singh et al. [30] reported a convenient access of secondary/tertiary amines from primary amine under water-SDS condition but a general approach for N-1 alkylation of benzimidazoles/imidazoles in water are lacking. Despite of such importance only few methods are reported for the synthesis of *N*-alkylated benzimidazoles and imidazoles. Generally *N*-1 alkylation of amines is achieved [31] by reaction with alkyl halide using anhydrous K_2CO_3 or Cs_2CO_3 in different organic solvent like acetone, methanol or DMF. Some

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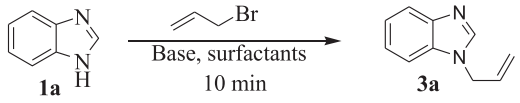
other reported methods include a convenient access for the *N*-alkylation of imidazoles and benzimidazoles using powdered KOH in acetone at room temperature with a slight excess of the alkyl halide at room temperature to give the mono alkylated product or using a KOH in the presence of 3–5 mol% of a crown ether, dicyclohexyl-18 crown-6 to afford the *N*-alkylated product [32]. Direct condensation between o-phenylene diamine and various aromatic aldehydes under different reaction conditions such as 'on water' approach or other catalysts also provides direct routes to *N*-1 alkylated 2-aryl substituted benzimidazoles [33–36]. In spite of having tremendous potentiality of these reported methods they suffer from some serious drawbacks [37,38] such as low yields, harsh reaction conditions, prolonged reaction time, selectivity issue, solubility and competitive side reaction, application of hazardous bases and also concomitant formation of quaternary ammonium salts. Moreover, the synthesis of these compounds is usually carried out in polar solvents such as ethanol, methanol, acetic acid, dimethyl formamide (DMF), and dimethyl sulfoxide (DMSO), leading to complex isolation and recovery products. Thus as a part of our ongoing program to develop a novel methodology for *N*- alkylated benzimidazole or its derivatives we herein report base mediated *N*-1 alkylation of substituted benzimidazoles/imidazoles, followed by alkylation induced ring opening of the benzimidazoles using in excellent yields under surfactants mediated organic solvent free condition. The present method has several advantages that include a mild reaction condition, operational simplicity, very short reaction time, excellent yield of products and no formation of quaternary salt.

2. Results and discussions

Initially we consider *N*-1 alkylation of benzimidazole as model reaction using allyl bromide as alkylating agent. To standardize the condition several attempt were made by variation of different parameter. Stirring of the suspension of benzimidazole **1a** (1 mmol) in 50% aq. NaOH (1.0 mL) with allyl bromide at room temperature afforded *N*- allylated benzimidazole **3a** in 65% yield (entry 1, Table 1) after 10 min, increasing or decreasing the amount of NaOH or reaction time did not improve the yield. We reasoned that the solubility problem may occur between the organic substrate and the aq. NaOH. As aqueous medium has always been considered as beneficial for carrying out organic reaction and the amount of aqueous solution may not good enough to get soluble the substrates, and hence the reaction did not occur with a satisfactory yield. Thus to improve the yield, various surfactants were planned to introduce into the system to increase the solubility of the organic substrates in aqueous phase [10–13,39]. The uses of cationic surfactants (10 mol%) like TBAB or CTAB gave a complex mixture with incomplete conversion of the organic substrate as revealed by TLC (entry 2, Table 1). The neutral surfactant Triton X100 provides improved yield of **3a** to some extent as compared to non-surfactant mediated reaction (entry 1 vs entry 3, Table 1). Gratifyingly, utilization of anionic surfactant SDS (10 mol%), remaining other reaction conditions being the same, the yield of **3a** was improved drastically to 97% (entry 4, Table 1). On decreasing the amount of SDS to 5 mol% and amount of NaOH (0.5 mL) the yield was again 97% (entries 5–6, Table 1). It was also observed that uses of quaternary ammonium hydroxide (50% aq. NBu_4OH) as base yielded poor yield of the allylated product (entry 7, Table 1). Under the similar reaction condition organic base such as Et_3N provides only trace amount of the product whereas in organic environment no product was traced (entries 8–9, Table 1). Most probably because of high pKa value (pKa of benzimidazole 12.8) Et_3N is unable to abstract N–H proton rather it gets quaternization (as indicated by the formation of white precipitate and TLC) in the presence of reactive allyl bromide. Thus it is assumed that water present in the medium [40,41] may play pivotal role in the alkylation process through H-bonding that facilitated substrate to get solubilize as additional effect with SDS. Being inspired by the optimization reaction allylation of benzimidazole (Table 1) at the *N*-1 position under aqueous environment we aimed to generalize the procedure using different substituted benzimidazoles and imidazoles. Subsequently, we carried out the *N*-1 alkylation of different benzimidazole derivatives according to the standard protocol as described in Table 1. The choice of alkyl halides were made considering reactivity of alkyl halides. Reactive alkyl halide, benzyl bromide underwent alkylation of different benzimidazoles **1a-e** to **3b-f** (entries 1–5 Table 2) in excellent yields in the range of 87–98% and 2-nitrobenzylbromide afforded corresponding alkylated products **3g-h** in 85% yields (entries 6–7, Table 2). The substrate 2, 6-dimethyl benzimidazole (**1d**) undergoes *N*-1 alkylation smoothly in good yields and shorter reaction time but resulted tautomers (equal population) of *N*-1 benzylated benzimidazoles (entry 4, Table 2) as revealed by NMR spectroscopy. In contrast, the less reactive alkyl bromides like butyl or hexyl bromide or long chain alkyl bromides like octyl, or hexadecyl bromide did not produce any alkylated product at room temperature but at the temperature of 60 °C a clean transformation to *N*-1 alkylated products (as shown in Table 2) were achieved in excellent yields within a short period of time (entries 8–14, Table 2). Apart from benzimidazoles, we then focused on the *N*-1 alkylation of imidazoles, substituted imidazoles which gratifyingly afforded *N*-1 alkylation in excellent yields and shorter reaction time. The imidazoles when treated with cetyl bromide (entry 15, Table 2) underwent smooth alkylation in excellent yield of **3p** (95%) at 60 °C. The other imidazoles like 2-methyl imidazole also gave *N*-1-benzylated (entry 16, Table 2) product **3q** in 93% yield and 2, 4, 5-triphenyl imidazole (**1h**) underwent *N*-1- allylation (entry 17, Table 2) in 20 min at 60 °C and the yield (**3r**) was found to be 80%. The imidazole derivative 2-(2-(allyloxy phenyl)- 4, 5-diphenyl imidazole (**1i**) also afforded *N*-1 allylated product **3s** (entry 18, Table 2) in 20 min. Another important feature of the present methodology is the alkylation of sugar based chiral benzimidazole (**1j**) [42] to the formation of corresponding *N*-benzyl derivative **3t** in 82% yield (entry 19, Table 2).

The results summarized in Table 2 indicated that in the cases of

Table 1
Optimization of the reaction condition.[a]



Entry	Base	Surfactant	Yield (%)
1	NaOH	No	65[b]
2	NaOH	TBAB or CTAB (10 mol%)	Mixture[b]
3	NaOH	Triton X 100 (10 mol%	73[b,c]
4	NaOH	SDS (10 mol%)	97[b,c]
5	NaOH	SDS (5 mol%)	97[b,c]
6	NaOH	SDS (10 mol%)	97[c,d]
7	Bu_4OH	SDS (10 mol%)	30[e]
8	Et_3N	SDS (10 mol%)	trace[f]
9	Et_3N	No	NR[g]

[a] Reaction performed in 1 mmol scale.
[b] 1 mL50% aq. NaOH was used.
[c] Isolated yield.
[d] 0.5 mL of 50% aq. NaOH was used.
[e] 0.5 mL aqueous Bu_4NOH was used.
[f] Reaction performed in water.
[g] Reaction performed in dichloromethane.