ABSTRACT

Zeolite catalyzed reactions in organic chemistry have been attracting considerable attention in recent years. The unique features of zeolite catalysts are acidity, shape-selectivity and thermal stability.

This thesis describes the zeolite catalyzed condensation of carbonimidodithioates with various active methylene compounds resulting in the synthesis of push-pull ethylene systems. This includes a totally new synthesis of 1-methylamino-1-methylthio-2-nitroethylene, a crucial intermediate for the antiulcer drug Ranitidine. This thesis also describes a novel route for the preparation of N-nitroacetyl aminoacid derivatives which are potential intermediates for the synthesis of dipeptides. Finally, zeolite catalyzed conversion of carbonimidodithioates of various primary amines and aminoacid derivatives to the corresponding S-methyl thiocarbamates has also been described.

The thesis has been divided into five chapters as follows:

Chapter-1: Introduction to zeolites and their importance in organic chemistry:

Zeolites are aluminosilicates with highly ordered crystalline structure. The use of zeolites as catalysts for industrial purpose began at the beginning of the 1960s and slowly they gained importance in synthetic organic chemistry. The combination of acidity and shape selectivity of the zeolite catalyst is an important factor for this purpose. In recent years the tendency to utilize this potential for highly selective synthesis in the field of intermediates and fine chemicals has increased enormously. Substitution reactions of aromatic as well as aliphatic moieties, addition and elimination reactions, oxidation, reduction, isomerization, etc. have been reported with the aid of zeolites.

In this chapter a brief review of some of the important reactions catalyzed by zeolites is presented.
Chapter-2: Synthesis of 1-methylamino-1-methylthio-2-nitroethylene and the kinetics of this reaction:

1-Methylamino-1-methylthio-2-nitroethylene (2) is a crucial intermediate for the synthesis of the antiulcer drug Ranitidine. The reported methods for the synthesis of this molecule are the following: a) Reaction of methylamine with 1,1-bismethylthio-2-nitroethylene. b) Reaction of nitromethane with methylisothiocyanate followed by methylation. Both these processes suffer from serious drawbacks such as hazardous reaction conditions, formation of unwanted byproducts, use of solvents such as DMSO etc.

A new method has now been developed by us\(^2\) for the synthesis of 2 which offers several advantages. The method involves the condensation of dimethyl N-methyl carbonimidodithioate (1) with nitromethane in presence of a zeolite to give the required compound 2, in good yields (Scheme I).

To optimize the yields and the reaction efficiency, various parameters in this reaction have been systematically studied. These include variation in reaction temperature, duration of the reaction, molar ratio of the reactants, catalyst concentration etc. The effect of different zeolites and clays on the product yield has also been studied.

Scheme I
Chapter-3: Scope of zeolite catalysis: Synthesis of push-pull ethylene systems:

Push-pull ethylene systems including functionalized ketene S,N-acetals and nitroenamines have been well studied both for their intrinsic properties and also as intermediates for the synthesis of other molecules. In such push-pull compounds one end of the double bond is attached to an electron withdrawing group and the other end to an electron donating group. Consequently there is a delocalization of electrons over the entire push-pull system.

Scheme II

Scheme III

The new method described in chapter 2 for the synthesis of 1-methylamino-1-methylthio-2-nitroethylene has been successfully extended for the synthesis of functionalized
ketene S,N-acetals. The method involves the condensation of carbonimidodithioates (Ia-d) derived from different amines with various active methylene compounds (3-6) in presence of zeolite catalysts. The successful products are shown in scheme II and scheme III.

Chapter-4: A new approach to N-nitroacetyl derivatives of aminoacid esters:

The nitroacetyl group is an attractive synthon for peptide synthesis, especially for those involving unnatural α-alkyl and α,α-dialkyl glycine derivatives.

Recently a method for the preparation of N-nitroacetyl derivatives of aminoacid esters has been developed in our group and used for the synthesis of a variety of dipeptides. The method consists in treating 1,1-bismethylthio-2-nitroethylene with aminoacid esters and hydrolysing the enol-thioether under Hg\textsuperscript{2+} catalysis.

A different method has now been developed for the synthesis of such nitroacetamides under mild conditions using zeolite catalysts. This method is discussed in this chapter. The aminoacid methyl esters (7a-c) are treated with carbondisulfide in presence of triethylamine as base followed by methylation to give the corresponding carbonimidodithioates (8a-c). These on reaction with nitromethane in presence of a zeolite lead to the 1-methylthio-1-substituted amino-2-nitroethylene 9. Hg\textsuperscript{2+} mediated hydrolysis of these compounds gives the required nitroacetyl derivatives of amino acid esters 10a-c (Scheme IV).

The scheme has been extended to the β-alanine derivative 8d. The scope of this reaction has been explored. The valine derivative 8e does not give rise to the required product probably because the pore size of zeolite cannot accommodate the isopropyl group of valine.

During the course of this study we have come across an interesting self condensation of the carbonimidodithioate derived from glycine methyl ester. The product has been shown to have the structure II.
Scheme IV

\[
\begin{align*}
\text{R} & = \text{a, H} ; \text{b, -CH}_3 ; \text{c, -CH}_2-\text{Ph} \\

\text{H}_3\text{CO}_2\text{C} - \text{NH}_2 + \text{CS}_2 & \xrightarrow{1) \text{Et}_3\text{N}/\text{CHCl}_3} \xrightarrow{2) \text{CH}_3\text{I}} \text{H}_3\text{CO}_2\text{C} - \text{NH}_3\text{SCH}_3 \\
\text{H}_3\text{CO}_2\text{C} - \text{NO}_2 & \xrightarrow{\text{Hg}^{+2}} \text{H}_3\text{CO}_2\text{C} - \text{NH}_3\text{SCH} = \text{CH}_2\text{NO}_2
\end{align*}
\]
Chapter-5: A novel synthesis of S-methyl thiolcarbamates using zeolite catalysts.

There are very few general methods available for the preparation of S-methyl thiolcarbamates. In two recent processes carbon monoxide acts as the source of the carbonyl group of S-alkyl thiolcarbamates. The first is the selenium-catalyzed reaction of amines with carbon monoxide and elemental sulfur, followed by alkylation. Very recently N,N-dialkylcarbamoyl lithium, generated from dialkylamide and carbon monoxide, has been reacted with elemental sulfur and then alkylated to produce the desired S-alkyl thiolcarbamates. Although the yields are good with secondary amines, the only primary amine tried, gave a complex mixture in this reaction.

The method which we have now developed for the synthesis of S-alkyl thiolcarbamates from primary amines has several advantages. It involves the zeolite catalyzed conversion of carbonimidodithioates of various primary amines and aminoacid derivatives to corresponding N-substituted S-methyl thiolcarbamates as shown in scheme V.

Scheme V

![Scheme V]

R —N

\[ \begin{align*}
R-N &\rightarrow R-NH-C-SCH_3 \\
\text{R — N =} & \quad \text{METHYLAMINE, n-PROPYL AMINE, CYCLOHEXYLAMINE, BENZYL AMINE, GLYCINE METHYL ESTER, ALANINE METHYL ESTER, VALINE METHYL ESTER, PHENYLALANINE METHYL ESTER} 
\end{align*} \]
References:


