RESEARCH PLAN PROPOSAL

"Michael Addition of some amines"

For registration to the degree of

Doctor of Philosophy

IN THE FACULTY OF SCIENCE

THE IIS UNIVERSITY, JAIPUR

Submitted by

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Enroll No. ICG/2011/13001

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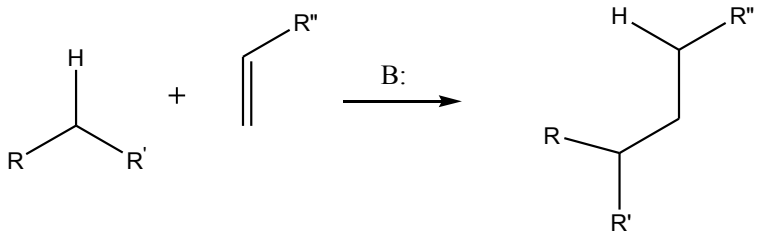
July, 2012

1. Introduction and Background information

The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile[1,2,3] to an α,β-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C-C and other such bonds[4]. Many asymmetric variants exist[5,6].



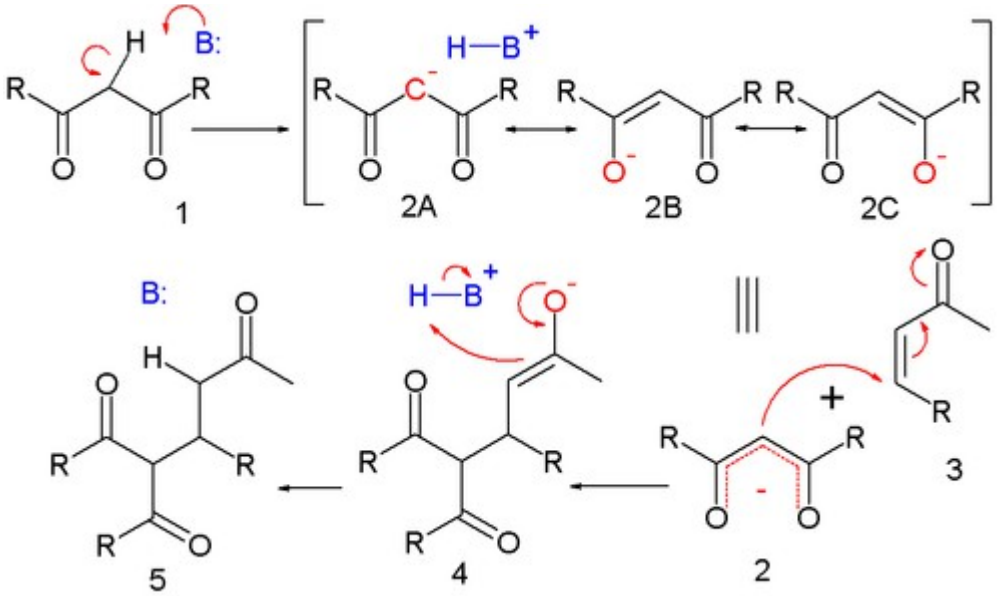
R" = CO, CN, NO_2 group etc.

Scheme 1: Michael addition reaction

In this scheme, the R and R' substituents on the nucleophile (a **Michael donor**) are electron-withdrawing groups such as acyl and cyano making the methylene hydrogen acidic forming the carbanion on reaction with a base **B:**. The substituent on the activated alkene, also called a **Michael acceptor**, is usually a ketone making it an enone, but it can also be a nitro or cyano group.

As originally defined by Arthur Michael,[7,8] the reaction is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon. A newer definition, proposed by Kohler[9] is the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. The Michael addition is an important atom-economical method for diastereoselective and enantioselective C-C bond formation. Subsequently the scope of the Michael addition has been further enlarged by including other nucleophiles, such as amine, amides, etc as Michael donors. **Thus Michael addition can be defined as 1,4-addition of a nucleophile to an activated alkene.**

The reaction mechanism is shown in scheme 2 (with R an alkoxy residue):



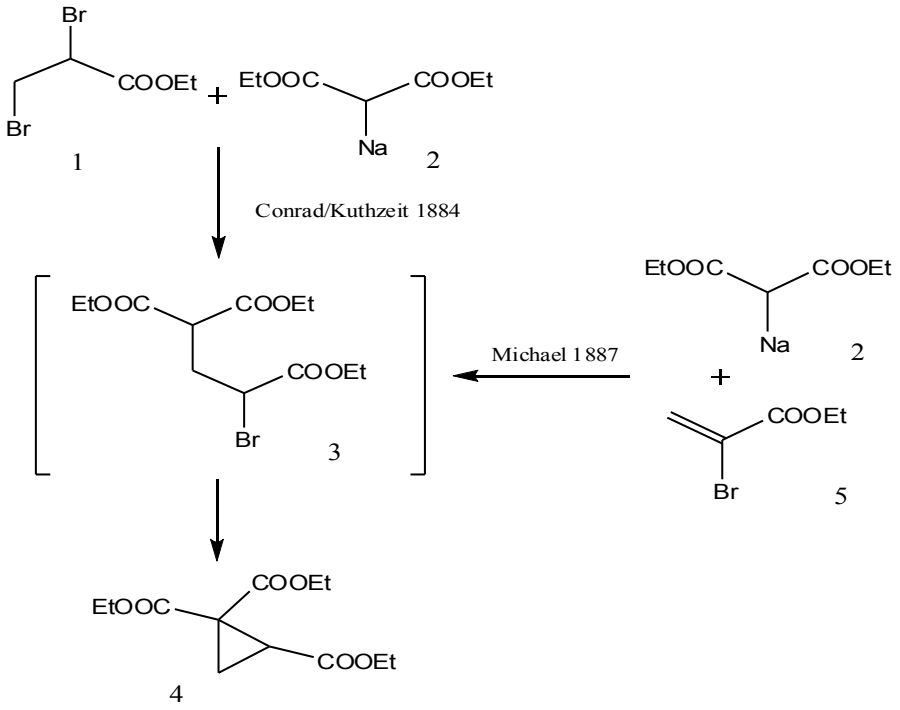
Scheme 2: Mechanism of Michael addition

Deprotonation of **1** by base leads to carbanion **2** stabilized by its electron-withdrawing groups. Structures 2A to 2C are three resonance structures that can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic alkene **3** to form **4** in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate **4** to **5** is the final step.

2. Review of Literature

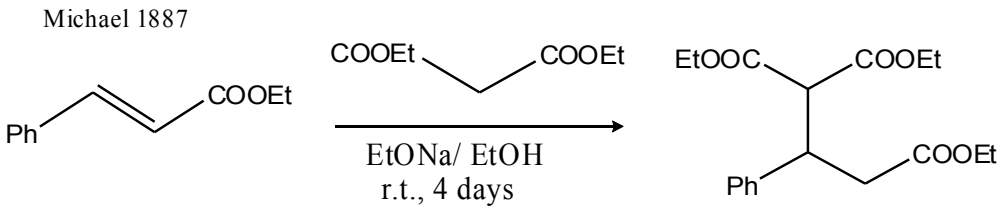
Over the years, the scope of Michael reaction has increased dramatically to include a broad range of acceptors and the Michael-type additions of non-carbon donors.

The research done by Arthur Michael in 1887 was prompted by an 1884 publication by Conrad & Kuthzeit on the reaction of ethyl *2,3-dibromopropionate* with *diethyl sodiomalonate* forming a[cyclopropane](#) derivative[10] (now recognized as involving two successive substitution reactions).



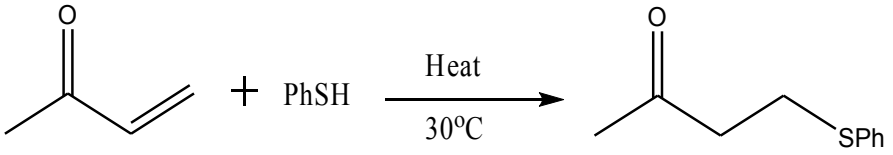
Scheme 3

Michael was able to obtain the same product by replacing the propionate by *2-bromacrylic acid ethylester* and realized that this reaction could only work by assuming an addition reaction to the double bond of the [acrylic acid](#). He then confirmed this assumption by reacting [diethyl malonate](#) and the ethyl ester of [cinnamic acid](#) forming the very first Michael adduct[11].



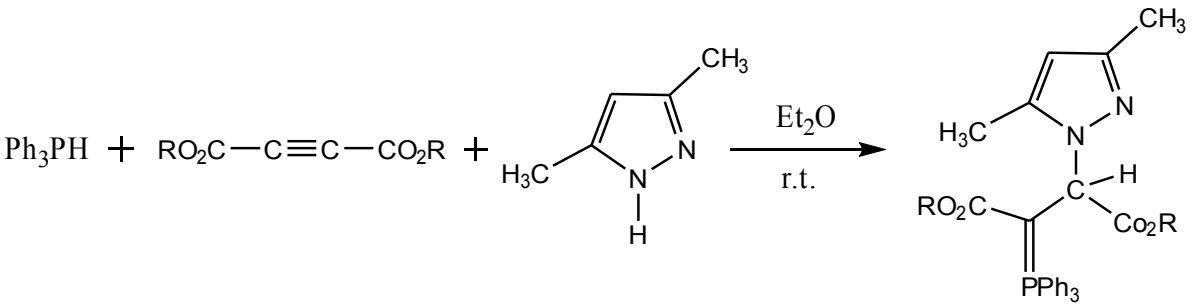
Scheme 4

A simple and efficient protocol has been introduced for the Michael addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions without the use of a catalyst[12].



Scheme 5

Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reactions between triphenylphosphine and dialkylacetylene dicarboxylates in the presence of an NH-acid, such as 3,5-dimethylpyrazole[13].



Scheme 6

A series of secondary amine-thiourea catalysts derived from L-proline and chiral diamine were prepared and successfully applied to the Michael addition of acetone to *trans*-nitroalkenes in excellent yields (up to 99%) and enantioselectivities (44-91% ee)[14].

Conjugate addition of 2-(bromomethyl)- and 2-(2-bromoethyl)piperidinehydrobromide to methyl and ethyl acrylate in the presence of triethylamine afforded the corresponding 3-[2-(bromomethyl)piperidin-1-yl]propanoates and 3-[2-(2-bromoethyl)piperidin-1-yl]propanoates for the first time. Furthermore, methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate was converted into the novel 2-(methoxycarbonyl)indolizidine upon treatment with lithium diisopropylamide in THF. The latter ester was easily reduced by means of lithium aluminium hydride in diethyl ether, affording 2-(hydroxymethyl)indolizidine in high yield[15].

Several primary and secondary amines were added to α,β-unsaturated esters, nitriles, amides and ketones to give the corresponding saturated amines mediated by solid lithium perchlorate under solvent free and environmentally friendly conditions at room temperature[16].

3. Objectives

- Michael addition reaction of secondary amines with Maleic anhydride and similar compounds.
- Michael addition reaction of primary amines with Maleic anhydride and similar compounds.
- Stereoselective Michael addition of amines to Maleic anhydride and similar compounds.
- To establish the structures and properties of the above compounds using NMR, IR and X-Ray Crystallography.
- To investigate theoretically the mechanism of the reaction and determine order of reactivity of various amines.

4. Significance

The aza-Michal addition is one of the widely used reactions for carbon-nitrogen bond formation[17]. Conjugate reaction of various amines with α,β-unsaturated carbonyl compounds provides β-amino carbonyls, which are useful synthons for the preparation of several nitrogen containing bioactive natural products[18], antibiotics[19], and chiral auxiliaries[20].

Michael addition is the first step for preparing dendrimers by divergent methods. So, we can also prepare some phosphorus-containing dendrimers through further reactions of these Michael addition products.

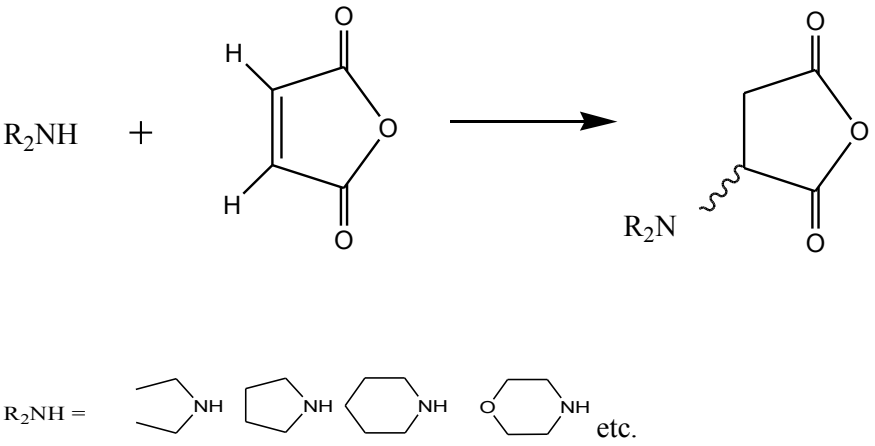
5. Hypothesis

The whole problem is based on Michael addition which is a 1,4-addition of the nucleophile to an activated alkene.

6. Plan of work and Methodology

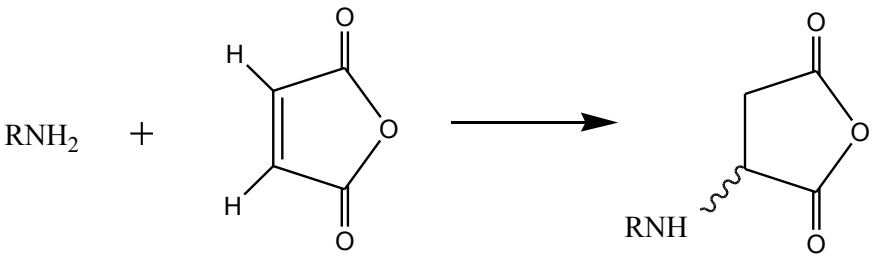
6.1 Proposed work

6.1.1 Michael addition of secondary amines with maleic anhydride and similar compounds[21,22]



Scheme 7

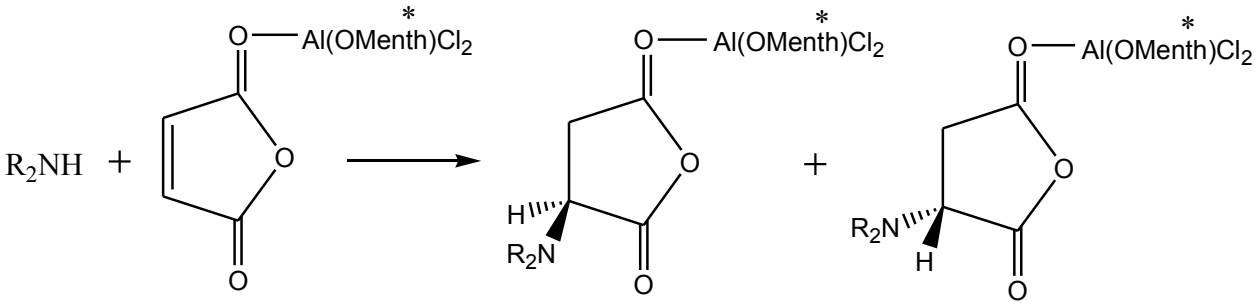
6.1.2 Michael addition reaction of primary amine with Maleic anhydride[21,22]



R1=C_6H_5-CH_2-, C_6H_5-, p-Cl-C_6H_5-, p-Cl-C_6H_5-CH_2-, p-CH_3-C_6H_5-, p-MeO-C_6H_5- etc.

Scheme 8

6.1.3 Stereoselective Michael addition of amines to maleic anhydride and similar compounds



Scheme 9

6.2 Methodology

Michael addition: The procedure described in the paper Janck Peterson; Arkadi Ebber; Veiko Allikmaa and Morgns Lopp, *Proc. Estonian Acad. Sci. chem*., **2001**, *50*, 3,156-166 will be followed.

7. Year- wise plan of work and targets to be achieved

- **First year-** Michael addition reaction of secondary and primary amines with Maleic anhydride and similar compounds.
- **Second year –** Stereoselective Michael addition of amines to Maleic anhydride and similar compounds.
- **Third year –** Consolidation, compilation and the publication of above results.

8. Place of Work and Facilities available

Department of chemistry, IIS University, Jaipur. A modern laboratory modestly equipped with instruments is available.

9. Limitation and Alternative Plan of Study

The non-availability of multinuclear NMR spectrometer is the main limitation. We shall try to take the help of the other institutions where this instrument is available.

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