



# Li–X-type zeolite mediated Michael addition of thiols to cyclic enones and its application in the synthesis of 13-thiaprostaglandins

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## Abstract

Michael addition of various thiols to cyclic enones in presence of Li–X-type zeolite has been described. 13-Thiaprostaglandins have been synthesized in good yields using substituted hydroxycyclopentenone as the Michael acceptor and arylthiols as Michael donors. © 2004 Elsevier B.V. All rights reserved.

*Keywords:* Michael addition; Thiaprostaglandins; Zeolites; Thiols; Enones

## 1. Introduction

There has been increasing emphasis on the development and use of environment-friendly solid base catalysts to replace soluble bases like metal hydroxides and alkoxides which are widely used in the C–C bond forming reactions [1]. Although the Michael addition reaction is one of the effective methods for C–C bond formation and is widely employed in organic synthesis, conjugate additions of mercaptans and amines are relatively less explored. Traditionally the 1,4-addition of mercaptans is catalyzed by strong bases such as alkali metal alkoxides, hydroxides [2] and amines [3]. Use of these strong bases lead to the formation of undesirable side products due to competing reactions like polymerization, self-condensation and rearrangements [4]. On the contrary, zeolites afford cleaner Michael addition products with good yields [5]. Several organic transformations including oxidations [6], protection of aldehydes and ketones [7], Heck reaction [8], deprotection of allyl and cinnamyl esters [9], transthioacetalization [10], etc. using heterogeneous catalysts have been reported from our laboratory. We have explored the utility of Li–X-type zeolite in the synthesis of 13-thiaprostaglandins by Michael addition of various thiols to substituted cyclopentenones as depicted in Scheme 1. To our knowledge there is no report available in the literature

in which Li–X-type zeolite is employed to promote the Michael addition and therefore the potential of Li–X-type zeolite has been investigated here. Present method demonstrates the utility of Li–X-type zeolite for Michael addition and its application in the synthesis of 13-thiaprostaglandins which are biologically active compounds [11].

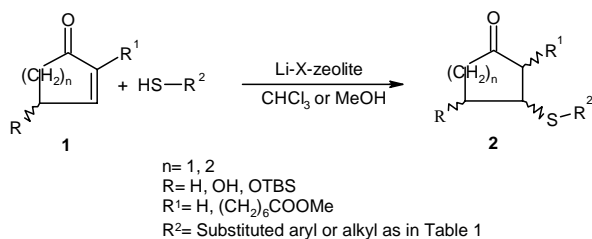
## 2. Experimental section

### 2.1. Synthesis of catalyst [12]

Zeolite-X was synthesized using the gel composition in terms of oxides 4.54 Na<sub>2</sub>O:3.44 SiO<sub>2</sub>:Al<sub>2</sub>O<sub>3</sub>:180 H<sub>2</sub>O. Sodium silicate (28.6% SiO<sub>2</sub>, 8.88% Na<sub>2</sub>O and 62.6% H<sub>2</sub>O) was used as the silicon (SiO<sub>2</sub>) source and NaAlO<sub>2</sub> was used as the alumina (Al<sub>2</sub>O<sub>3</sub>) source. In a typical synthesis 18.6 g of sodium silicate was taken in a beaker and a mixture of 5.9 g sodium aluminate, 3.9 g sodium hydroxide and 70 g water was added to it. The mixture was stirred for 1 h, transferred into an autoclave, aged for 24 h at room temperature and then heated at 373 K for 6 h. The product was filtered, washed with distilled water and dried at ambient temperature.

Ion exchange of zeolite-X was carried out using the hydroxide and chloride solutions (1 M) of cesium, potassium and lithium. Ion exchange was carried out at 353 K using 50 ml of solution per g of sample (6 h elution). The exchange

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Scheme 1.

procedure was repeated six times. The ion-exchanged zeolites were washed with deionized water and dried at 383 K for 12 h. The degree of ion exchange was estimated by flame photometry and atomic absorption spectroscopy and the percentage of exchange was found to be Cs 52%, K 88%, and Li 75%. XRD revealed that all the alkali (Cs, K, Li) loaded silica samples were amorphous.

## 2.2. Typical reaction procedure for Michael addition

A mixture of 4-hydroxy cyclopentenone (98 mg, 1 mmol), 2-hydroxy-3-(1-naphthoxy)-1-propanethiol (468 mg, 2 mmol) and Li-X-zeolite (20 mg, 20 wt.% of enone) in dry chloroform was stirred at 0 °C under inert atmosphere for 1 h. Stirring was continued further at room temperature until the completion of the reaction (monitored by TLC). The zeolite was filtered off and washed with chloroform (5 ml). Removal of the solvent followed by chromatographic purification on a column of silica gel using petroleum ether–ethyl acetate as eluent afforded the pure product in 80% yield. It was observed that methanol was the solvent of choice for entries no. 1–4 in the Table 2 while for rest of the examples chloroform gave better results.

## 2.3. Typical procedure for the preparation of 1-mercapto-3-(naphthalen-1-yloxy)-propan-2-ol

(a) Preparation of 2-(naphthalen-1-yloxymethyl)-oxirane: A mixture of 1-naphthol (14.4 g, 0.1 mol), epichlorohydrin (100 ml) and potassium carbonate (27.6 g, 0.2 mol) in presence of catalytic amount of tetra-n-butyl ammonium bromide (0.312 g, 0.001 mol) was refluxed for 15 h (TLC analysis indicated completion of reaction). The excess of epichlorohydrin was removed under reduced pressure; the residue was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 ml  $\times$  100 ml). The organic layer was washed with dilute sodium hydroxide solution followed by water and brine, dried over sodium sulfate and concentrated under reduced pressure to give the 2-(naphthalen-1-yloxymethyl)-oxirane (18.8 g, 90%).

(b) The mixture of 2-(naphthalen-1-yloxymethyl)-oxirane (3.03 g, 0.015 mol) and sodium hydrosulfide (1.5 g, 0.027 mol) in methanolic carbon disulfide (10 ml) was stirred at room temperature for 8 h (TLC analysis showed completion of reaction). The reaction mixture was then

acidified and extracted with ethyl acetate (3 ml  $\times$  25 ml), organic layer washed with water followed by brine, dried over sodium sulfate, concentrated under reduced pressure and purified by column to give the 1-mercapto-3-(naphthalen-1-yloxy)-propan-2-ol (2.80 g, 80%).

## 2.4. Preparation of thiaprostaglandins

### 2.4.1. General procedure for Michael addition

To a mixture of enone **22** (0.5 mmol) and thiol (0.5 mmol) in dry chloroform (1 ml) at 0 °C under argon atmosphere was added lithium-X-type zeolite (20 wt.% of enone) and stirred at 0 °C for 2 h. The reaction mixture was then brought to room temperature and stirred for 24 h (reaction progress was monitored by TLC). Catalyst was filtered off and washed with chloroform (2 ml). Organic layer was washed with water followed by brine, dried and concentrated under reduced pressure. Column chromatography on silica gel afforded the corresponding novel thiaprostaglandins **23–25** which were characterized by IR, NMR and mass spectral data.

### 2.4.2. General procedure for sodium borohydride reduction of thiaprostaglandins

Thiaprostaglandins **23–25** (0.25 mmol) in dry methanol (10 ml) were treated with excess sodium borohydride (2.5 mmol) at –20 °C for 2 h after which the reaction was quenched with water and the product was extracted with ethyl acetate. Chromatographic purification afforded the novel thiaprostaglandins **26–28** in almost quantitative yields.

## 3. Results and discussion

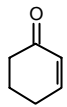
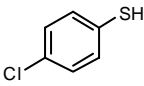
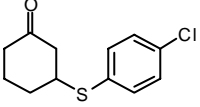
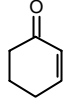
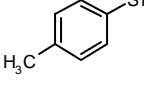
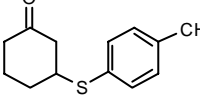
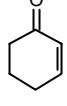
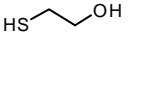
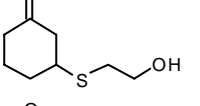
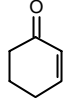
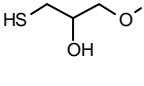
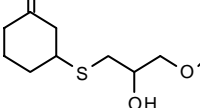
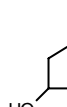
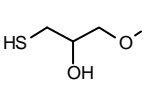
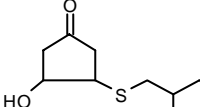
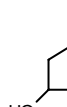
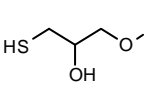
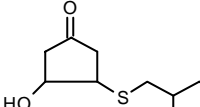
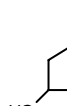
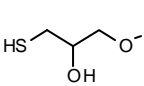
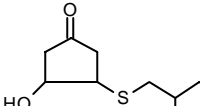

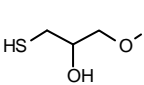
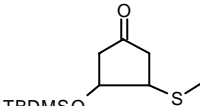

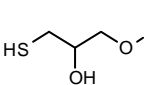
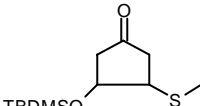

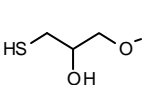
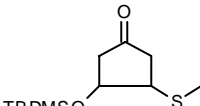
The X-type zeolites incorporated with lithium, potassium or cesium were employed for the preparation of 3-sulfanyl cyclic ketones from the corresponding  $\alpha,\beta$ -unsaturated ketones. We studied the 1,4 addition of 1-mercapto-3-(naphthalen-1-yloxy)-propan-2-ol with cyclohexenone (Scheme 2) in dry methanol under argon atmosphere using KX, LiX and CsX zeolite catalysts. The results obtained are displayed in Table 1.

Though there was not much difference in yield, when reaction was carried out with LiX catalyst there was no formation of disulfide (Scheme 2, B). In most of the substrates used, the disulfides and Michael addition products had very close *r<sub>f</sub>* values and the separation was tedious therefore it was necessary to avoid the formation of disulfide. Consequently

Table 1

Entry no.	Catalyst used	Percentage of Product A in Scheme 2	Percentage of Product B in Scheme 2
1	KX	69	11
2	LiX	75	Nil
3	CsX	71	7

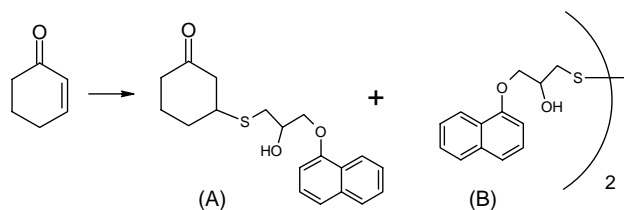
Table 2  
Li–X-zeolite mediated 1,4-addition of thiols to cyclic enones

Entry no.	Enone	Thiol	Product <sup>a</sup>	Yield <sup>b</sup>
1	 <b>3</b>	 <b>6</b>	 <b>12</b>	<b>82</b>
2	 <b>3</b>	 <b>7</b>	 <b>13</b>	<b>81</b>
3	 <b>3</b>	 <b>8</b>	 <b>14</b>	<b>71</b>
4	 <b>3</b>	 <b>9</b>	 <b>15</b>	<b>75</b>
5	 <b>4</b>	 <b>9</b>	 <b>16</b>	<b>80</b>
6	 <b>4</b>	 <b>10</b>	 <b>17</b>	<b>79</b>
7	 <b>4</b>	 <b>11</b>	 <b>18</b>	<b>78</b>
8	 <b>5</b>	 <b>9</b>	 <b>19</b>	<b>65</b>
9	 <b>5</b>	 <b>10</b>	 <b>20</b>	<b>65</b>
10	 <b>5</b>	 <b>11</b>	 <b>21</b>	<b>63</b>

R<sup>3</sup>: 1-naphthyl, R<sup>4</sup>: 2-naphthyl, R<sup>5</sup>: 4-methoxyphenyl.

<sup>a</sup> Reaction time was 20–24 h, all products were characterized by IR, <sup>1</sup>H NMR and mass spectral data.

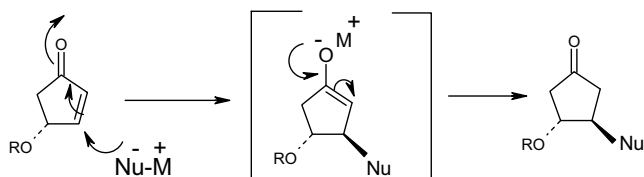
<sup>b</sup> Isolated products.



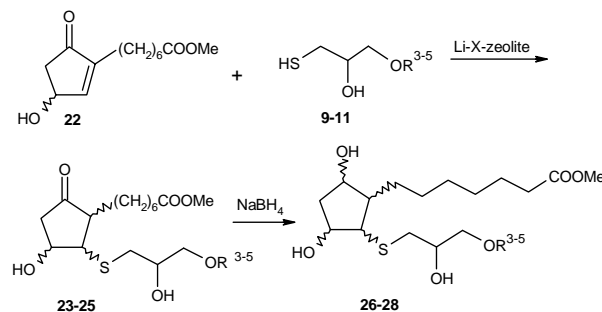
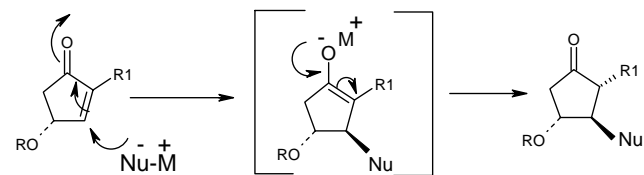
Scheme 2.

Li-X zeolite was selected as the catalyst of choice for further studies.

Substituted 3-aryloxy-2-hydroxy-1-propanethiols (compounds **9–11**) were prepared from the corresponding phenols or naphthols. The phenols or naphthols were treated with epichlorohydrin in presence of potassium carbonate and tetra-*n*-butyl ammonium bromide to obtain epoxy ethers which on nucleophilic opening with sodium hydrosulfide in methanolic carbon disulfide, followed by acidification provided the corresponding thiols **9–11** in 70–85% yields. Presumably, the basic oxygen of the zeolite abstracts proton from the thiol and the resultant anion adds in 1,4-fashion to the enone which acts as the Michael acceptor. The enolate thus formed (Scheme 3) is stabilized by the metal incorporated in the zeolite. It was observed that the selectivity for 1,4-addition and minimization of competing reactions (e.g., disulfide formation) were best achieved with lithium-incorporated zeolite. Table 2 shows the results obtained in the Michael addition of various thiols to cyclic enones. The reaction proceeded with selectivity for thioether formation in presence of free hydroxy group in the thiols used (entries 5–7 in Table 2). It is well known [13] that 1,4-addition on optically active 4-hydroxy-2-cyclopentenone provides *trans* addition product (Scheme 3) depending on the asymmetry of the starting material. However the present study deals with the role of zeolite catalyst in this reaction in the absence of any base. Therefore racemic starting materials (enones as Michael acceptor) were used which would lead to the mixture of diastereomers. This methodology was applied for the synthesis of 13-thiaprostaglandins, which involved 1,4-addition of the appropriately substituted thiols to 2-substituted-4-hydroxycyclopentenone as shown in Scheme 4. Michael addition of 2-substituted 4-hydroxy-cyclopentenone is known to lead to rearranged product under basic conditions [4]. However, Li-X-type zeolite catalyst gave Michael addition product and formation of such rearranged product could be avoided.



Scheme 3.



(mixture of stereoisomers) (mixture of stereoisomers)

**23:** R<sup>3</sup>= 1-naphthyl  
**24:** R<sup>4</sup>= 2-naphthyl  
**25:** R<sup>5</sup>= 4-methoxyphenyl  
**26:** R<sup>3</sup>= 1-naphthyl  
**27:** R<sup>4</sup>= 2-naphthyl  
**28:** R<sup>5</sup>= 4-methoxyphenyl

Scheme 4.

The required enone **22** (Scheme 4) was prepared from methyl 8-oxooctanoate as reported in literature [14–16]. Michael addition of thiols **9–11** to enone **22** resulted in formation of 13-thiaprostaglandins **23–25** (60–80% yields). Ketone functionality in these thiaprostaglandins (**23–25**) was reduced with sodium borohydride to yield the corresponding hydroxy derivatives **26–28** in almost quantitative yields.

#### 4. Conclusion

Thus in conclusion, we have demonstrated that lithium incorporated X-type zeolite catalyst (basic in nature) provides mild conditions for the Michael addition of cyclic enones with variety of substituted thiols which minimizes the side reactions such as dimerization of thiols or rearrangements. Further application of this catalyst for the synthesis of 13-thiaprostaglandins which have potential biological activity was also demonstrated with efficiency and selectivity. Use of Li-X type zeolite in Michael addition leading to important class of biologically active molecules is noteworthy as it brings all advantages of heterogeneous catalysis such as mild conditions, ease of work-up as well as separation, recycling of the catalyst, non-toxic, inexpensive and environmentally-friendly conditions. This protocol offers an alternative to the routine basic reaction conditions.

#### Acknowledgements

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