One-pot Synthesis of 4H-1,3-Benzothiazines via Cu(I) Catalyzed Intramolecular Cyclisation from Dithioesters

This chapter represents the novel method synthesis and characterization of 4H-[1,3]-Benzo[e]thiazines under solvent free along with optimization, mechanism and spectral data.

3.1. Introduction:

Nitrogen- and sulfur-containing heterocycles are ubiquitous structures in huge number of biologically active natural products and small-bioactive molecules.\(^1\) Benzothiazines has attracted significant interest due to their interesting pharmacological properties.\(^2\)-\(^8\) The synthetic and biological properties of the 1,3-benzothiazine nucleus is relatively unexplored class of compounds from the standpoint of both synthetic and biological chemistry. Sohar and co-workers reported the synthesis of 4H-1,3-benzothiazines from arylamide thioethers through an acid catalyzed intramolecular rearrangement with prosperous oxychloride (Scheme 1). 4H-1,3-benzothiazines are key intermediates for many biologically active rings like 1,5-benzothiazocines, and angularly condensed β-lactam derivatives. A series of benzothiazine derivatives like triazolobenzothiazines are known as centrally acting muscle relaxants also exhibit anitconvulsant activity and active in inhibiting various spinal polysynaptic reflexes Consequently, the development of facile and novel route for the synthesis of these sulfur-based heterocycles is of high interest.\(^9\)-\(^11\)

![Scheme-49: Synthetic route to benzothiazines from arylamide thioethers.](image)
3.2. Recent reported methods for the synthesis of 4H-1,3-benzothiazines:

Vladimir T. Abaev and *et al* reported the new synthetic approach to 2,4-diaryl-4H-3,1-benzothiazines based on the rearrangement of 2-isothiocyanotriarylmethanes in the presence of AlCl₃:\(^{18}\)

**Scheme-50:** Synthesis of 2,4-diaryl-4H-3,1-benzothiazines.

Ruihong Wang and *et al* reported the efficient method for the preparation of various imidazobenzothiazines derivatives from readily available 2-mercaptoimidazoles and bromobenzyl bromides via copper catalyzed one-pot cascade process.\(^ {19}\)

**Scheme-51:** Synthesis of imidazolobenzothiazines from 2-Antonio Herrera, and *et al* were reported the one-pot synthesis of Substituted (4z)-2-Alkyl-4-benzylidene-4H-1,3-benzothiazines.\(^ {20}\)

**Scheme-52:** Synthesis of benzothiazines from the reaction of S-phenyl thioesters with substituted benzyl nitriles.
Peter C Somos and et al reported the synthesis of 2-aryl-4H-3,1-benzothiazine derivatives by the condensation of o-aminobenzyl chloride with substituted thiobenzamide.\(^{21}\)

![Scheme 53: Synthesis of 2-aryl-4H-3,1-benzothiazines by the condensation of o-aminobenzyl chloride with substituted thiobenzamide.](image)

**Synthesis of 4H-1,3-Benzothiazines from dithioesters via S-arylation.**

Most of the reported methods involve hazardous reagents, solvents and synthetic strategy requires multistep reaction sequence. This encouraged us to consider for a direct reaction in the synthesis of functionalized benzothiazines. In continuation of our work on synthesis of heterocyclic compounds,\(^{12}\) herein, we report a novel method to access of benzothiazines from range of dithioesters via S-arylation.

**3.3 Result and discussion:**

![Scheme 54: Synthesis of benzothiazines from range of dithioesters via S-arylation.](image)
We set out to identify the possible mild conditions under which, the reaction of (2-bromophenyl)methanamine 178a and phenyl dithioester 178b would proceed with synthetically useful rate. The reaction requirements including catalysts were screened and the results are listed in Table 1. Initially, the reaction was conducted with (2-bromophenyl) methanamine 178a and phenyl dithioester 178b was examined in THF in the absence of CuI, at reflux, the intermediate product $N$-(2-
bromobenzyl)benzothiaomide was isolated in 75% yield. Encouraged by this initial result the reaction was screened with various solvents like toluene, THF, DMF, CH$_3$CN, ethyl acetate, DMSO, dioxane, CHCl$_3$ were screened and DMF was found to be the better choice. We also studied the effect of temperature it was found that optimum temperature is 80 °C. We evaluated the effect of catalyst on the reaction rate and yield, the reaction was found to proceed efficiently in the presence of CuI (20 mol %) giving the highest yield of 179a (76%). An increase in the loading to 50 mol% failed to offer any significant advantages over the 20 mol% catalyst loading (Table 1, entry 9). A reduction in the loading of CuI showed negative effect on the yield of 179a (Table 1, entry 10), whereas the yield was drastically decreased in the absence of CuI, (Table 1, entry 11). Other copper salts were also tested but CuI remained as the best one (Table 1, entries 15-16). In another set of experiments, effect of additive was tested. No significant improvement was observed in the presence of additives like proline, pivalic acid, picolic acid. Copper-catalyzed nitrogen free intramolecular C-S bond formation was shown to proceed efficiently without any bases and additives. With the optimized reaction conditions established, the substrate scope was examined, and results are summarized in (Table 2). Different dithioesters with electron-donating and electron-withdrawing groups on the benzene ring reacted smoothly with (2-bromorophenyl) methanamine 178a to give the corresponding benzothiazines in moderate to good yields at 80 °C (Table 2). This reaction was not limited to aromatic dithioesters, but heterocyclic dithioester also underwent the reaction equally under mild conditions.

Dithioesters with –Me, methoxy functionalities obtained with good yields 179(b-c). Dithioesters bearing halogens such as –F, –Cl, –Br were employed and the desired products were obtained in moderate to good yields 179(f–h). Heterocyclic
dithioester also underwent the reactions to offer the corresponding products with comparable yield 179(i-j) Reactions of (2-bromorophenyl)methanamine with a range of dithioesters derived from differently substituted dithioesters were evaluated under the optimized conditions (Scheme 2). In all cases, products were obtained in good yields at 80 °C temperature or slightly at elevated temperatures products 179(a–j). Importantly, other amine (-bromo-5-fluorophenyl) methanamine also underwent the title reaction under equally mild conditions. To prove the particularity of the present method in the synthesis of polycyclic amines, a gram scale synthesis of 179a was performed.

**Scheme 55:** Substrate scope for the synthesis of benzothiazines

![Scheme 55](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Dithioester</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161a.png" alt="Image" /></td>
<td><img src="181a.png" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161b.png" alt="Image" /></td>
<td><img src="181b.png" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161c.png" alt="Image" /></td>
<td><img src="181c.png" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161b.png" alt="Image" /></td>
<td><img src="181d.png" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="180b.png" alt="Image" /></td>
<td><img src="161b.png" alt="Image" /></td>
<td><img src="181e.png" alt="Image" /></td>
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<tr>
<td>6</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161d.png" alt="Image" /></td>
<td><img src="181f.png" alt="Image" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="180a.png" alt="Image" /></td>
<td><img src="161e.png" alt="Image" /></td>
<td><img src="181g.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Table: 2 Synthesis of 4H-[e] 1,3- benzothiazines from dithioesters.

Possible mechanism for the formation 4H-1,3-Benzothiazines
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The mechanism starts with reaction of 2-bromobenzyl amine with phenyl dithioesters to give thioamide A followed by the substitution reaction. Next the oxidative addition of arylbromide to copper takes place to give an intermediate B. In the final step C undergoes reductive elimination with the formation of 4H-1,3 Benzothiazines.

3.4. Conclusion:

In summary, we are successful in developing a new efficient method to produce substituted benzothiazine derivative via copper (I)-catalyzed intramolecular C-S bond formation. This approach is valuable alternative to widely used arylaminde thioethers reactions. This method is complimentary to existing methods for the benzothiazines.

3.5: Experimental Section:

General Procedure for the synthesis of 4H-1,3 Benzothiazines (Scheme-55)

General procedure for the synthesis of 4H- 1,3 Benzothiazines. To a solution of (2-bromorophenyl) methanamine (185.06mg, 1mmol, 1.0eq) (180a) and phenyl dithioester (161a) (183.03mg, 1.0mmol, 1.0eq), cuprous iodide (38.0mg, 0.2 mmol, 0.2eq) were added. The mixture was stirred at 80°C and progress was monitored by TLC. When the dithioesters could no longer be detected, the reaction mixture was extracted with EtOAc (3×10mL). The organic layer was dried over anhydrous Na₂SO₄. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

Data of representative examples of the synthesized compounds:

2-Phenyl-4H-benzo[e][1,3]thiazine (181a): Following the general procedure, compound 181a was obtained from the reaction of 2-(bromophenyl) methanamine and methylbenzodithioate as a white solid in 66% yield; ¹H NMR (400 MHz, CDCl₃δ
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ppm): $\delta = 4.83$ (s, 2H, CH$_2$) 7.33-7.31 (m, 1H$_3$), 7.36-7.34 (m, 2H$_2$), 7.41-7.38 (m, 1H$_3$), 7.47-7.45 (m, 2H$_2$), 7.52-7.50 (m, 1H$_3$), 8.07-8.05 (m, 2H$_2$); $^{13}$C NMR (100 MHz,CDCl$_3$ $\delta$ ppm): $\delta = 29.6$, 55.3, 126.5, 127.5, 127.7, 127.8, 128.1, 128.7, 129.8, 130.7, 132.0, 135.4; $m/z$ (ESI–MS) [M + H]$^+$ Calculated 226.1623 Found 226.1688; Anal.Cald for C$_{14}$H$_{11}$NS C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.65; H, 4.90; N, 6.23; S, 14.21.

2-(4-methoxyphenyl)-4H-benzo[e][1,3]thiazine (181b): Following the general procedure, compound 181b was obtained from the reaction of 2-(bromophenyl) methanamine and methyl 4-methoxy benzodithioate as a pale Yellow solid in 61% yield $^1$H NMR (400 MHz, CDCl$_3$ $\delta$ ppm): $\delta = 3.83$ (s, 3H$_3$), 4.74 (s, 2H$_2$), 6.93-6.90 (m, 2H$_2$), 7.31-7.26 (m, 3H$_3$), 7.38-7.36 (m, 1H$_3$), 7.97-7.95 (m, 2H$_2$); $^{13}$C NMR (100 MHz,CDCl$_3$):$\delta = 55.3$, 56.5, 113.7, 126.6, 126.8, 127.3, 127.4, 129.4, 131.1, 131.7, 161.2, 162.0; $m/z$ (ESI–MS) [M + H]$^+$ Calculated 256.04 Found 256.10; Anal.Cald for C$_{15}$H$_{13}$NOS C, 70.56; H, 5.13; N; 5.49; O, 6.27; S, 12.56. Found: C, 70.52; H, 5.10; N, 5.46; O, 6.28; S, 12.58.

2-(p-tolyl)-4H-benzo[e][1,3]thiazine (181c): Following the general procedure, compound 181c was obtained from the reaction of 2-(bromophenyl) methanamine and methyl 4-methylbenzodithioate as a yellow solid; in 57% yield $^1$H NMR (400 MHz, CDCl$_3$ $\delta$ ppm): $\delta = 2.26$ (s, 3H$_3$), 4.65 (s, 2H$_2$), 7.11 (d, $J = 8$Hz, 2H), 7.25-7.15 (m, 4H), 7.81 (d, $J = 8.4$Hz, 2H ); $^{13}$C NMR (100 MHz,CDCl$_3$ $\delta$ ppm): $\delta = 56.4$, 126.8, 127.50, 127.53, 127.8, 129.26, 129.28, 130.9, 131.4, 134.0, 141.6, 161.8; $m/z$ (ESI–MS) [M + H]$^+$ Calculated 240.11 Found 240.20; Anal.Cald for C$_{15}$H$_{13}$NOS C, 75.28; H, 5.47; N, 5.85; S,13.40. Found: C, 75.20; H, 5.44; N, 5.83; S, 13.41.
7-fluoro-2-(p-tolyl)-4H-benzo[e][1,3]thiazine (181d): Following the general procedure, compound 181d was obtained from the reaction of 2-(bromophenyl) methanamine and methyl-4-fluorobenzodithioate as a brown oily compound in 62% yield. 

$^{1}$H NMR (400 MHz, CDCl$_3$δ ppm): δ = 2.29 (s, 3H), 4.61 (s, 2H), 7.04-7.00 (m, 2H), 7.11 (d, $J$=8.4Hz, 2H), 7.31-7.27 (m, 1H), 7.93 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$δ ppm): δ = 21.4, 28.9, 38.7, 113.8, 114.6, 114.8, 127.7, 128.0, 129.4, 132.4, 142.2, 160.6, 163.1; m/z (ESI-MS) [M + H]$^+$ Calculated 258.1173, Found 258.1188; Anal. Caled for C$_{15}$H$_{12}$FNS C, 70.01; H, 4.70; F, 7.38; N, 5.44; S, 12.46. Found: C, 70.03; H, 4.68; F, 7.39; N, 5.46; S, 12.45.

7-fluoro-2-(4-methoxyphenyl)-4H-benzo[e][1,3]thiazine (181e): Following the general procedure, compound 181e was obtained from the reaction of 2-(2-chloro-4(trifluoromethyl)phenyl)acetonitrile and methyl 4-methoxy benzodithioate as a pale yellow solid in 61% yield. 

$^{1}$H NMR (400MHz, CDCl$_3$δ ppm): δ = 3.79 (s, 3H), 4.68 (s, 2H), 6.89-6.87(m, 2H), 6.96 (d, $J$=2Hz, 1H), 7.07, 7.07 (dd, $J$=11.2, 5.6Hz, 1H), 7.24-7.19( m, 1H), 7.96-7.94 (m, 2H); $^{13}$C NMR (100MHz, CDCl$_3$δ ppm): δ =55.4, 113.7, 114.8, 115.0, 126.9, 127.0, 128.1, 128.2, 130.0, 132.0, 160.7, 163.0.
163.1; m/z (ESI–MS) [M + H]⁺ Calculated 274.3223 Found 274.3288; Anal.Cald for C₁₅H₁₂FNOS C, 65.91; H, 4.43; F, 6.95; N, 5.12; O, 5.85; S, 11.73. Found: C, 65.89; H, 4.45; F, 6.92; N, 5.14; O, 5.84; S, 11.75.

2-(4-chlorophenyl)-4H-benzo[c][1,3]thiazine (181f): Following the general procedure, compound 181f was obtained from the reaction of 2-(bromophenyl)methanamine and methyl 4-chloro benzodithioate as a pale yellow solid in 64% yield

$^1$H NMR (400 MHz, CDCl₃, δ ppm): δ = 2.27 (s, 3H), 4.67 (s, 2H, 7.13 (d, J=8.4Hz, 2H), 7.27-7.17 (m, 4H), 7.82 (d, J=8Hz, 2H); $^{13}$C NMR (100 MHz, CDCl₃, δ ppm): δ= 21.4, 56.3, 126.8, 127.53, 127.54, 127.7, 127.8, 129.2, 130.8, 131.4, 133.9, 141.7, 162.1; m/z (ESI–MS) Calculated 259.2231 Found [M + 1]⁺ 260.2246; Anal.Cald for C₁₄H₁₀ClNS C, 64.73; H, 3.88; Cl; 13.65; N, 5.39; S, 12.34. Found: C, 64.71; H, 3.89; N, 5.37, S, 12.36.

2-(4-fluorophenyl)-4H-benzo[c][1,3]thiazine (181g): Following the general procedure, compound 181g was obtained from the reaction of 2-(bromophenyl)methanamine and methyl 4-fluoro benzodithioate as a pale yellow solid in 60% yield

$^1$H NMR (400 MHz, CDCl₃, δ ppm): δ = 4.71 (s, 2H), 7.13 (d, J=8.4Hz, 2H), 7.17-7.27 (m, 4H) 7.82 (d, J=8Hz, 2H); $^{13}$C NMR (100 MHz, CDCl₃, δ ppm): δ = 56.3, 116.5, 127.53, 127.54, 127.81, 129.6, 130.8, 131.4, 132.0, 141.7, 162.1, 165.5; m/z (ESI–MS) [M + H]⁺ Calculated 244.1223 Found 244.1288; Anal.Cald for C₁₄H₁₀FNS C, 69.11; H, 4.14; F, 7.81; N, 5.76; S, 13.18. Found: C, 69.10; H, 4.15; F, 7.83; N, 5.75; S, 13.17.
2-(4-bromophenyl)-4H-benzo[e][1,3]thiazine (181h): Following the general procedure, compound 181h was obtained from the reaction of 2-(bromophenyl) methanamine and methyl 4-bromo benzodithioate as a white solid in 60% yield. 

1H NMR (400 MHz, CDCl₃ δ ppm): δ = 4.80 (2H, s), 7.13 (d, 2H, J= 8.4 Hz), 7.17-7.27 (4H, m), 7.72 (d, 2H, J= 8 Hz,).; 13C NMR (100 MHz, CDCl₃ δ ppm): δ = 56.3, 125.4, 126.5, 126.8, 127.5, 127.8, 129.2, 130.8, 131.4, 133.9, 135.7, 162.1; m/z (ESI–MS) Calculated [M + H]+ 305.1923 Found [M + 3]+ 307.1939; Anal. Cald for C₁₄H₁₀BrNS C, 55.28, H, 3.31; Br, 26.27, N, 4.60; S, 10.54. Found: C, 55.26; H, 3.32; Br, 26.28; N, 4.59; S, 10.55.

2- (Pyridin-3-yl)-4H-benzo[e][1,3]thiazine (181i): Following the general procedure, compound 181i was obtained from the reaction of 2-(bromophenyl) methanamine and methyl pyridine 3- carbodithioate as a pale yellow solid in 65% yield. 

1H NMR (400 MHz, CDCl₃ δ ppm): δ = 4.83 (s, 2H), 7.33-7.31 (m, 1H), 7.36-7.34 (m, 2H), 7.41-7.38 (m, 1H), 7.47-7.45 (m, 2H), 7.52-7.50 (m, 1H), 8.07-8.05 (m, 1H,); 13C NMR (100 MHz,CDCl₃ δ ppm): δ = 55.3, 126.5, 127.5, 127.7, 127.8, 128.1, 128.7, 129.8, 130.7, 132.0, 135.4, 151.5, 151.9; m/z (ESI–MS) [M + H]+ Calculated 277.2980 Found 277.2890; Anal.Cald for C₁₃H₁₀N₂S C, 69.00, H, 4.45, N, 12.38, S, 14.17. Found: C, 69.09, H, 4.42, N, 12.39, S, 14.18.

2-(thiophene-2-yl)-4H-benzo[e][1,3]thiazine (181j): Following the general procedure, compound 181j was obtained from the reaction of 2-(bromophenyl) methanamine and methyl 4,5 dihydrothiophene -3-carbodithioate as a white solid in 64% yield. 

1H NMR (400 MHz, CDCl₃ δ ppm): δ= 4.61 (s, 2H), 6.96(t, J= 3.6 Hz, 1H), 7.15-7.18 (m, 3H),7.23-7.25 (m, 1H, ) 7.32 (d,J= 4.8Hz, 1H), 7.58-7.59(m, 1H,);
$^{13}$C NMR (100 MHz, CDCl$_3$ δ ppm): δ = 56.0, 126.6, 127.0, 127.6, 129.42, 129.40, 130.01, 130.07, 130.3, 131.8, 141.6, 155.6; $m/z$ (ESI–MS) [M + H]$^+$ Calculated 232.1423 Found 232.1453; ESIMS [M + H]$^+$ m/z; 232.32 Anal.Cald for C$_{12}$H$_9$NS$_2$ C, 62.30; H, 3.92; N, 6.05; S, 27.72. Found: C, 62.29; H, 3.93; N, 6.04; S, 27.70
\[ \text{2-Phenyl-4H-benzo[e][1,3]thiazine (181a)} \]

\[ \text{\(^1\text{H NMR in CDCl}_3\)} \]

\[ \text{\(^{13}\text{C NMR in CDCl}_3\)} \]

\[ \text{\(^1\text{H NMR, \(^{13}\text{C NMR and Mass spectra of selected compounds:}} \)]} \]
2-(4-methoxyphenyl)-4H-benzo[e][1,3]thiazine (181b)

$^1$H NMR in CDCl$_3$

$^{13}$C NMR in CDCl$_3$
LCMS for (181b)
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2-(p-tolyl)-4\textit{H}-benzo[e][1,3]thiazine(181c)

\textsuperscript{1}H NMR in CDCl\textsubscript{3}

![\textsuperscript{1}H NMR spectrum of 2-(p-tolyl)-4\textit{H}-benzo[e][1,3]thiazine(181c)]

\textsuperscript{13}C NMR in CDCl\textsubscript{3}

![\textsuperscript{13}C NMR spectrum of 2-(p-tolyl)-4\textit{H}-benzo[e][1,3]thiazine(181c)]
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LCMS for (181c)

MASS REPORT

Data File: C:\Chem32\DATA\MAY-15\A289892FA.D
Method: FAC18_9010.M
Sample Name: FS00024264

Instrument: LC-MSD-Trap-XCT

![Mass spectrum image](image-url)
7-fluoro-2-(p-tolyl)-4H-benzo[e][1,3]thiazine(181d)

$^{1}H$ NMR in CDCl$_3$

7-fluoro-2-(p-tolyl)-4H-benzo[e][1,3]thiazine(181d)

$^{13}C$ NMR in CDCl$_3$
2-(4-chlorophenyl)-4H-benzo[e][1,3]thiazine (181f)

$^1$H NMR in CDCl$_3$

$^{13}$C NMR in CDCl$_3$
2-(4-fluorophenyl)-4\textit{H}-benzo[e][1,3]thiazine(181g)

$^1$H NMR in CDCl$_3$

[Image of 1H NMR spectrum]

2-(4-fluorophenyl)-4\textit{H}-benzo[e][1,3]thiazine(181g)

$^{13}$C NMR in CDCl$_3$

[Image of 13C NMR spectrum]
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2-(4-bromophenyl)-4H-benzo[e][1,3]thiazine (181h)

$^1$H NMR in CDCl$_3$

![NMR spectrum of 2-(4-bromophenyl)-4H-benzo[e][1,3]thiazine (181h)]

$^{13}$C NMR in CDCl$_3$

![NMR spectrum of 2-(4-bromophenyl)-4H-benzo[e][1,3]thiazine (181h)]
2- (Pyridin-3-yl)-4H-benzo[e][1,3]thiazine(181i)

$^1$H NMR in CDCl$_3$

$^1$C NMR in CDCl$_3$
2-(thiophene-2-yl)-4H-benzo[e][1,3]thiazine(181j)

$^1$H NMR in CDCl$_3$

![1H NMR spectrum](image)

2-(thiophene-2-yl)-4H-benzo[e][1,3]thiazine(181j)

$^{13}$C NMR in CDCl$_3$

![$^{13}$C NMR spectrum](image)
3.6. References:


