CHAPTER III

Montmorillonite K-10 Mediated Thioether Synthesis

\[
\begin{align*}
&\text{OH} &+ &R^3\text{SH} &\xrightarrow{\text{Montmorillonite K-10}} &\text{SR}^3 \\
&\text{R}^1 & &\text{R}^2
\end{align*}
\]

\[
\begin{align*}
&\text{R} &+ &\text{Ph} &\xrightarrow{\text{Montmorillonite K-10}} &\text{Ph} \\
&\text{R} & &\text{R} \\
\end{align*}
\]

\[
\begin{align*}
&\text{R} &+ &\text{Ph} &\xrightarrow{\text{Montmorillonite K-10}} &\text{Ph} \\
&\text{R} & &\text{R} \\
\end{align*}
\]
CHAPTER III

Montmorillonite K-10 Mediated Thioether Synthesis

Points to be studied:

1. Significance of Thioether Functional Group.
2. Literature Survey for the synthesis of Thioethers.
3. Present Work.
4. Result and Discussion.
5. Reaction Mechanism.
6. Experimental Section.
7. Characterization.
8. Merits of the Methodology and Conclusion.
9. References.
1] Significance of thioether functional group:

Thioethers are versatile substrates in organic synthesis. They are widely used as:

a) Valuable precursors for several reactions.

b) Protecting group for the thiol functionality.

c) A substructural unit of many natural products.

A) Thioethers as valuable precursors:

Thioethers serve as valuable precursors for chiral sulfoxides and sulfoxides. Sulfonium salts required for ylide preparation, are also accessible from thioethers.

\[
\begin{align*}
\text{R} & \quad \text{R—S—R} \quad \\
& \quad \text{R—X} \quad \\
& \quad \text{[O]} \quad \\
& \quad \text{R—S—R} \quad \\
& \quad \text{S-ylide}
\end{align*}
\]

Allylphenyl thioether is a starting material for the multi-manipulate [3,3] thio-Claisen rearrangement.

\[
\begin{align*}
\text{[3,3]Claisen} & \\
\text{Rearrangement}
\end{align*}
\]

B) Thioethers as Protecting Group:

Protection of thiol groups is important in many areas of organic research, particularly in peptide, protein and β-lactam synthesis. A free SH group can be protected as a thioether or a, or, after oxidation as disulfide. The most commonly employed thioethers as protecting groups are:
<table>
<thead>
<tr>
<th>Protecting Groups for –SH</th>
<th>Formation</th>
<th>Cleavage</th>
<th>Lit. Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. S-Benzyl Thioether ( (RSCH_2C_6H_5) )</td>
<td>( \text{PhCH}_2\text{Cl,}2\text{NaOH, EtOH} )</td>
<td>( \text{Na, NH}_3 )</td>
<td>6,7</td>
</tr>
<tr>
<td>2. S-4-Methoxybenzyl Thioether ( (RSCH_2C_6H_4-p-OCH_3) )</td>
<td>( 4\text{-MeOC}_6\text{H}_4\text{CH}_2\text{Cl, NH}_3 )</td>
<td>( \text{CF}_3\text{COOH, reflux [RSC}_6\text{H}_5 )</td>
<td>8</td>
</tr>
<tr>
<td>3. S-Diphenylmethyl Thioether ( [RSCH(C_6H_5)_2] )</td>
<td>( \text{Ph}_2\text{CHOH, BF}_3\text{OEt}_2 )</td>
<td>( \text{Na, NH}_3 )</td>
<td>9, 10</td>
</tr>
<tr>
<td>4. S- Phenyl Thioether ( [RSC_6H_5] )</td>
<td>( \text{RX/ base Electrolysis conditions} )</td>
<td></td>
<td>11, 12</td>
</tr>
</tbody>
</table>

C] **Thioethers as a Substructural Unit of Natural Products:**

Many natural products containing a thioether as a structural unit are found to exhibit useful biological properties such as pesticides and bactericides.\(^{13}\)
2.1] Mitsunobu Condensation:

The Mitsunobu reaction has become a valuable synthetic method in organic chemistry over the past two decades.\textsuperscript{14} The Mitsunobu condensation between an alcohol and a thiol is a widely accepted synthetic procedure for thioether preparation.

\[
\text{R}_1\text{SH} + \text{ROH} \xrightarrow{\text{Mitsunobu conditions}} \text{R}_1\text{S-R}
\]

The most commonly used Mitsunobu reagents/conditions are:

\[\text{[a]} \quad \text{Ph}_3\text{P} + \begin{array}{c}
\text{O} \\
\text{N=N=O}
\end{array} \quad \cdots \cdots \cdots \quad \text{Ref. (15)}\]

\[\begin{array}{l}
\text{[b]} \\
\text{Me}_3\text{P} + \begin{array}{c}
\text{N} \\
\text{N=O} \\
\text{N=O}
\end{array} + \text{HN} \\
\end{array} \quad \cdots \quad \text{Ref (16)}\]

This method is applicable to a variety of combinations of alcohols and thiols such as alkyl, benzyl, phenyl, t-butyl, alkyl, and propargyl systems. For example,

- \(\text{MeO-SH} + \text{HO-C} \quad \xrightarrow{\text{MeO}} \quad \text{MeO-S-C} \quad 75\%\)
- \(\text{C-SH} + \text{HO-C} \quad \xrightarrow{} \quad \text{C-S-C} \quad 80\%\)
- \(\text{C-SH} + \text{HO-C} \quad \xrightarrow{} \quad \text{C-S-C} \quad 88\%\)
However, the use of Mitsunobu method is associated with a complicated reaction work up resulting from complex mixtures containing product, triphenylphosphine oxide and the reduced azodicarboxylate, as well as unreacted starting material. Diethyl ether precipitation can help to remove some of the byproducts and assist in purification of products. But most of the time, extensive chromatography is often required to separate the desired product from the large mass of byproducts.17

2.3] Modified Mitsunobu Condensation:

Modified Mitsunobu condensation utilizes salts for the synthesis of unsymmetrical sulfides from alcohols and thiols.18

\[
R'^{1}OH \xrightarrow{i] \text{NaH}} R'^{1} - S - R^{2} \xrightarrow{ii] \text{Ph}_3P^+\text{N}\text{CH}_3 + I^-} \xrightarrow{iii] \text{R}^2\text{SH}}
\]

For example:

\[
\text{PhCH}_2\text{CH}_2\text{OH} + \text{SH} \rightarrow \text{PhCH}_2\text{CH}_2\text{S}\text{Ph} \quad 84 \%
\]

\[
\text{PhCH} = \text{CHCH}_2\text{OH} + \text{PhSH} \rightarrow \text{PhCH} = \text{CHCH}_2\text{SPh} \quad 88 \%
\]

The mechanistic reaction of this methodology is as follows:

\[
R'^{1}OH \xrightarrow{\text{NaH}} R'^{1}\text{ONa} \xrightarrow{\text{Ph}_3P^+\text{N}\text{CH}_3 \text{I}^-} \left[ R'^{1}\text{O}\text{PPh}_3 \right] \left[ \text{N}\text{CH}_3 \right] + \text{NaI} \xrightarrow{\text{R}^2\text{SH}} R'^{1} - S - R^{2} + \text{Ph}_3\text{P}=\text{O} + \text{NH(\text{CH}_3)Ph}
\]
- Sufficient acidity of thiols / alcohols to participate in Mitsunobu condensation is an important requirement of the above mechanistic rationale. But aliphatic thiols / alcohols generally lack sufficient acidity to participate in Mitsunobu condensation.

- The reaction was carried out in DMF at RT for 8 hr (long reaction time). The removal of DMF after reaction work up is tedious by means of distillation under reduced pressure.

- Extensive chromatographic purification is required.

2.3] Lewis acid catalyzed direct thioether synthesis from thiols and alcohols:

Some of the Lewis acids can mediate direct thioetherification reaction between thiols and alcohols. The most commonly employed Lewis acids are BF$_3$OEt$_2$, SmCl$_2$ and ZnI$_2$.

**BF$_3$OEt$_2$**: This catalyst is particularly useful to prepare allyl sulfides from allyl alcohols and thiols.$^{19}$ We can directly convert aliphatic, alicyclic, benzylic, conjugated, aromatic and fused ring allyl alcohols to the corresponding sulfides with a sulfur reagent (RSH or RSSiMe$_3$) in the presence of the Lewis acid BF$_3$OEt$_2$.

\[
\begin{align*}
R^1\text{-}CH_2\text{-}OH & \quad \text{or} \quad R^2\text{-}SH \quad \text{or} \quad RSSiMe_3 \\
\text{BF}_3\text{OEt}_2 / CH_2Cl_2 & \quad R\text{-}SH \quad \text{or} \quad RSSiMe_3 \\
r. t., 5 - 48 h, \quad \text{NaHCO}_3 / H_2O & \quad R^1\text{-}CH_2\text{-}SR^2
\end{align*}
\]

- Yields of the reaction are very good; 70 – 90 % yields.

- Mild reaction conditions.
- Primary allyl alcohol forms allyl sulfides without allylic rearrangement but secondary and tertiary allyl alcohol forms allyl sulfides via SN₂ and SN₂⁻ fashion.

- The reaction is restricted only to allylic alcohols.

- The reaction conditions allowed chemoselectivity between allylic and homoallylic alcohols. For example,

\[
\text{BF}_3\text{OEt}_2 / n-\text{BuSH} \rightarrow \text{CH}_2\text{Cl}_2, \text{r.t.} \ 18 \text{ h} \rightarrow 96\%
\]

**Samarium Trichloride (SmCl₂):**

An isolated report on the use of SmCl₂ in the preparation of allyl sulfides from allyl alcohol and thiol has become documented.²⁰ For example,

\[
\text{Geraniol} + \text{PhSH} \rightarrow \text{CH}_2\text{Cl}_2, \text{reflux} \rightarrow 57\%
\]

- Yields are relatively poor.

- Reaction is sometimes accompanied by diallyl ether formation.

**Zinc Iodide (ZnCl₂):**

A very simple and convenient synthesis of a wide range of thioethers from thiols and alcohols using a Lewis acid, ZnCl₂ in possible.

\[
\text{R} = \text{aryl, alkyl}; \quad \text{R}^1 = \text{H, alkyl, aryl}; \quad \text{R}^2 = \text{alkyl, aryl}
\]
The methodology is attractive for its simplicity, effectiveness and the very mild conditions employed.

It can be advantageous extended to protect the thiol function as p-methoxybenzyl thioether.

\[ \text{MeO} \text{Me} + \text{PhSH} \xrightarrow{\text{ZnI}_2 (0.5 \text{ eq.})} \text{OMe} \text{SPh} \]

Preparation of allyl sulfides is also possible.

\[ \text{OH} + \text{PhSH} \xrightarrow{\text{ZnI}_2 (0.5 \text{ eq.})} \text{SPh} \]

Basic substituents such as amides and amines present as a part of thiol substrate can interface in the reaction.

2.4] Base Catalyzed Thioether Synthesis from Thiols and Allyl Halides:

\[ \text{R—SH} + \text{R}^1—\text{X} \xrightarrow{\text{base}} \text{R—S—R}^1 \]

The conversion of thiols to thioethers is conventionally achieved by reaction of thiolate with organic halides. The yields and reaction conditions depend on the solvent, the basic catalyst and the acidity of thiol. This reaction can be carried out under homogeneous as well as heterogeneous reaction conditions depending on the nature of base. The various base catalyst to bring about this transformation are:

1] NaOH, NH₃, Cs₂CO₃

2] CsF – Celite

2] Montmorillonite-3-aminopropyl triethoxysilane
1] NaOH, NH₃, Cs₂CO₃:

A variety of the bases like NaOH⁶, NH₃,⁸ Cs₂CO₃²² have been used to bring about thioether synthesis form reactive alkyl halides and thiols.

\[
R-\text{SH} + R^1-X \xrightarrow{\text{NaOH or NH₃ or Cs₂CO₃}} R-S-R^1
\]

- The reaction work up is somewhat tedious.
- A competitive elimination reaction can occur when a tertiary alkyl halide is used for thioetherification process.

2] CsF – Celite:

The CsF-Celite assisted coupling of aliphatic and aromatic thiols with various alkyl and benzyl halides resulted in thioether formation.²³

\[
RSH + R^1X \xrightarrow{\text{CsF -- Celite}} \xrightarrow{\text{CH₃CN, r. t. or reflux}} R-S-R^1
\]

R = Phenyl or Benzyl
X = Cl, Br or I
R¹ = alkyl or benzyl

- The reaction is usefully extended to the preparation of thioethers.

\[
\text{ArSH} + \xrightarrow{\text{CsF -- Celite}} \xrightarrow{\text{}} \text{O}
\]

- Only filtration is required to remove the catalyst.
- It is a convenient, inexpensive, NONCORROSIVE and practical method for preparing thioethers.
Montmorillonite-3-aminopropyl triethoxysilane:

A basic clay, synthesized by introducing 3-aminopropyltriethoxysilane into Montmorillonite, catalyses the reaction between benzyl chloride and thiols to affect high yields of the corresponding sulfides.24

\[
\text{Cl} \quad + \quad \text{RSH} \quad \xrightarrow{\text{Cat.}} \quad \text{Cl-SR}
\]

\( R = \text{C}_6\text{H}_5, \text{p-MeOC}_6\text{H}_4, \text{p-ClC}_6\text{H}_4, \text{C}_4\text{H}_9, \text{C}_6\text{H}_8, \text{C}_8\text{H}_{17} \)

- The basic catalyst is prepared by refluxing 5 g of sodium exchanged clay with 50 ml of 0.3 mol dm\(^{-3}\) 3-aminopropyl-triethoxysilane in water for 38 hours.
- The pH of the catalyst is around 8.7 – 9.2.
- FT-IR of the clay sample clearly shows the stretching frequency of the alkyl chain and primary amino group.
- After completion of the reaction, the catalyst can be easily filtered off and reused several times, giving similar results. This is the biggest advantage of this protocol.
- Economical methodology.

2.5] Thioether Synthesis via Addition of Thiols Onto Olefins:

Thioether can be synthesized by the addition of thiols onto olefins. This addition can be effected via electrophilic as well as radial pathways.25

\[
\text{R-SH} \quad + \quad \text{C-H} \quad \xrightarrow{\text{Electrophilic}} \quad \begin{array}{c}
\text{C-H} \\
\text{SR}
\end{array} \\
\text{OR} \\
\text{Radical addition}
\]
The electrophilic addition of thiols is catalyzed by protic acids (H$_2$SO$_4$, HClO$_4$, and p-TSA) and Lewis acids (AlCl$_3$, BF$_3$, TiCl$_4$, SnCl$_2$, ZnCl$_2$, SO$_2$). However, the use of conventional protic or Lewis acid catalyst entails the problem of corrosively, work up and effluent pollution. The Markounikov addition of thiols across the double bond occurs under electrophilic pathway.

The radical addition of thiols onto the olefins promotes anti-Markounikov product formation. Various free radical initiates such as benzyl peroxide, AIBN etc. has been reported.

Recently, heterogeneous catalytic method for the addition of thiols to a variety of olefins compounds has also been documented for thioether preparation. Recently, the Anti-Markounikov as well as Markounikov addition of thiols O=C bonds has been reported.

Recyclability of the catalyst coupled with its ecofriendly nature are the important features of the methodology.

Thiols readily react with alkenes in the presence of Al$^{3+}$ exchanged Montmorillonites and other clays. This process requires quite high temperature (150 – 250 °C) and long reaction time. For example, 1-hexene reacts with butane-1-thiol are 200 °C to give three addition products.
Deoxygenation of Sulfoxides to Sulfides:

The reduction of sulfoxides is a viable method for the preparation of thioethers. A survey of the literature has revealed that a variety of reducing agents have been employed for the transformation of sulfoxides into the corresponding sulfides. Herein, we wish to mention only two reducing agents, which are recently reported.

(1) Magnesium amide:

Magnesium amide generated in situ from the reaction of ethylmagnesium bromide and secondary amine; such as di-isopropyl amine (DIPA) or 2,2,8,6-tetramethylpiperidine (TMP) in diethyl ether, acts as a reducing agents to convert sulfoxides into sulfides.

\[
\text{R} - \text{S} - \text{R} \xrightarrow{\text{Reduction}} \text{R} - \text{S} - \text{R}
\]

Reaction conditions are very delicate.

(2) Zn / AcOH - Dichlorodimethylsilane:

A stepwise reduction of arylsulfonyl chlorides followed by coupling with activated alcohols yields thioethers.
- It is a one pot strategy.
- Intermediate thiol 4 is not isolated.
- Yields are relatively poor.
- It is a good functional group manipulation.

2.7) **Miscellaneous Strategy for Thioether Preparation:**

1. Synthesis of allyl aryl sulfides by palladium mediated alkylation of thiols.\(^\text{35}\)

\[
R^1\text{OCO}_2R^1 + \text{R}^3\text{SH} \xrightarrow{\text{THF/60 °C}} R^1\text{OCO}_2\text{SR}^3 + \text{R}^3\text{alkene}
\]

2. Synthesis of aryl sulfides by palladium-catalyzed reaction of hypervalent iodonium salts with mercaptans.\(^\text{36}\)

\[
\text{RSH} + \text{Ar}_2\text{BF}_4^+ \xrightarrow{\text{Pd(PPh}_3)_4/\text{Na}_2\text{CO}_3} \text{R} - \text{S} - \text{Ar}
\]

R = aryl or alkyl

\[\text{THF, r.t.}\]
(3) Synthesis of benzyl sulfides via Sm/BiCl$_3$\textsuperscript{37} or Zn/AlCl$_3$\textsuperscript{38} system in aqueous media:

\[
\text{PhCH}_2\text{Br} + \text{RSSR} \xrightarrow{\text{Sm/BiCl}_3, \text{THF/H}_2\text{O}} \text{RCH}_2\text{SR}
\]

\[
\text{RSSR} + 2\text{R'}\text{X} \xrightarrow{\text{Zn/AlCl}_3, \text{DMF/H}_2\text{O}} 2\text{RSR'}
\]
3] Present Work

Herein, we wish to report the Montmorillonite K-10 catalyzed thioetherification of 1,3-diaryl-2-propen-1-ol with thiols.

\[
\text{R}^1\text{OH} + \text{R}^3\text{SH} \xrightarrow{\text{Mont. K-10}} \text{R}^1\text{R}^2\text{SR}^3
\]

The starting material, 1,3-diaryl-2-propen-1-ol, was prepared according to the following reaction sequence.

a] Preparation of Chalcones:

Variously substituted aromatic aldehydes and ketones were condensed in presence of NaOH to afford the chalcones. (See Table 1)

\[
\text{R}^1\text{R}^2\text{O} \xrightarrow{\text{EtOH} \quad \text{NaOH}} \text{Chalcones}
\]

The obtained chalcones were purified by crystallization process and characterized by the melting point.

b] 1,2-Reduction of Chalcones:

Chalcones obtained in the above reaction were subjected to 1,2-reduction at 0 °C by using sodium borohydride, leading to the preparation of 1,3-diaryl-2-propen-1-ol. (See Table 2)

The 1,2-reduction products of chalcones were not purified further and were used as isolated for the actual thioetherification process.
After the synthesis of variously substituted 1,3-diaryl-2-propen-1-ol, we have chosen the reaction of 1,3-diaryl-2-propen-1-ol with thiophenol in presence of Montmorillonite K-10 as a model reaction. The above reactants and the catalyst were stirred in CH$_2$Cl$_2$ for 1½ hour and indeed, the corresponding allylphenyl thioether was obtained in 74% yield.

The reaction conditions such as the temperature and time were examined in detail. The scope and limitation of allyl phenyl thioether synthesis by the above procedure, were studied by a panel of variously substituted 1,3-diaryl-2-propen-1-ol. The results are summarized in Table 3.

4] Results and Discussion

The present methodology for thioetherification was found to be quite general as a wide range of 1,3-diaryl-2-propen-1-ol can be treated with thiols. Allyl phenyl thioether, which is a starting material for [3,3] thio-Claisen rearrangement, can thus be obtained in good to excellent yields (Table 3).

The reaction is likely to proceed through carbocation mechanism (SN$_1$) and therefore, the product formation may be accompanied by allylic rearrangement reaction. The formation of SN$_1$ and SN$_1$ products depends on the nature of substituents present on the aromatic rings. The electron releasing
groups like -OMe, -OH and -Cl inhibits the allylic rearrangement, thereby, yielding only normal SN$_{1}$ products. (Table 3, entries r, s, t and u).

However, SN$_{1}$ products were observed for some 1,3-diaryl-2-propen-1-ol (Table 3, entries v and w) because of double bond migration as demanded by carbocation stabilization factor.

In the following reaction, allylic rearrangement also take place, perhaps, owing to the kinetic stability of the final product.

To gain some insight about this thioetherification strategy, 1,3-diaryl-2-propen-1-ol alone was treated with Montmorillonite K-10. It is worth pointing out that in the absence of thiol, the carbocyclization of 1,3-diaryl-2-propen-1-ol was observed leading to the formation of indenes.
In support of these finding, we have also tried the direct condensation between the “weekly activated” benzyl alcohol and thiophenol in the presence of Montmorillonite K-10.

Needless to mention, this attempt was unsuccessful and no thioether formation took place. However, the “highly activated” benzhydrol and fluorenol undergo thioetherification in excellent yields with thiophenol in the presence of Montmorillonite K-10.

This reaction is particularly important in the selective protection of thiols as diphenyl-methyl (DPM) thioethers which is commonly used in organic synthesis.9

As above mentioned, benzyl alcohol does not react with thiophenol in presence of Montmorillonite K-10 to form thioether. This is because of inability of Montmorillonite K-10 to form a “highly stable” carbocation from benzyl alcohol. However, this problem can be solved by using activated esters like benzyl benzoate and cinnamyl acetate as the substitutes for the “weakly activated” benzyl alcohol and cinnamyl alcohol respectively.
In these activated esters, the good leaving group ability of the benzoate or acetate anion facilitates the development of a benzylic or allylic carbocation after the initial complexation with Montmorillonite K-10. Thus, Montmorillonite K-10 clay can bring about thioether synthesis by condensation between activated esters and thiols, but not from substituted benzyl alcohols and thiols.
### Table 1: Preparation of Chalcones.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>82</td>
</tr>
<tr>
<td>b)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>83</td>
</tr>
<tr>
<td>c)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>79</td>
</tr>
<tr>
<td>d)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>87</td>
</tr>
<tr>
<td>e)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>83</td>
</tr>
<tr>
<td>f)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>78</td>
</tr>
<tr>
<td>g)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>86</td>
</tr>
<tr>
<td>h)</td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>79</td>
</tr>
</tbody>
</table>
Table 2: 1,2-Reduction of chalcones at 0 °C using NaBH₄ in methanol.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>i)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>j)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>k)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>l)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>m)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>n)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>o)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>p)</td>
<td><img src="image" alt="Chalcone" /></td>
<td><img src="image" alt="Product" /></td>
<td>30</td>
<td>91</td>
</tr>
</tbody>
</table>
Table 3: Montmorillonite K-10 mediated thioetherification of 1,3-diaryl-2-propen-1-ol.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>q)</td>
<td></td>
<td>PhSH</td>
<td></td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>r)</td>
<td>MeO</td>
<td>PhSH</td>
<td></td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>s)</td>
<td>HO</td>
<td>PhSH</td>
<td></td>
<td>60</td>
<td>82</td>
</tr>
<tr>
<td>t)</td>
<td>Cl</td>
<td>PhSH</td>
<td></td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>u)</td>
<td>Cl</td>
<td>PhSH</td>
<td></td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>v)</td>
<td>OMe</td>
<td>PhSH</td>
<td></td>
<td>50</td>
<td>77</td>
</tr>
<tr>
<td>w)</td>
<td>O2N</td>
<td>PhSH</td>
<td></td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>x)</td>
<td></td>
<td>PhSH</td>
<td></td>
<td>50</td>
<td>83</td>
</tr>
</tbody>
</table>
4] Reaction Mechanism

The success of this thioetherification reaction is due to the ability of Montmorillonite K-10 to generate a carbocation only from the highly (doubly) activated 1,3-diaryl-2-propen-1-ol. Montmorillonite K-10 is insufficient to generate a carbocation from the weakly activated benzyl alcohol under the above reaction conditions.

Montmorillonite K-10 is an inorganic solid acid possessing both Bronsted and Lewis acidic sites. For the sake of convenience in writing the reaction mechanism, we consider Montmorillonite K-10 equivalent to proton. The mechanistic reaction sequence for the thioetherification process is as follows:

Step I: Protonation of 1,3-diaryl-2-propen-1-ol:

This converts a bad leaving -OH group into a good leaving $-\text{OH}_2^+$ group.

Step II: Formation of Resonance Stabilized Carbocation:

The good leaving group ability of $-\text{OH}_2^+$ brings about the conversion of protonated 1,3-diaryl-2-propen-1-ol into an exhaustively resonance stabilized carbocation. The migration of olefinic double bond (called as allylic rearrangement) through resonance phenomenon justifies the formation of SN$_2^+$ product.

Step III: Attack of Nucleophile on Carbocation:

Finally the nucleophilic thiol will attack on potentially electrophilic carbon numbered 1 and 3 to form allyl thioether.
Thioetherification Mechanism

Step I

\[ \text{Rearranged SN}^1 \text{ Product} \]

Step II

Protonated 1,3-diaryl-2-propen-1-ol

\[ \text{Step III} \]

\[ \text{Normal SN}^1 \text{ propanol} \]

\[ \text{Rearranged SN}^1 \text{ Product} \]
Similarly, the reaction of thiophenol with activated esters in the presence of Montmorillonite K-10 will proceed through the following mechanism.

\[
\text{PhOPh} \xrightarrow{\text{H}^+ \text{Mont. K-10}} \text{PhO}^+\text{Ph} \quad \text{Protonated ester} \\
\text{PhCH}_2\text{-S-Ph} \xrightarrow{\text{PhSH}} \text{PhCH}_2^+ + \text{Ph-C-OH} \quad \text{Formation of electrophile} \\
\text{PhCH}_2^- \quad \text{Attack of nucleophile} \\
\text{Resonance stabilised carbocation, a potential electrophile.}
\]

\[
\text{PhCH}_2\text{-S-Ph} \xrightarrow{\text{PhSH}} \text{PhCH}_2^+ + \text{Ph-C-OH} \quad \text{Formation of electrophile} \\
\text{Resonance stabilised carbocation, a potential electrophile.}
\]

\[
\text{PhOCH}_2\text{Ph} \xrightarrow{\text{H}^+ \text{Mont. K-10}} \text{PhO}^+\text{CH}_2\text{Ph} \quad \text{Protonated ester} \\
\text{PhCH}^+\text{CH}_2 + \text{CHO} \quad \text{Formation of electrophile} \\
\text{PhCH}_2\text{-S-Ph} \xrightarrow{\text{PhSH}} \text{PhCH}^+\text{CH}_2 + \text{CHO} \quad \text{Attack of nucleophile} \\
\text{Resonance stabilised carbocation, a potential electrophile.}
\]
Experimental Section

Montmorillonite K-10 was purchased from Fluka and dried at 100 °C prior to use. All chemicals were of commercial quality from freshly opened container or distilled before use.

Purification by column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether and ethyl acetate for elution. Commercial grade solvents were used for column chromatography and were distilled before use. Petroleum ether refers to the fraction boiling between 60-80 °C. Analytical thin layer chromatography was performed on glass plates coated with silica gel.

Chalcone Preparation:

Equimolecular quantities of substituted acetophenones and aromatic aldehydes in minimum quantity of ethanol was dissolved. 40 % NaOH in water was added in portions as room temperature. The flask was stirred for about 12-16 hours. The content of the flask was poured over crushed ice. The solid obtained was filtered, washed with cold water and dried. Then recrystallized from ethanol to get pure chalcone. (Table 1)

Reduction of Chalcones:

In a 100 ml round bottom flask, chalcone (10 mmol) was taken in methanol (20 ml). This mixture was cooled to 0 °C and sodium borohydride (2.5 mmol) was added slowly with magnetic stirring of the reaction mixture. The reaction was carefully monitored by TLC. After the completion of reaction, water was added and filtered the mixture. The product was washed with methanol and used as it is for subsequent reactions. (Table 2)
Thioetherification Procedure:

In a typical reaction procedure, to a stirred solution of 1,3-diaryl-2-propen-1-ol (10 mmol) and the thiol (10 mmol) in dichloromethane (20 ml) were added Montmorillonite K-10 (30 wt % w. r. t. alcohol) and the mixture was stirred at room temperature for the time as mentioned in Table 3. The reactions were monitored by TLC. After completion of the reaction, the clay was filtered off and washed with CH₂Cl₂; the filtrate was then washed with 10 % aqueous NaOH solution to remove unreacted thiophenol and then further washed with water and brine and dried over anhydrous sodium sulphate. Removal of the solvent and subsequent silica gel chromatography afforded the allylphenyl thioether in pure form.
7] Characterization of the Products:

IR spectra were recorded on a Perkin-Elmer 137-E spectrometer. The $^1$H NMR spectra were recorded on a 300 MHz instrument and the chemical shifts were reported with TMS as an internal standard. The representative spectral analysis for few of the products is given below:

1] Benzyl phenyl sulfide:

![Benzyl phenyl sulfide structure]

$^1$HNMR: $\delta$ 3.9 (2H, s)
7.3 – 7.6 (5H, m)
7.8 – 7.9 (5H, m)

IR (cm$^{-1}$, Neat): 3031, 2934, 1608, 1426, 1255, 1067, 957, 751.

Melting Point 40 – 42 °C (lit. 38 – 41 – 43 °C)

2] 4-Methylphenyl benzyl sulfide:

![4-Methylphenyl benzyl sulfide structure]

$^1$HNMR: $\delta$ 2.3 (3H, s)
3.8 (2H, s)
7.1 – 7.9 (9H, m)

IR (cm$^{-1}$, Neat): 3010, 2928, 2824, 1610, 1486, 1444, 1085, 963, 751.

Melting Point 44 – 45 °C (lit. 38 – 45 – 46 °C)

3] Thioether of fluorenol:

![Thioether of fluorenol structure]

$^1$HNMR: $\delta$ 4.0 (1H, s)
6.8 – 7.4 (13H, m)

IR (cm$^{-1}$, Neat): 3025, 2927, 1596, 1432, 1067, 726, 702.

Melting Point 79 °C
4] Phenyl (3-phenyl-2-propenyl) sulfide:

\[
\text{HNMR: } \delta 4.6 (2H, d) \\
5.3 (1H, m) \\
5.8 (1H, m) \\
7.0 - 7.6 (10H, m)
\]

IR (cm\(^{-1}\), Neat): 3025, 2934, 2865, 1640, 1437, 1271, 724.

Melting Point 76 °C

5]  

\[
\text{HNMR: } \delta 4.5 (1H, d) \\
5.0 (1H, dd) \\
5.7 (1H, d) \\
7.3 - 7.6 (14H, m)
\]

IR (cm\(^{-1}\), Neat): 3011, 2924, 2852, 1608, 1590, 1476, 1120, 973, 740.

Melting Point 117 °C

6]  

\[
\text{HNMR: } \delta 3.7 (9H, m) \\
4.7 (1H, d) \\
5.5 (1H, dd) \\
5.7 (1H, d) \\
7.2 - 7.5 (12H, m)
\]

IR (cm\(^{-1}\), Neat): 3017, 2934, 2859, 1607, 1520, 1486, 1391, 1252, 967, 823, 724.

Melting Point 109 °C
**SPh**

**IR (cm⁻¹, Neat):**

Melting Point 112 °C

**¹H NMR:**

δ 2.6 (2H, t)
3.5 (2H, t)
5.1 (1H, s)
5.0 (1H, s)
7.1 - 7.4 (14H, m)

**IR (cm⁻¹, Neat):**

3025, 2929, 2893, 1641, 1577, 1475, 1019, 740, 637.
Regn. No. 4468
PYPh-6
Ih in CDC13
NMR Group. IICT
GEHINI-200 MHz; s2pul
ppm
Merits of the Methodology and Conclusion:

Following are the merits associated with the reported thioetherification reaction:

- This is the first kind of report of thioetherification of 1,3-diaryl-2-propen-1-ol with the thiols.
- Use of Montmorillonite K-10 clay as a cheap, safe and environmentally benign catalyst.
- Mild reaction conditions.
- Easy reaction work up.
- Economically viable, rapid and high yielding protocol for thioethers synthesis.
- Activated esters and thiols in presence of Montmorillonite K-10 also gives thioethers.

Conclusion:

We have demonstrated a novel inexpensive methodology for thioether preparation employing solid acid catalyst, Montmorillonite K-10, which has advantages of operational simplicity, environmental acceptability, non-corrosivity, mild conditions and high yields.
References:


