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One Pot Synthesis of Substituted Imidazopyridines and Thiazoles from Styrenes in Water Assisted by NBS

Mahesh H. Shinde and Umesh A. Kshirsagar*

Abstract: Just heating of commercially available styrenes with NBS in water followed by reaction with 2-aminopyridines and thioamides, important heterocyclic scaffold were prepared in one pot manner. Reaction proceed via co-oxidant free, in-situ formation of α-bromoketone using NBS as bromine source as well as oxidant followed by trapping with suitable nucleophiles to provide imidazopyridines and thiazoles.

Nitrogen and sulphur containing privileged heterocyclic scaffolds such as imidazo[1,2-a]pyridines and thiazoles plays an important role in the modern synthetic and medicinal chemistry due to their promising biological and pharmaceutical activities. Of particular, imidazo[1,2-a]pyridine is important motif due to presence in various top commercial drugs such as zolpidem, zolimidine, olprinone, GSK812397, anxiolytic agents alpidem, necopidem, saripidem (Figure 1). Imidazo[1,2-a]pyridines also have applications in N-heterocyclic carbene chemistry and material chemistry. The thiazole nucleus is present in several biologically active natural products such as etopthione, leinamycin, barakacin. Numerous thiazole based drug are also known such as ritonavir, abafungin, sulfathiazole. Various synthetic methods have been reported for the construction of these motifs such as C-H amination, oxidative cyclization, multicomponent reaction, hydroamination and tandem processes from various starting materials. Most of these reaction are metal catalysed and/or use of oxidants. Traditional method for the construction of these scaffolds includes condensation of α-haloketones with suitable nucleophiles in the various organic solvents and bases which involves the heating for longer time (Scheme 1). Most stern issue is the handling of lachrymatory phenacyl bromides or their analogues. In-situ preparation of α-haloketones from ketone are also known in literature but involves the use of toxic bromine sources. Donohoe group recently reported two step approach for the synthesis of these heterocycles from alkenes which involves the preparation of α-iodoketone by reaction of olefins with IBX/Iodine in DMSO and these α-iodoketones were treated with suitable nucleophiles in the presence of K2CO3/DMF to give the diverse heterocycles.

Use of the water as solvent for organic reactions is the most interesting and attracted step because of its economic and...
environmentally friendly nature.\textsuperscript{11} NBS has numerous applications in the synthetic organic chemistry such as simple and non-toxic cationic and radical bromine source as well as oxidant.\textsuperscript{12} In view of this, here we would like to report the NBS promoted, simple, one pot method for the construction of diverse heterocyclic building blocks in water as solvent from commercially available styrenes without using co-oxidant. NBS plays dual role such as safe bromine source and oxidant, whereas reaction was carried out using water which also act as ‘O’ source for the in-situ preparation α-bromoketones. These in-situ formed α-bromoketones upon reacting with appropriate nucleophiles in one pot manner provided the diverse heterocycles.

We initiated the optimization of reaction on simple styrene (1a) (table 1). Reaction of styrene 1a with iodine in the presence of tert-butyl hydroperoxide (TBHP, entry 1) or 2-iodoxybenzoic acid (IBX, entry 2) as oxidant in DCE and DMSO as solvent at 40°C or 80°C followed by addition of 2-aminopyridine gave the desired imidazo[1,2-a]pyridine 2a in very trace product in very trace amount. Treatment of styrene with other iodine source, N-iodosuccinimide (NIS) in the presence of IBX as oxidant in DMSO at 40°C followed by addition of 2-aminopyridine provided desired imidazo[1,2-a]pyridine 2a in 30% yield (entry 3). When same reaction was carried out at higher temperature, yield was not improved significantly. Use of KI in the presence of oxone was unable to give the desired product (entry 4) but KI in the presence of K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} provided the imidazo[1,2-a]pyridine 2a in 35% yield (entry 5). Treatment of styrene (1a, 1.0 equiv.) with NBS (2.0 equiv.) in H\textsubscript{2}O:dioxane at 80°C for 1.2 hr followed by addition of 2-aminopyridine gave the imidazo[1,2-a]pyridine 2a in 41% yield after heating at 80°C for 2 hr (entry 6). Change in the solvent system from H\textsubscript{2}O:dioxane to H\textsubscript{2}O:acetonitrile or H\textsubscript{2}O:acetone, decrease in the yield was observed (entry 7/8). To our delight, when reaction was performed using only water as solvent, it furnished the imidazo[1,2-a]pyridine 2a in 89% yield (entry 9).

**Table 1. Optimization of the reaction condition.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>X-source</th>
<th>oxidant</th>
<th>2a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>I\textsubscript{2}</td>
<td>TBHP</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>I\textsubscript{2}</td>
<td>IBX</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>NIS</td>
<td>IBX</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>DMSO: H\textsubscript{2}O</td>
<td>KI</td>
<td>oxone</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>CH\textsubscript{2}CN: H\textsubscript{2}O</td>
<td>KI</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}</td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td>H\textsubscript{2}O: dioxane</td>
<td>NBS</td>
<td>-</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>H\textsubscript{2}O: CH\textsubscript{3}CN</td>
<td>NBS</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>H\textsubscript{2}O: acetone</td>
<td>NBS</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>H\textsubscript{2}O</td>
<td>NBS</td>
<td>-</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>H\textsubscript{2}O</td>
<td>NBS</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>H\textsubscript{2}O</td>
<td>NCS</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>H\textsubscript{2}O</td>
<td>NIS</td>
<td>-</td>
<td>40</td>
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<tr>
<td>13</td>
<td>H\textsubscript{2}O</td>
<td>Br\textsubscript{2}</td>
<td>air</td>
<td>0%</td>
</tr>
<tr>
<td>14</td>
<td>H\textsubscript{2}O</td>
<td>TBAB</td>
<td>air</td>
<td>0%</td>
</tr>
</tbody>
</table>

(a) Condition: Styrene (1 mmol), X-source (2 mmol), oxidant (2 mmol), solvent (2 mL), 80°C, 1.2 hr, then 2-aminopyridine (2.0 mmol), 80°C, 2 hr. (b) isolated yields, (c) NBS was added in two portions at 30 min. interval.

H\textsubscript{2}O:dioxane to H\textsubscript{2}O:acetonitrile or H\textsubscript{2}O:acetone, decrease in the yield was observed (entry 7/8). To our delight, when reaction was performed using only water as solvent, it furnished the imidazo[1,2-a]pyridine 2a in 89% yield (entry 9).

**Scheme 2. Possible reaction pathway.**

Reaction includes the NBS/H\textsubscript{2}O promoted formation of bromohydrin (B) followed by NBS mediated oxidation of secondary benzylic alcohol for the in-situ formation of phenacyl bromide (D) (Scheme 2). Condensation of phenacyl bromide with 2-aminopyridine furnished the desired product imidazo[1,2-a]pyridine 2. No improvement in the yield was observed by portion wise additon of NBS (entry 10). When NBS was replaced with NIS, it gave the compound 2a in 32% yield (entry 11) whereas with NCS, formation of 2a was not observed (entry 12). We have also screened other bromine sources such as molecular bromine and tetrabutylammonium bromide (TBAB) using air as oxidant but formation of 2a was not observed (entry 13/14).

Having optimized condition in hand, we pursued for the exploration of substrate scope. Reacting NBS with aryl olefin with electron withdrawing groups on aromatic ring such as -F and -Br (1b, c) provided corresponding imidazo[1,2-a]pyridine (2b, c) smoothly in very good yields (82 and 81%). Styrenes...
with electron releasing groups such as 4-methyl and 4-tert-
butyl also afforded the corresponding imidazo[1,2-a]pyridine
(2d,e) in very good yield (79 and 75%). Use of 2-amino-5-
bromo-pyridine as nucleophilic partner with styrene afforded
imidazo[1,2-a]pyridine (2f) in 85% yield. Reaction of 4-
methoxy styrene with NBS followed by 2-amino pyridine
provided complex reaction mixture. Reaction with 4-methyl
and 5-methyl-2-aminopyridines afforded corresponding
imidazo[1,2-a]pyridine (2g,h) in good to moderate yield (78
and 73%). Styrene having strong electron withdrawing group
such as NO2 works smoothly to afford the corresponding
imidazo[1,2-a]pyridine (2i) in 72% yield.

Encouraged by preparing various imidazo[1,2-a]pyridine we
shifted to investigate the scope of other nucleophiles.
Thioamide was selected as next nucleophilic partner for
condensation due to its potential for the
intermediate followed by condensation with various
nucleophiles in one pot manner. Reactions were carried out in
water as solvent and are co-

When thionicotinamide
and other nucleophiles
proceeded via formation of α-bromoketone as versatile
intermediate followed by condensation with various
nucleophiles in one pot manner. Reactions were carried out in
water as solvent and are co-oxidant free where the NBS plays
dual role.

Conclusions
In conclusion, we have demonstrated the facile one pot
procedure for the synthesis of substituted imidazopyridines
and highly substituted thiazoles starting from important
feedstock such as styrenes promoted by NBS. Reaction
proceeds via formation of α-bromoketone as versatile
intermediate followed by condensation with various
nucleophiles in one pot manner. Reactions were carried out in
water as solvent and are co-oxidant free where the NBS plays
dual role.

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