

Asymmetric michael adducts as key building blocks for synthesis of bioactive molecules

Abstract

A over view of the synthesis of enantiopure bioactive molecules such as, Nepetalactol, isofebrifugine, (R)-Montelukast, phosphanyl amino acids and (S)-Pregabalin are efficiently synthesized from common intermediate as Michael adducts by various types of Michael addition reaction and further Michael adduct are potentially leading towards the synthesis of varieties bioactive molecules.

Keywords: michael addition, thio michael addition, aza-michael addition, oxo-michael, phosphate michael addition

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Introduction

Michael reaction involves the addition of a nucleophiles (also known as donor, which can be C and heteroatom i.e. O, S, P, N) on alkenes, or alkynes attached to electron withdrawing groups (also known as acceptor).¹ The conjugate addition of carbon nucleophiles to α, β unsaturated compounds is an important C-C-bond formation reaction.² This transformation shows a broad scope due to the large variety of acceptors (α, β -unsaturated aldehydes, esters, ketones, phosphonates, sulfones, cyanoester thioesters and nitrostyrenes) and nucleophiles (organometallic reagents, Michael donors, other carbanions).³

The carbon centered nucleophilic addition may take place in

enantioselective or non-enantioselective manner. As result the increase the demand for optically active compounds in the recent years, tremendous progress has been made in the field of asymmetric version of reaction, providing the Michael adduct having high enantiomeric purity. The asymmetric Michael reaction could be categorized in three categories:

- Asymmetric addition of prochiral donor compounds to acceptor;
- Asymmetric addition of a donor to a prochiral acceptor compounds;
- Asymmetric addition of enantioselective as well as distereoselective addition of prochiral donor to prochiral acceptor in Figure 1.

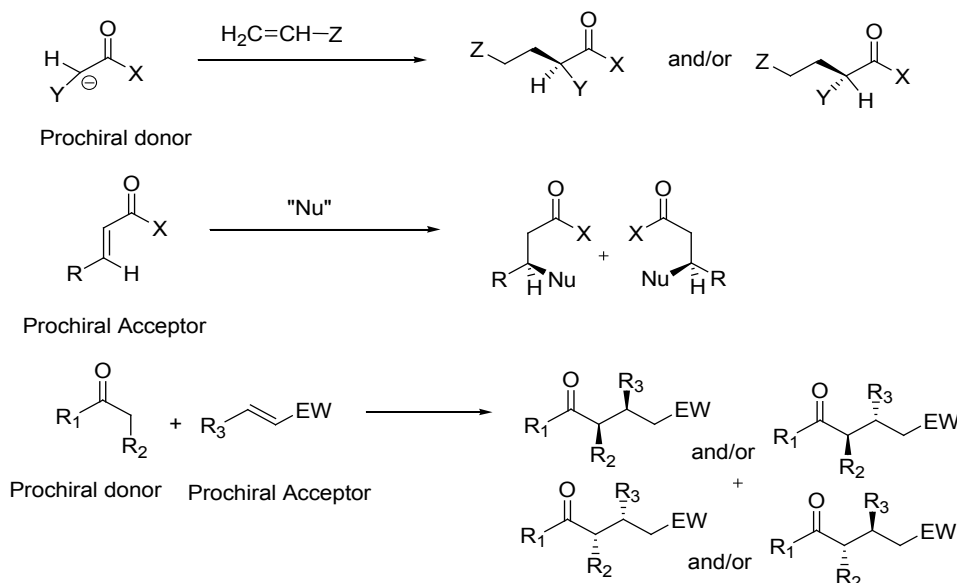


Figure 1 Asymmetric michael addition reaction.

Enantioselective synthesis, also called chiral synthesis or asymmetric synthesis, in the form of many of the building blocks in biological systems, such as sugars, lipids, nucleotides and amino acids are the major biochemical compounds essential for normal functioning of the human organism.⁴ The Michael adducts can bear a single substituent or dual substituents adjacent to the carbonyl. The Michael adducts can be efficiently converted to cyclically constrained protected compounds, which are essential for systematic conformational studies of cyclic compound. Despite that now a day's variety methods for the asymmetric synthesis of sulphur⁵ and phosphates derivatives.⁶

In the recent years, Michael addition is one of the powerful and versatile methods for the construction of C-C, C-N, C-S, C-O bond containing enantiomerically pure compounds and has found wide application in the field of both novelty and high selectivity attained by Michael adducts.⁷ Enantioselective synthesis of natural product and drug has gained significant importance because of their interesting pharmacological applications as biological activities as well potent insecticidal properties.⁸

The objective of this review paper is to discuss the asymmetric conjugate addition associated with the various Michael reactions i.e. Michael addition, Thio Michael addition, Aza-Michael addition, Oxo-Michael and Phosphate Michael addition reaction to produce various significant intermediate in the field of organic synthesis, and

shown its relevance in biological activities. Further advantages of this methodology are connected to economy, simplicity and inculcate a new catalyst for various organic transformations.⁹

Types of michael additions

Oxo michael addition¹⁰

Stereoselective synthesis of nepetalactol has been achieved by Oxo-Michael addition is key step. 10-hydroxygeranial 1 is oxidized to 10-Oxogeranial 2 by SeO_2 in DCM. The 10-Oxogeranial 2 which on Iridoid synthesis by NADPH to form enol/enolate intermediate 3, then intermediate 3 on Oxo-Michael addition and terpene cyclization to form open form of iridodial 4 finally tautomerism afford target molecule 5a i.e. Nepetalactol (Figure 2).

Aza-michael reaction¹¹

Isofebrifugine was synthesized from starting material D-mannitol 6. D-mannitol is converted to Michael acceptor intermediate 7. It was then intermediate 7 on intramolecular cyclization under the aza-Michael reaction to form desirable protected cyclic unit 8 of target molecule. The intermediate 8 on bromination followed by coupling with 10 to get protected intermediate 11. The protected intermediate 11 on deprotection using 6N HCl in reflux condition to form febrifugine, febrifugine 12 treated with acidic condition to get desired target molecule i.e. Isofebrifugine 13 (Figure 3).

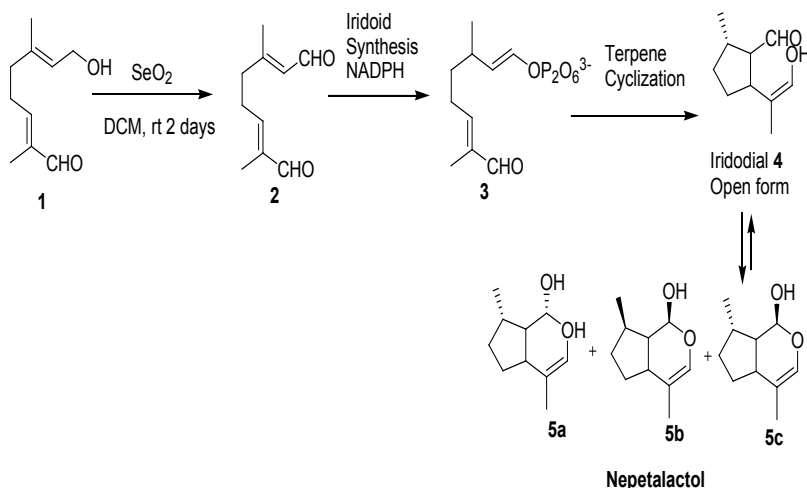


Figure 2 Oxo michael addition.

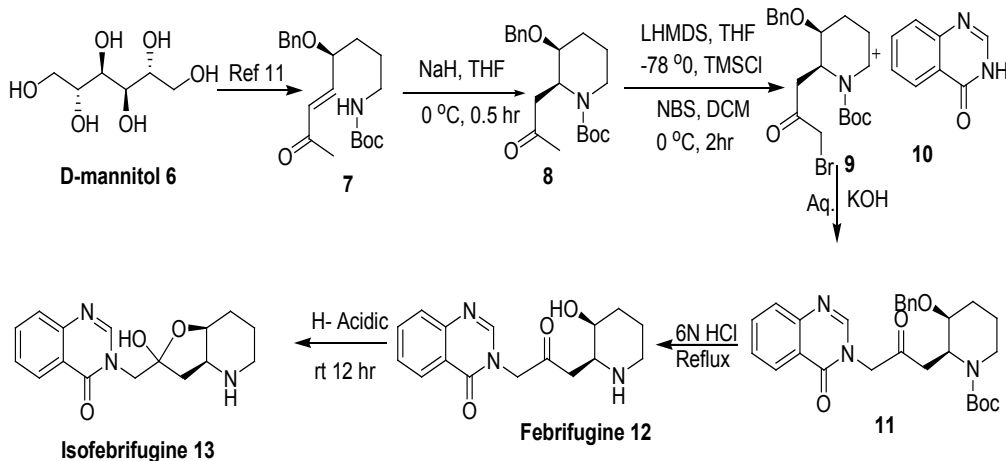


Figure 3 Aza-Michael reaction.

Thio michael addition reaction¹²

The total synthesis of (R)-Montelukast 19 involves asymmetric addition of thiols to α , β -unsaturated ketones is a key step. Michael addition of 1-(mercaptomethyl)cyclopropylacetic acid 15 to substituted chalcone 14 to afford Michael adduct 16, which on condensation with tosylhydrazine followed by reduction with sodium borohydride to obtain sulphide 18. Finally, sulphide 18 on Grignard reaction by addition of methyl magnesium bromide on ester furnished (R)-Montelukast 19. The sulfa-Michael addition reaction on substituted chalcone to form β -thioketones in excellent yield with high enantioselectivity and experimental that probe to the scope of aliphatic and aromatic thiols (Figure 4).

Phosphate michael addition reaction¹³

Enantioselective Michael addition of dialkyl phosphate to provide β -nitro phosphate followed by reduction of nitro group would afford

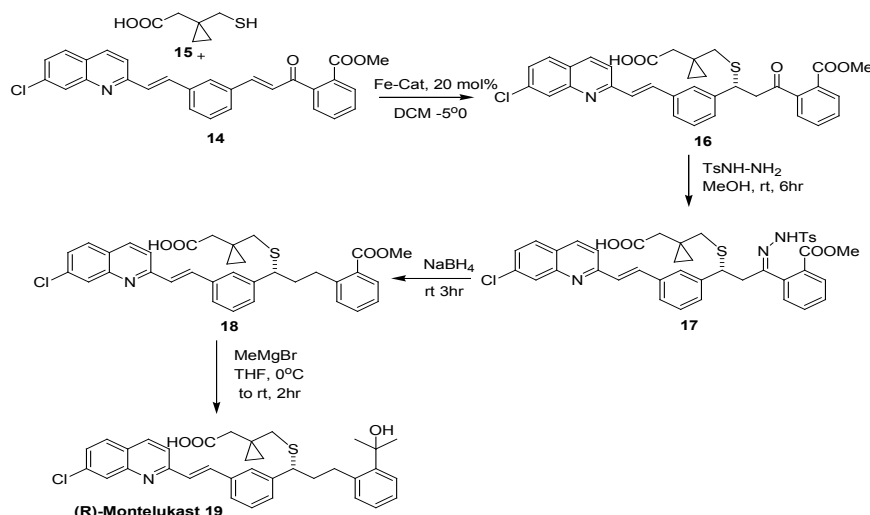


Figure 4 Thio Michael addition reaction.

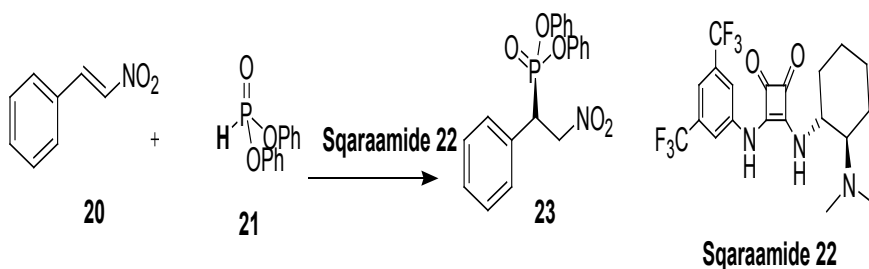


Figure 5 Phosphate Michael addition reaction.

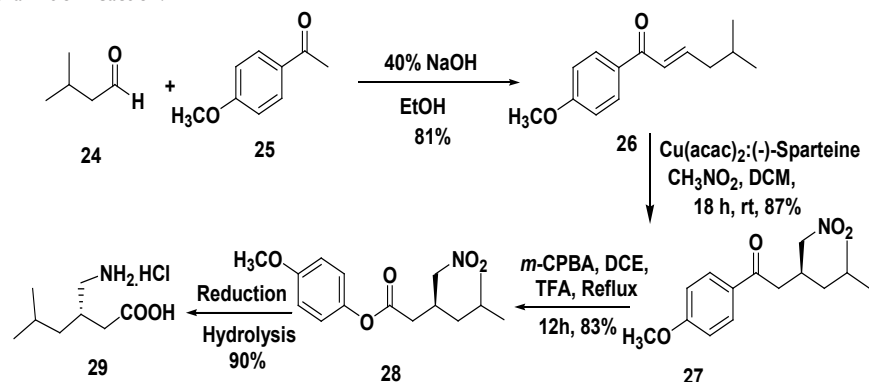


Figure 6 Michael addition reaction.

β -amino phosphate as valuable bioactive molecules. Phosphorus is essential for many reagents in organic synthesis, for ligands of transition metals and for phosphono and phosphanyl amino acids. Certainly represents one of the most versatile and powerful tools for the construction of P-C bonds since many different electrophiles and Phosphorus nucleophiles can be combined with each other (Figure 5).

Michael addition reaction¹⁴

Synthetic strategy for obtaining the (S)(+)-Pregabalin (29) involved asymmetric Michael addition of nitromethane on chalcone to give γ -nitro ketone. Furthermore, in order to complete synthesis of (S)-Pregabalin a further step includes Baeyer-Villiger rearrangement followed by reduction. The reduction of nitro group can be reduced by Parr hydrogenation apparatus, presence of Raney Ni. It resulted in the formation of intermediate amine which subsequently cyclise to generate pyrrolidine moiety and was finally hydrolysed with 5N HCl afforded enantiomerically pure (S)-Pregabalin 29 (Figure 6).

Conclusion

In summary, the asymmetric induction can originate by all types of asymmetric Michael addition reaction to construct the enantiopure key intermediate unit of drug molecule, the importance of key intermediate compounds tremendous progress has been made in the recent years. The class of all enantioselective Michael addition has contributed immensely in stereoselective synthetic methods and valuable synthesized building blocks bearing varieties of biological activities and improved novel asymmetric Michael reactions are applicable for their future in asymmetric synthetic world.

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Conflict of interest

The author declares no conflict of interest.

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