A CONVENIENT SYNTHETIC PROTOCOL FOR THE SYNTHESIS OF 2, 3-DISUBSTITUTED 1, 4-BENZOTHIAZINES

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Abstract
Rapid one pot synthetic route has been developed for cyclocondensation of 2-aminothiophenol and 1,3-dicarbonyls/diketones using relatively safe oxidants like metaperchlorobenzoic acid (M-CPBA) and 2-iodoxybenzoic acid (2-IBX). The details of synthetic route and characterization of the product carried by spectral analysis are also presented.

Keywords: 1, 4-Benzothiazines; M-CPBA; 2-IBX.

INTRODUCTION
1,4-Benzothiazines have attracted great deal of interest as a synthetic target because of their broad biological activities. 1,4-Benzothiazines have been reported a wide range of pharmacological activities such as antiarrhythmic, anticancer, vasorelaxant, antidiabetic, antihypertensive, antimicrobial and antifungal agent. Recently Reddy’s Lab has reported the use of 1, 4-benzothiazines to reduce obesity. 1, 4-Benzothiazines are also known for their utility as dyestuffs in industry and also used as photographic developers. Due to their diverse biological significance synthetic chemist have developed numerous routes for the synthesis of biodynamic 1, 4-benzothiazines. One of the most widely employed method for the synthesis of 1, 4-benzothiazines is the oxidative cyclocondensation of 2-aminobenzenethiols with 1, 3-dicarbonyls/diketones compounds using DMSO/Al₂O₃ microwave irradiations, baker’s yeast as a catalyst, and triethyl amine as catalyst. This synthesis has two steps first step includes the oxidation of 2-aminobenzenethiols to respective disulphides. In the second step cyclocondensation of disulphides with 1, 3-dicarbonyls/diketones occurs to the corresponding 1, 4-benzothiazines. In another method separate condensation of 2-aminobenzenethiols with acetylins and α-haloketones or α-haloesters has been reported for obtaining 1, 4-benzothiazines. These methods require the use of costly, toxic organic solvents, organic/inorganic bases and corrosive oxidants. These methods are time consuming so there is a scope to increase the rate of reaction. Therefore design of new, concise and efficient synthetic route for this important class of compounds using easily available solvents and catalyst is highly desired.

The use of oxidants, metaperchloro benzoic acid (M-CPBA) and 2-iodoxybenzoic acid (2-IBX) in organic synthesis is very promising. It is a strong oxidant generally used in variety of chemical transformations such as oxidation of carbonyl compounds, olefins, imines, N and S heterocyclic etc. It is superior to H₂O₂ and other oxidizing agents due to their reactivity, steroeselectivity purity and yield of the products. Number of transformations have been carried using viz Bayer-villiger oxidation epoxidation, oxidation of 4-substituted chiral oxazolines using gives ring opened nitroso compound is chemoselective oxidation of benzophenazines, oxidation of sulphides to sulfoxide and sulfones.
2-IBX is a mild, selective, efficient, eco-friendly oxidant, used as a hypervalent iodine reagent in an organic synthesis.\textsuperscript{21} 2-IBX emerged as a powerful oxidant for several oxidative transformations.\textsuperscript{22-25} There are some reports on facial synthesis of quinoxaline derivatives from 1, 2-diketones and o-phenylenediamines at room temperature\textsuperscript{26}, one pot condensation of β-naphthol, aldehydes, and 1,3-dicarboxyl compounds\textsuperscript{27} and oxidation of alcohols with 2-IBX in DMSO, a new insight into an old hypervalent iodine reagent gives good yield \textsuperscript{28}. Preferential hydrolysis of benzylic/allylicdithi nes and dithiolanes\textsuperscript{29} need 2-IBX. A mild and efficient oxidation of alcohols with o-iodoxybenzoic acid (2-IBX) catalyzed by β- cyclodextrin in a water-acetone (6:4) mixture has been reported and various alcohols have been oxidized at room temperature with excellent yields\textsuperscript{30} has been reported.

Considering the demerits of the classical synthesis of 1, 4-benzothiazines and to explore the use of oxidants and 2-IBX in the cyclocondensation here, we thought to develop an efficient, rapid route for this cyclocondensation. In the present work we explored the use of oxidants, M-CPBA and 2-IBX for the Synthesis of 2, 3-disubstituted 1, 4-, benzothiazines.

**RESULTS AND DISCUSSION**

Here, we described very simple one pot protocol for the synthesis of 1, 4-benzothiazines (3a-i). This involves the oxidative cyclocondensation of 2-aminobenzenthiol and 1, 3-dicarbonyls compounds, expedited by the oxidants M-CPBA/2-IBX in the presence of aprotic solvent acetonitrile Scheme 1 and 2 at 70°C.

Our investigation started with an optimization study of model reaction by separately allowing cyclocondensation of 2-aminobenzenthiol and acetyl acetone in the presence of oxidants M-CPBA, 2-IBX and DMSO separately. To see the effect of reaction medium on the rate and yield of the reaction, we carried the model reaction in various solvents like ethanol, acetonitrile, dimethylsulphoxide at temperature 70°C (Table -1).

Initially, when the reaction was run in solvent and oxidant DMSO the noticeable yield of 1, 4-benzothiazines was observed after 90 minutes (Table- 1). When the model reaction was performed in aprotic solvent acetonitrile at the same temperature 80% yield was obtained but time required was more (Table –1). Inspired by this, we next investigate the effect of solvent ethanol and oxidant DMSO on the yield and time of reaction but the reaction time was increased and yield also decreased (Table- 1).

After having these results we decided to carry the model reaction by using the different oxidants such as M-CPBA and 2-IBX. Here we condensed 2-aminobenzenthiol and 1, 3-dicarboxyls in presence of oxidant m-CPBA in solvent acetonitrile at 75°C and obtained 90% yield of the product within 45 minutes (Table- 1). The same cyclocondensation was carried by using oxidant 2-IBX in acetonitrile at 75°C even
increasing reaction time also by 30 minutes and yield was relatively less (Table-1). In view of these observations we have selected aprotic, greener solvent, acetonitrile and oxidant M-CPBA and 2-IBX for the synthesis of 1, 4-benzothiazines.

Table-1: Synthesis of 1,4-benzothiazines in different oxidants and solvents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Oxidant</th>
<th>Time in min</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>M-CPBA</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>2-IBX</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>DMSO</td>
<td>145</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>DMSO</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol</td>
<td>DMSO</td>
<td>210</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>NO catalyst</td>
<td>240</td>
<td>00</td>
</tr>
</tbody>
</table>

Subsequently the other substituted of 1; 3-dicarbonyls/diketones and 2-aminobenzothiophenol were subjected under the optimized reaction conditions to obtain the respective 1, 4-benzothiazines. The results are recorded in Table-2. From these results it seems that the oxidant M-CPBA an 2-IBX accept broad array of substrate combinations. To investigate the role of oxidants in the cyclocondensation of 2-aminobenzenethiol and 1, 3-dicarbonyl the model reaction was run in the absence of oxidants; no formation of product was observed (Entry 1 to 6).

Table-2: Synthesis of 1, 4-benzothiazines using oxidants M-CPBA and 2-IBX.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>M.P.</th>
<th>Yield% M-CPBA</th>
<th>Yield% 2-IBX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3a</td>
<td>189-190</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH₃</td>
<td>OC₂H₅</td>
<td>3b</td>
<td>141-142</td>
<td>84</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CH₃</td>
<td>C₆H₆</td>
<td>3c</td>
<td>188-189</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>C₆H₆</td>
<td>C₆H₆</td>
<td>3d</td>
<td>90-92</td>
<td>75</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3e</td>
<td>187-188</td>
<td>82</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>CH₃</td>
<td>OC₂H₅</td>
<td>3f</td>
<td>177-178</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>CH₃</td>
<td>CH₃</td>
<td>C₆H₆</td>
<td>3g</td>
<td>141-142</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3h</td>
<td>192-193</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>CH₃</td>
<td>OC₂H₅</td>
<td>3i</td>
<td>148-150</td>
<td>54</td>
<td>50</td>
</tr>
</tbody>
</table>

²The. M.P are in good agreement with those reported literature.³², ³³, ³⁴
³Reaction condition : 2-aminobenzenethiol (10 mmol) and 1,3-dicarboxyls (10 mmol) oxidants (10 mmol) in 25 ml solvent acetonitrile

The mechanism of the cyclocondensation of 2-aminobenzenethiol and 1,3-dicarboxyls, carried in the presence of oxidants has been already established and it is confirmed that the oxidants initially oxidize 2-aminobenzenethiol to disulphide which subsequently undergo cyclocondensations with 1,3- dicarboxyls to give the desired 1, 4-benzothiazines.

The conversion of 2-aminothiophenol to disulphide take place due to oxidants and 2-IBX. The oxidant might be abstracting hydride ion from one of thiol molecule and then mercapto group of other molecule would be nucleophilic attack on the electron deficient sulfur to form intermediate disulphide.
Probably these sites might be helping for the reaction with 1,3-dicarbonyl and the rate of the condensation of the disulphide and 1, 3-diketone would have been increased, resulting into 1, 4- benzothiazines. A proposed mechanisms are represented as follows-

1. Oxidation of 1, 4-benzothiazines. (Generation of anilinodisulphide)

\[
\begin{align*}
2 & \quad \text{Fast} \\
\text{DMSO} & \quad \text{Oxidation of 1, 4-benzothiazines. (Generation of anilinodisulphide)} \\
\end{align*}
\]

2. Mechanism for cyclocondensation

\[
\begin{align*}
\text{A} & \quad \text{Slow} \\
\text{R} & \quad \text{Mechanism for cyclocondensation} \\
\text{B} & \quad \text{K}_1 \\
\text{D} & \quad \text{K}_2 \\
\text{P} & \quad \text{K}_3 \\
\end{align*}
\]

**EXPERIMENTAL**

Melting points were determined by open capillary method and are uncorrected. Progress of the reaction was monitored by thin layer chromatography on Merck silica plates. \(^1\)H NMR spectra were recorded on a Varian USA 400 MHz NMR spectrometer in CDCl\(_3\) using tetramethylsilane (TMS) as an internal standard and chemical shift in \(\delta\) (in ppm). Mass spectral data were obtained by a Sciex model API 3000 LCMS/MS instrument.

The oxidizing agent M-CPBA and 2-IBX were LR/synthetic grade and used directly. Anilinodisulphide was freshly prepared by literature procedure. All chemicals used were reagent grade and used without further purification.

**General procedure for the synthesis of 2-acyl /ethoxy carbonyl-3-methyl-4H-l, 4- benzothiazines (3a-i) using oxidant MCPBA**

A mixture of 2-aminothiophenol (10 mmol), acetyl acetone/l, 3-dicarboxylic (10 mmol) and M-CPBA (10mmol) in acetonitrile was heated at 70 °C on oil bath with constant stirring. The progress of the reaction was monitored by TLC. After 45 min of the reaction the content was poured in ice cold water. The obtained solid was filtered and washed with aqueous sodium bicarbonate and finally with water. The
solid crude was crystallized from ethyl alcohol. Purity of the product was checked by TLC and structures were confirmed by spectral analysis. Yields and melting points are presented in (Table 2).

**General procedure for the synthesis of 2-acyl/ethoxy carbonyl-3-methyl-4H-I, 4-benothiazines (3a-i) using oxidant 2-IBX**

A mixture of acetyl acetone/1,3-dicarbonyls (10 mmol) 2-aminothiophenol (10 mmol) and 2-IBX (10 mmol) was dissolved in aprotic solvent, acetonitrile and the solution was heated at 70°C on oil bath with constant stirring. The progress of the reaction was monitored by thin layer chromatography. After 75 min the reaction mixture was cooled and poured in ice cold water. The dark brown colored solid obtained was filtered and purified by charcoal treatment. The product was further crystallized from ethanol. The purity of product was checked by TLC and spectral analysis, Yield and Melting points are recorded in (Table 2).

**Spectral data of selected compounds**

1-(3-Methyl-4H-benzo[b][1,4]thiazine-2-yl)ethanone (3a).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.16 (s, 3H), 2.22 (s, 3H, CH$_3$), 6.61–6.86 (m, 4H), and 8.74 (s, 1H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.40, 29.89, 97.59, 115.31, 120.36, 124.71, 126.14, 127.05, 139.51, 153.81 and 191.23. HRMS (ESI* mode) (m/z): Calculated for C$_{11}$H$_{11}$NOS [M + Na]$^+$: 228.0456; found: 228.0461.

1-(3,7-Dimethyl-4H-benzo[b][1,4]thiazin-2-yl)ethanone (3e).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.96 (s, 3H), 2.20 (s, 3H), 2.45 (s, 3H), 5.91 (s, 1H, NH), 7.01 (t, 1H, $J$ = 4.0 and 8.0 Hz), 6.37 (d, 1H, $J$ = 8.0 Hz), 6.75 (d, 1H, $J$ = 4.0 Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 22.49, 28.96, 29.92, 110.12, 114.61, 127.33, 129.37, 133.49, 135.13, 136.17, 153.54 and 194.13. ESI DARTMS: Calculated for C$_{12}$H$_{13}$NOS [M + 1]: 220.0717; found: 220.1154.

Ethyl 3,7-dimethyl-4H-benzo[b][1,4]thiazine-2-carboxylate (3f).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.19 (t, 3H), 2.08 (s, 3H), 2.38 (s, 3H), 4.13 (q, 3H), 6.15 (s, 1H, NH), 7.15 (d, 1H, $J$ = 8.0 Hz), 7.24 (t, 1H, $J$ = 4.0 and 8.0 Hz), 7.63 (d, 1H, $J$ = 4.0 Hz). ESI DARTMS: Calculated for C$_{13}$H$_{15}$NO$_2$S [M + 1]: 250.0823; found: 250.0796.

**CONCLUSION**

First time we have demonstrated the use of oxidants m-CPBA and 2-IBX to accelerate the oxidative cyclization of 2-aminobenzenethiol and 1,3dicarbonyls in an aprotic medium, carried for obtaining l,4-benothiazines. The role of oxidant is to accelerate the rate of the model reaction and cyclocondensation has also been monitored. The principle of this strategy could be useful for another type of reaction.

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