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RECENT ADVANCES AND DIFFERENT APPLICATIONS OF PETASIS-BORON MANNICH REACTION

K. Daware *, S. Jadhav, K. Varma, K. Valve, S. Shinde, V. Pardesi, A. Shelke and T. Lokhande

Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir's Pharmacy College, Panchavati, Nashik - 422003, Maharashtra, India.

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Correspondence to Author:
Dr. Tushar N. Lokhande

Associate Professor,
Department of Pharmaceutical Chemistry, Mahatma Gandhi Vidyamandir's Pharmacy College, Panchavati, Nashik - 422003, Maharashtra, India.

E-mail: tusharlokhande@hotmail.com

ABSTRACT: The Petasis boron-Mannich process, also referred to as the Petasis reaction, combines boronic acid, an amine, and a carbonyl derivative in a multi component coupling process**.** Recent progress on petasis reaction is discussed in this review. The various merits of petasis reaction over the other multi-component coupling reactions are explain here. Noncanonical substrates are used to explore the expansion of a variety of petasis reactions, including two-component, three-component, and four-component reactions, processes, and products**.** In this review, Microwave-assisted reactions are also explored. The optimal conditions are involved in the microwave heating process. The conditions are successfully applied for petasis reaction. Different solvents are used in petasis boron-mannich reactions, such as glycerol and water. Both solvents are suitable for the reaction and give favorable yield. The reactivity along with numerous synthetic applications of the Petasis reaction are given in this review. The natural product synthesis are given by Petasis boron-Mannich reaction in which loline alkaloid and sialic acid synthesis are given.

INTRODUCTION: A multi-component reaction is a chemical transformation that uses three or more starting elements as input to a synthetic product. The advantages of MCRs include the preservation of atom and step economics, shorter reaction times, and the ability to access highly diverse chemical space rapidly and efficiently.[1]

Classification of Multi-component Reactions: The fundamental conceptual issue in developing newer forms of MCR is finding unusual combinations and sequences of elementary chemical reactions under similar conditions.

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Regarding the reversibility of reactions, Ivar Ugi, the pioneer of modern multi-component reaction chemistry, outlines three ideal forms of MCRs. Type I**:** All of the reactions involved are reversible**.** Type II**:** Most reactions are reversible; however, the very last product is fashioned through an irreversible response. Type III**:** All of the reactions are irreversible [2].

History of Multi-component Reactions: For over 150 years, multi-component reactions have been reported**.** History is given below.

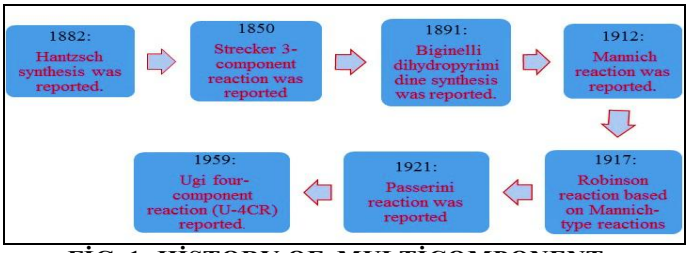
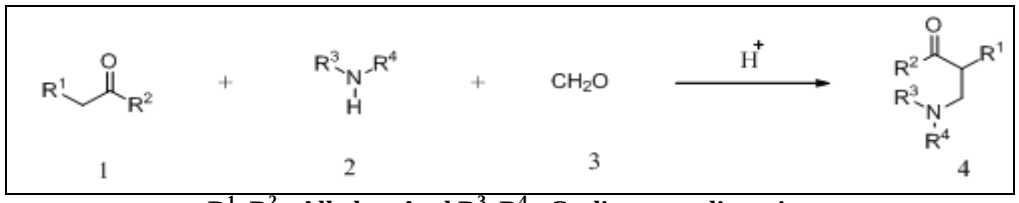


FIG. 1: HISTORY OF MULTICOMPONENT REACTION [3-8]

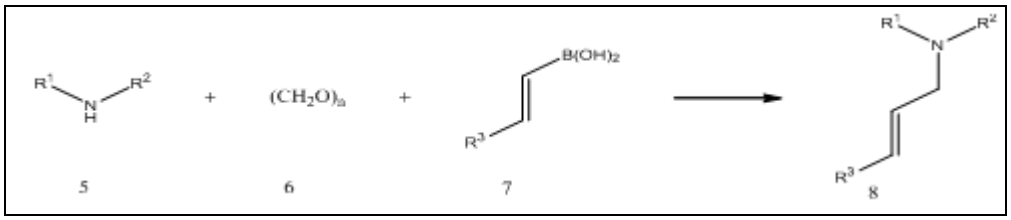
Mannich Reaction: The mannich reaction produces the β-aminocarbonyl 4 molecule indicated in **Scheme 1** by combining an enolizable carbonyl molecule 1 with ammonia 2 and a nonenolizable aldehyde 3. The Mannich reaction forms a carbon-carbon bond, one of the most fundamental and crucial in organic synthesis. Mannich reaction is a large variety of functional groups, and therefore it observes a continuous growth in the field of organic chemistry. The Mannich reactions and their variations offer a vigorous technique for the arrangement of the aminocarbonyl and a few other derivatives [9].



R^1, R^2 =Alkyl or Aryl R^3, R^4 =Cyclic or acyclic amine

SCHEME 1: MANNICH REACTION TO FORM B-AMINO CARBONYL DERIVATIVE

Petasis Reaction: In Mannich-type reactions, the Petasis reaction uses vinyl boronic acids as a nucleophile. Scientists Petasis and Akritopoulou initially described the Boronic acid Mannich reaction in 1993 [7]. An amine 5, an aldehyde 6 and an organoboron component7are involved in the three-component process **Scheme 2**. The reaction allows for the quick synthesis of nitrogen-containing chemicals and it was first employed to generate geometrically pure allylamines.



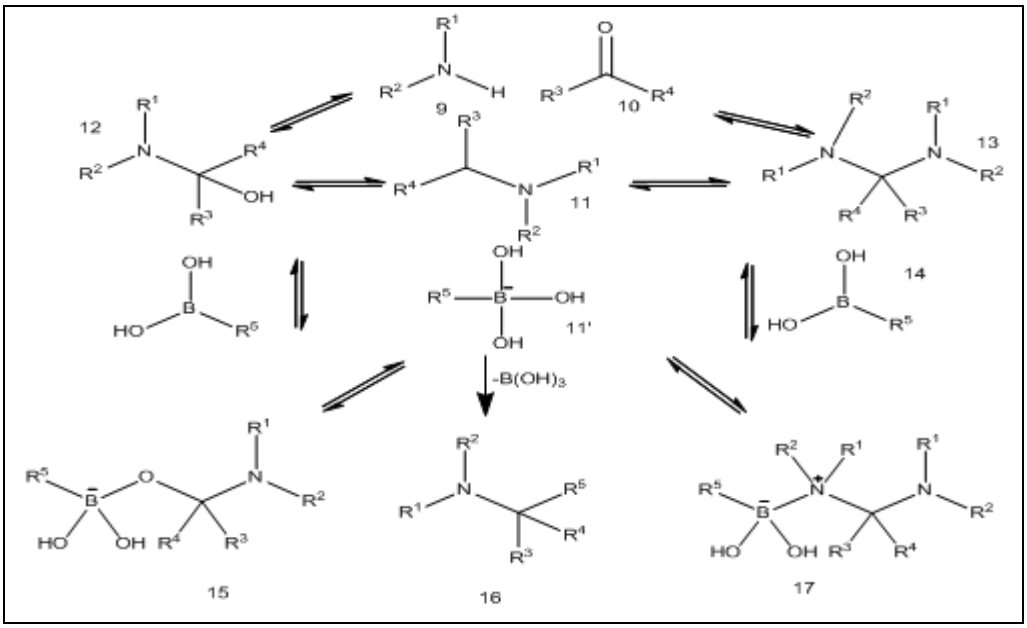
SCHEME 2: INITIAL PETASIS REACTION

Organoboron substances deliver a good choice of nucleophile. Vinyl and aryl boronic acids are commonly used in organic synthesis and have gained popularity through their use in the Suzuki-Miyaura reaction [10].

Development of Petasis Reaction: The term "Petasis" was given to several other revolutions, including the Petasis olefination reaction, which was first described in 1990 [11]. In the year 1962, Ferrier *et al.* gives the formation of Ferrier-Type-I reaction [12]. In 1979, a Ferrier-type II reaction was reported [13]. Researchers Petasis and Lu reported advances to the Ferrier-type-ll reaction in 1995 and 1996 [14]. Minbiole and colleagues described the homo petasis- Ferrier rearrangement in 2005, is a variant of the Petasis-Ferrier rearrangement [15]. In 2009, Rhee and colleagues reported gold catalysis and in-situ vinyl acetal/aminal synthesis as progress in the Petasis-Ferrier rearrangement [11]. In 2014, Terda and coworkers established ring contraction of an acid-catalyzed in the Petasis Ferrier reaction [16].

Mechanism of the Petasis Reaction: The reversible and irreversible phases of the petasis reaction are involved in the reaction's mechanism. The formation of a c-c bond at the α-position, formed by the translocation of the organoboron substance by the electrophilic carbon of the imine or iminium ion, is the irreversible phase of the Petasis reaction [7]. The Petasis reaction**'**s mechanism is unknown**.** It's unknown whether the Petasis reaction's intermediates act as the electrophile**.** According to Petasis, the reaction is characterized by a complex equilibrium between the three starting materials and the several intermediates, and the end product is created by a rate-determining and rate-determining product**.** Hemiaminal 12 is made in the same way that iminium particle 11 and aaminal 13 are made from amine 9 and carbonyl 10. Boronic acid 14 reacts reversibly with hemiaminal 12 and aminal 13 through moderate 15 and 16, forming electrophilic iminium ion 11 again, this time with nucleophilic boronate 11'. It's worth noting that there are no

guarantees that boronic acid alone can react with iminium particles: despite the fact that acid is required to generate a significant amount of iminium salt, it's been demonstrated that vinyl boronic acids does not react with iminium salts when produced.



SCHEME 3: MECHANISM OF PETASIS REACTION

It depends on the permanent movement of the C-C bond between 11 and 11', resulting in the optimal product 17 with the loss of boric acid.

Because the reaction between 11 and 11' is irreversible, all intermediates will eventually lead to the final product, driving the equilibrium of the entire system towards it **Scheme 3.**

The occurrence of a nucleophilic functional group, usually a hydroxyl, at the α-position of the aldehyde facilitates the petasis reaction [17].

Merits of Petasis Reaction over the Other Multi-component Reaction: In comparison to other multi-component reaction petasis reaction have several merits they are describe below [18].

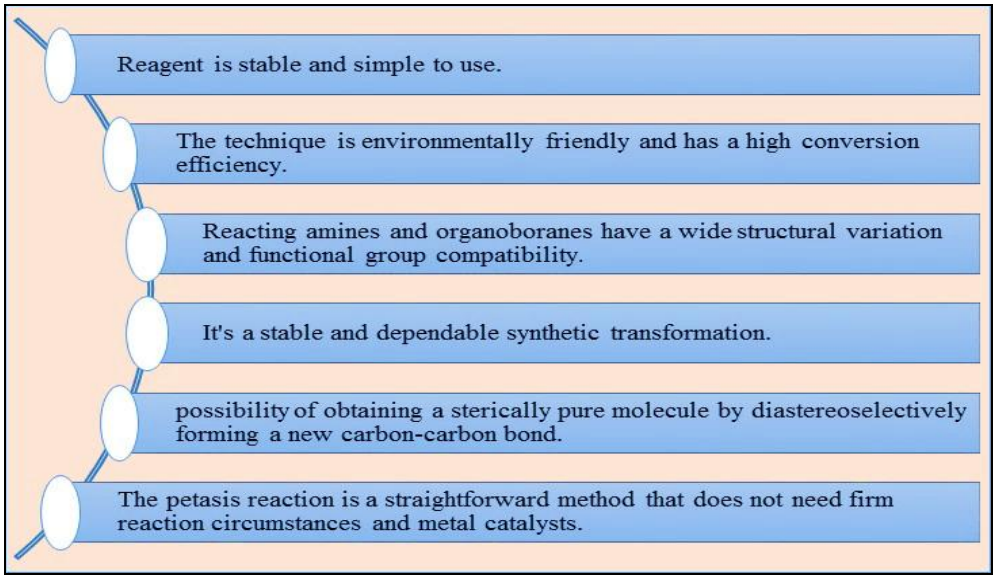
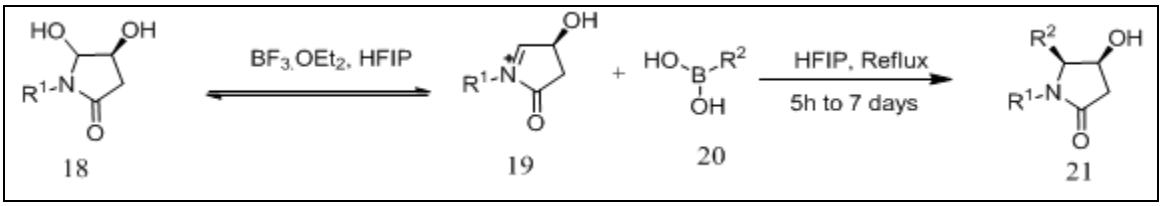


FIG. 2: MERITS OF PETASIS REACTION

Types of Petasis Reaction:

Two-Component Petasis-Type Reactions: The formation of N-substituted β,γ-dihydroxy-γ-lactams, which are employed as precursors to form a cyclic N-acyliminium ion species when boron trifluoride-diethyl ether is utilized, has recently

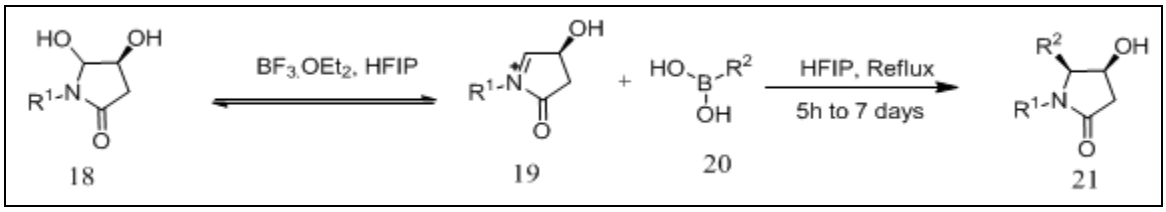
been reported as an effective reductive cyclization technique [19]**.** On several hemi-aminal components, Batey and Pyne conducted preliminary research on cis-diastereoselective additions to cyclic n-acyliminium ions [20, 21]**.** Boronic acids give petasis-like chelation controlled addition, involving the β-hydroxy group 18 to form γ–lactams with high cis-diastereoselectivity under modified reaction conditions hexafluoro-2-propanol **(**HFIP**) Scheme 4.** Direct nucleophilic addition of electron-rich boronic acid, on the other side, results in substituted lactams 21 with low diastereoselectivity [19]**.**



SCHEME 4: TWO COMPONENT PETASIS REACTION: ADDITION TO N-ACYLIMINIUM ION SPECIES FROM DIHYDROXY-Γ-LACTAMS

Three-component Petasis Reaction:

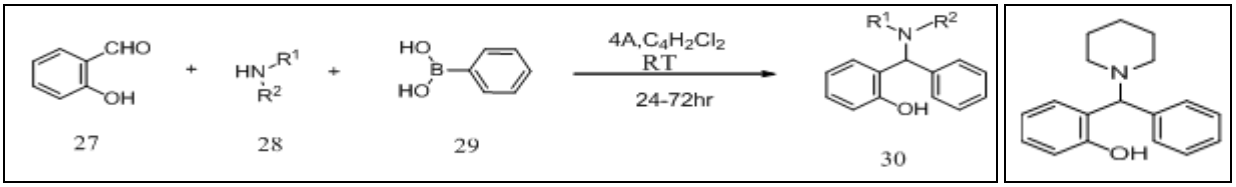
As a Carbonyl Component, Glyoxylic Acid Derivatives: Glyoxylic acid monohydrate is frequently employed in PRs to produce phenylglycine byproducts, acting as tissue factors and factor VIIa inhibitors **(**TFFVIIa**).** A phenylpyrrolidine and phenylglycinamides derivatives were produced and evaluated as TF-FVIIa inhibitors with good oral bioavailability and a favourable *in-vitro activity* for the treatment of thromboembolic disorders**.** Glyoxylic acid 22 Boc-protected 1,6 diaminoisoquinoline 23 and phenylboronic acids 24 were mixed to make phenyl glycines 25 which were subsequently linked to phenyl pyrrolidine 26 to generate a series of TF-FVIIa inhibitors **Scheme 5.** Enantiomerically pure composites were made using chiral separation**.** The carboxypyrrolidine molecule had a new *in-vitro* safety panel against receptors and enzymes and an effective distribution volume and moderate clearance [22].



R = 3-Ethoxy-4-isopropoxy

SCHEME 5: THREE COMPONENT PETASIS REACTION: GLYCOXYLIC ACID AS CARBONYL COMPONENT

As a Carbonyl Component, Salicylaldeyde Derivatives: Petasis reaction involving salicylaldehyde can be used to produce tertiary phenolamines.This product can be synthesized under variety of conditions [23-26]. To remove water molecular sieve (MS) used at room temperature [27-32]. The production of alkylaminophenols30, the reaction between salicylaldehyde [27], secondary amines28 and aryl boronic acid [29] gives moderate to good yield shown in scheme 6 [33].

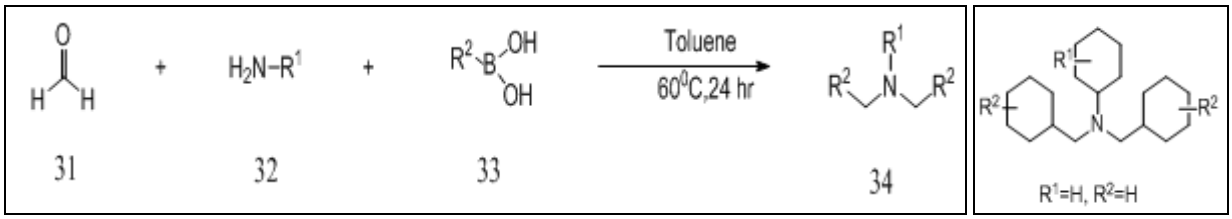


SCHEME 6: THREE COMPONENT PETASIS REACTION: SALICYLALDEHYDE AS CARBONYL COMPONENT

Miscellaneous Carbonyl Components:

Formaldehyde: Through a double PR route, formaldehyde 31 and aromatic amines 32 and boronic acids 33, when reacted it produce aromatic tertiary amines 34. When aniline, formaldehyde, and phenylboronic acid heatedat 60°C in toluene

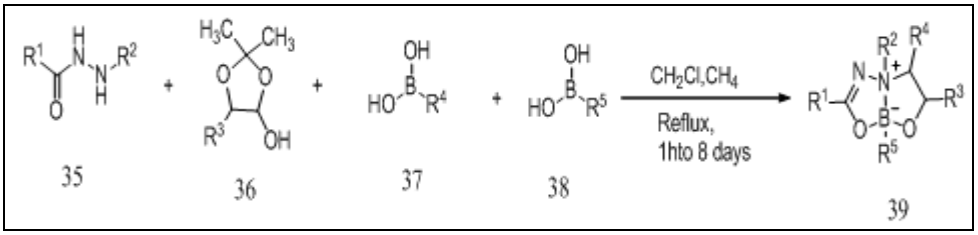
for 24 h, the following chemical was obtained in 89 % yield. The reaction possibilities were investigated using electron-rich and electron-deficient anilines and boronic acids **Scheme 7** [34].

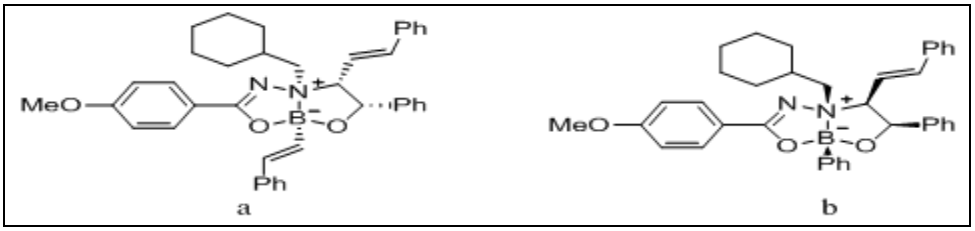


SCHEME 7: THREE COMPONENT PETASIS REACTION: FORMALDEHYDE AS CARBONYL COMPONENT

Four–component Petasis Reaction: In recent years, certain PR deviations with four components have been reported. Four-component PRs can be divided into two groups based on their chemical nature and discovery route. The first category comprises reactions that were originally intended as three-component reactions but have since been expanded to incorporate a fourth boronic acid component. The second category includes replies, in which the fourth component is an unusual PR component. The second category includes replies, in which the fourth component is an atypical PR component.

Boronic Acid as the Fourth Ingredient: A four-component PR was created by adding reactive boronic acids to three-component PR combinations of hydrazides [35], α-hydroxy aldehydes [36,] and boronic acids [37, 38, 35, 36]. The reaction was carried out in a three-component PR step, with the carbon nucleophile being the first, electron-rich and reactive boronic acid, which formed -hydrazido alcohol, which then condensed with the boron molecule from the next boronic acid, which was acting as a boron electrophile, to give bicyclic dioxadiazaborocines. Boron substrates used in this study include phenyl, heteroaromatic, vinyl, and aliphatic boronic acid **Scheme 8**. It's significant that both boronic acids with similar characteristics can be employed in this four-component transition [36].

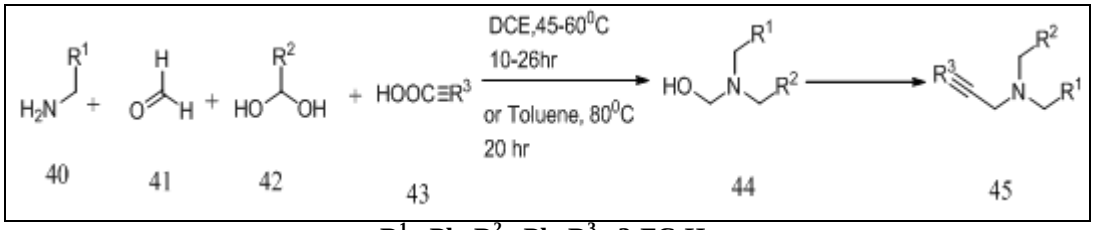




SCHEME 8: FOUR COMPONENT PETASIS REACTION

Noncanonical Building Block as the Fourth Ingredient: Using amines 40, formaldehyde 41, boronic acids 42 and alkynes 43, tertiary propargyl amines 45 were synthesised via a four-component Cu(II)-catalyzed Petasis-like reaction [37]. The alkyne component is replaced with propionic acid, and the carbon nucleophile's reactivity was increased, permitting it to strike the iminium component of the Petasis three-component product without using a Cu(II) catalyst. Two groups give this type of metal-free four-component PR for producing N-benzyl propargyl amines [38, 39].

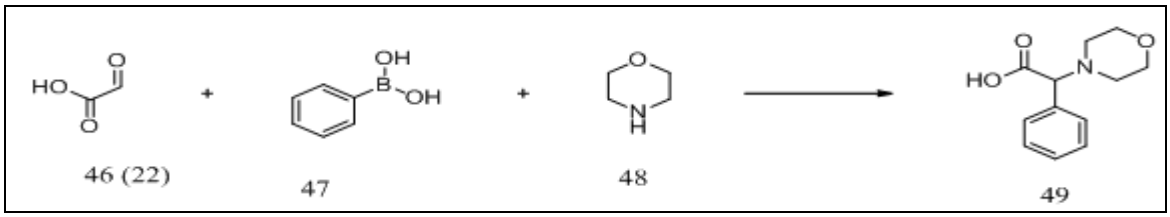
It's worth noting that two formaldehyde constituents are involved in forming the initial benzyl hemiaminal intermediate in this transformation, making it a five-component reaction **Scheme 9** [40], [41].



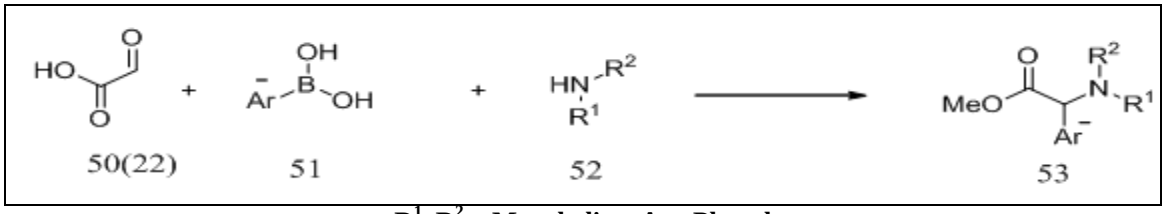
R^1 =Ph, R^2 =Ph, R^3 =3-FC_6H_4

SCHEME 9: FOUR COMPONENT PETASIS REACTION

Green Chemical Synthesis for Petasis Reaction: The Petasis reaction is commonly performed under conditions that include stirring at room temperature for 24 h or more**.** Dichloromethane, toluene, ethanol, and acetonitrile are among the solvents used, depending on the purpose. Refluxing conditions have been used in some circumstances, however, these conditions usually feature the second transition in accumulation to the Petasis first stage**.** Efficient microwave-assisted synthesis reaction reported for petasis reaction. Amino acid derivatives are produced by the response of glycoxylic acid 46 **(**22**)**, phenylboronic acid 47 and morpholine 48 shown in scheme 10. The reaction was handed out by using a microwave to consume the design of experiments **(**DOE**)**, reaction temperature **(**50-100 ^{0}C**)**, period **(**10-30 min**)**, concentration **(**0**.**1-0**.**5Mol**)**, and **(**MeOH or DCM**)** solvent**.** The best solvent is DCM**.** Two reactions are given, one for 10 minutes at 120°C and the other for 30 minutes at 120°C. Subsequently, the product was esterified and separated, yielding the end product in 40**%** and 60**%** yields, respectively**.** A shorter time, i.e. 10 min, should be used for future investigations to increase the procedure's throughput. The green chemical reaction is then used on aryl boronic acids and amines to provide microwave-assisted products **Scheme 11.**



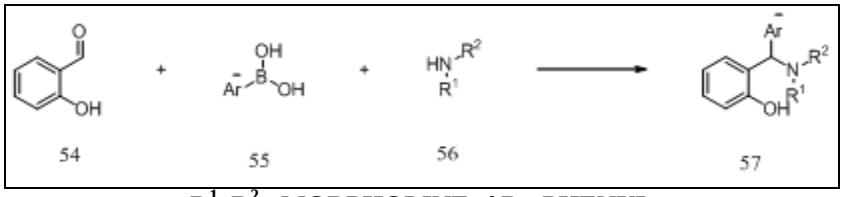
SCHEME 10: PETASIS REACTION OF GLYCOXYLICACID, PHENYLBORONIC ACID AND MORPHOLINE USING MICROWAVE IRRADIATION



R^1, R^2 = Morpholine, Ar =Phenyl

SCHEME 11: THE PETASİS REACTİON OF GLYCOXYLİC ACİD UNDER OPTİMİZED CONDİTİONS: 120°C, 10 MİN, DCM

The microwave-assisted approach was then used for a salicylaldehyde synthesis shown in scheme 12**.** The product is isolated directly using column chromatography in this process**.** The reaction was stable when boronic acid was used**.**



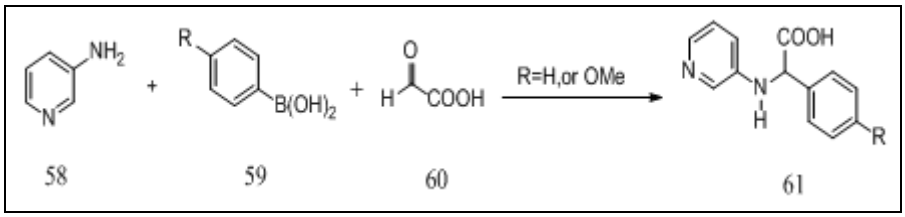
R^1, R^2 =MORPHOLINE, AR =PHENYL

SCHEME 12: THE PETASIS REACTION OF SALICYLADEHYDE UNDER -OPTIMIZED CONDITION: 120°C, 30 MIN, DCM

The quick, microwave-assisted approach for glycoxylic acid or salicylaldehyde petasis reaction yields a similar result but takes 10 min to complete [42].

Electron Poor Petasis Reaction: Under microwave irradiation, electron-poor aromatic amines such as aminopyridines is performed as a petasis reaction**.** Several unconventional N-aryl-alpha-amino acids 61 can be produced quickly using this method. Amines such as primary and seconadary, hydrazines and anilines are used in the process, which is carried out at room temperature in dichloromethane solvent**.** At room temperature, 3-aminopyridine produces a poor conversion when utilized in the Petasis reaction with phenylboronic acid 59. The conversion rate was only approximately 10**%**, even with a very extended reaction time of 1 week.

However, based on a 60**%** conversion, screening several solvents and using the microwave procedure results in the final product's 25% isolated yield**.** Several efforts to modify the temperature or increase the reaction time resulted in minor progress.



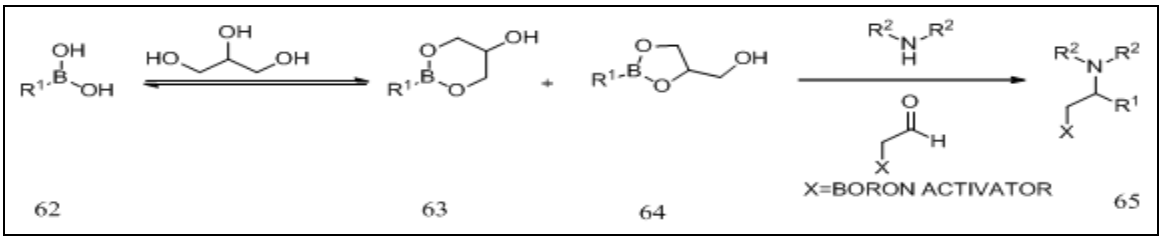
SCHEME 13: THE ELECTRON POOR PETASIS REACTION

This is a rapid and simple methodology for Petasis reactions of a wide range of electron-poor anilines and heterocyclic anilines [43].

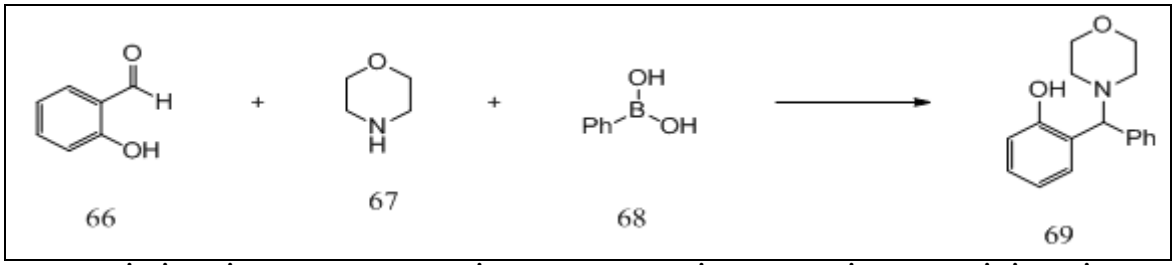
Different Solvents in Petasis Reaction:

Glycerol: Glycerol, which is made up of a strong hydrogen-bond organization, is anplentiful, decomposable, inexpensive, harmless, and deeply hydrophilic solvent. Like dimethyl sulfoxide **(**DMSO**)** or N, N-dimethylformamide **(** DMF**)**, it has a low vapor pressure, elevated boiling point, dielectric constant, and polarity value**.** Because of these characteristics, it is an ideal solvent for microwave and ultrasound irradiation measures [44].

Unfortunately, there are several drawbacks to using glycerol as a reaction solvent, such as high viscosity, which gives difficulty in mass transfer, and the low solubility of extremely hydrophobic compounds and gases [45]**.** The reaction of a boronic acid with glycerol results in glycerol boronic esters, which can then react to form the Petasis boron mannich product 65. Glycerol's strong hydrogen-bonding network could help speed up the iminium production process**.** Salicylaldehyde 66, when reacted with morpholine 67 and boronic acid 68 in the presence of glycerol as a solvent, gives favorable product 69 Scheme 15 [46].

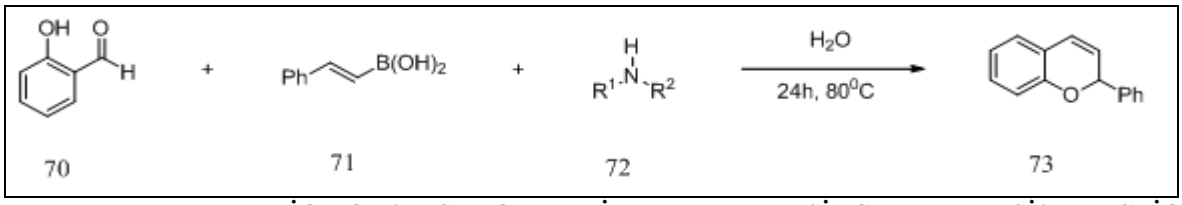


SCHEME 14: PETASIS BORON-MANNICH REACTION IN GLYCEROL



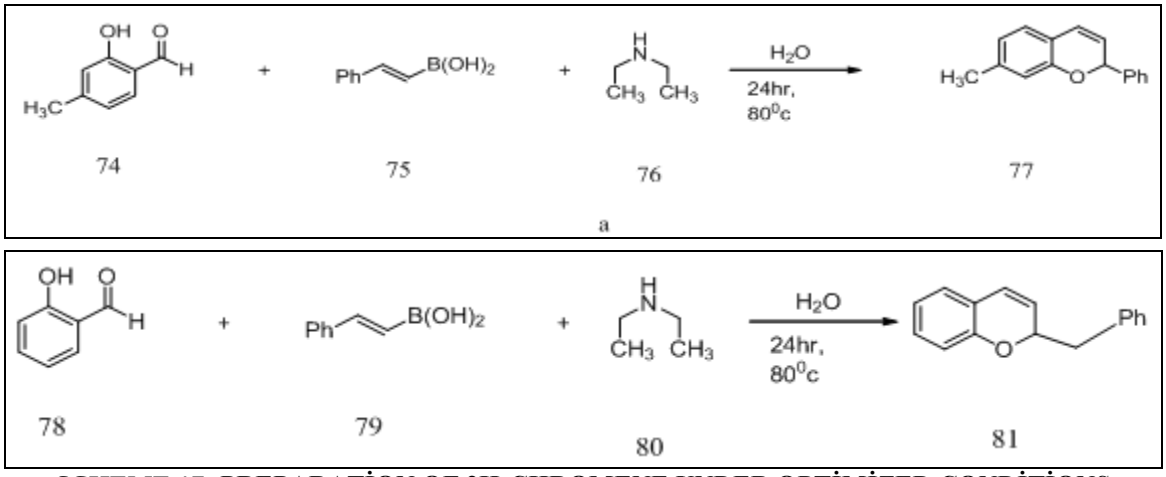
SCHEME 15: OPTİMİZATİON OF THE PETASİS BORON-MANNİCH REACTİON CONDİTİONS İN GLYCEROL

Water: Water is one of the plentiful, inexpensive, and clean most attractive solvents is water. Recognition of water does not end with this ecological significance since it frequently impacts the chemical processes that occur in this media [47]. According to Finn and coworkers, Salicylaldehydes is a resin-bonded amine, and vinyl boronic acids were used to make 2H-chromenes 73**.** After condensation of the three components, the phenol hydroxy group promotes intramolecular cyclization, resulting in the ejection of the amine moiety **Scheme 16**. There are several transitions in water using several amines as cyclization promoters based on this precedence [48].



SCHEME 16: PREPARATİON OF 2H-CHROMENE İN WATER BY USİNG THE PETASİS REACTİON

In contrast to Finn and coworker**'**s method, a stoichiometric quantity of amine is required for efficient transformation in water**.** Diethylamine was the most efficient of the amines examined, yielding the cyclized product in 92**%** of cases**.** The optimized reaction conditions resulted in satisfactory yields of 2H-chromenes 77, 81 **Scheme 17** [49].

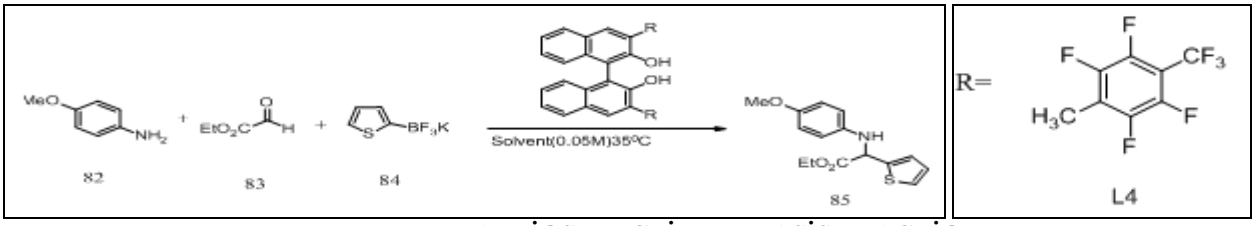


SCHEME 17: PREPARATİON OF 2H-CHROMENE UNDER OPTİMİZED CONDİTİONS

Application of Petasis Reaction:

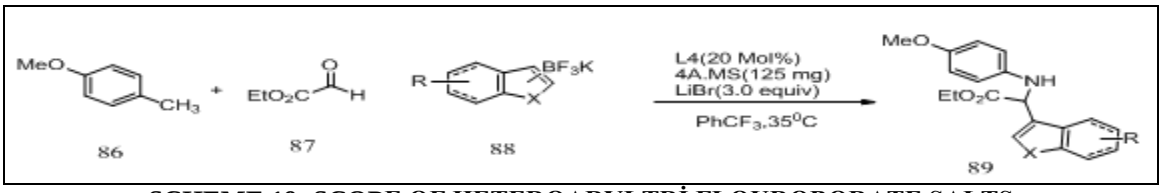
Enantioselective Petasis Reaction: In the presence of 4 ^{0}A MS and chiral ligand L4, the reaction was carried out using amine 82, ethyl glyoxylate 83, and trifluoroborate salts 84**.**

The target product, α -amino ester 85, was obtained as shown in scheme 18. The amine intermediate was not totally consumed throughout the reaction, as indicated by thin-layer chromatography **(**TLC**).** BF3**.**OEt2 **(**Boron Trifluoride ethyl etherate**),** LiBr **(**Lithium bromide**),** (nBu) 4NHSO^{4} **(**Tetrabutylammonium sulphate**)** and **(**nBu**)** 4NBr **(**Tetrabutylammonium bromide**)** were all extensively tested for trifluoroborate salt activation**.** In terms of yield and enantioselectivity, 3 equiv of LiBr in combination with a solvent such as benzotrifluoride **(**PhCF3**)** was determined to be the optimum choice**.**



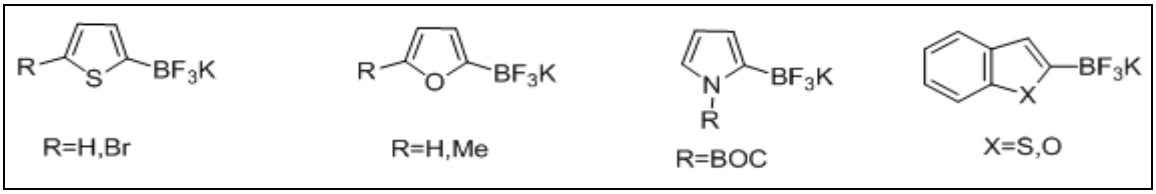
SCHEME 18: ENANTİOSELECTİVE PETASİS REACTİON

The heteroaryl trifluoroborate salts like thiophene, furan, pyrrole and indole under optimized reaction conditions result in compounds with high enantioselectivity [50, 51].

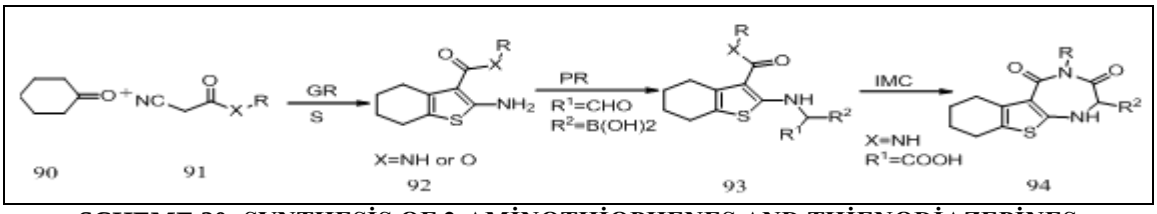


SCHEME 19: SCOPE OF HETEROARYLTRİ FLOUROBORATE SALTS

Nucleophile

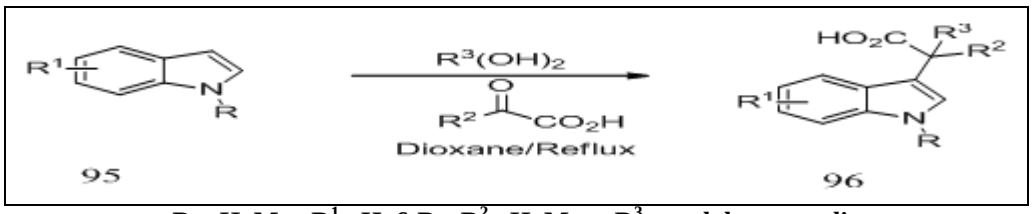


Synthesis of 2-Aminothiophenes and Thienodiazepines: A Gewald Reaction **(**GR**)** of a ketone **90**, an α –cyanoester 91 and sulphur produces 2-aminothiophenes 92**.** The scheme 20 shows the GR-PR approach was used to synthesize a sequence of functionalized 2-aminothiophenes, an intramolecular cyclization **(**IMC**)** used to yield thienodiazepines 94 [52-55].



SCHEME 20: SYNTHESİS OF 2-AMİNOTHİOPHENES AND THİENODİAZEPİNES

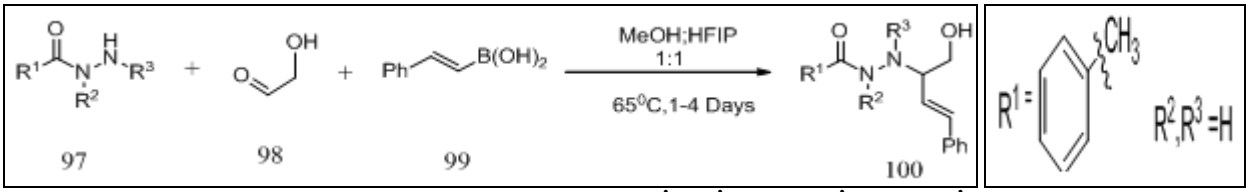
Synthesis of Indol-3-yl-aryl-acetic Acid: The stirring of glycoxylic acid monohydrate and an organoboronic acid under reflux conditions in dioxane for 12 h, the petasis-boronic acid-mannich reaction is employed to generate the two C-C bonds in alpha- **(**N-substituted indole**)** carboxylic acid 96 **Scheme 21** [56].



R = H, Me R[1] =H, 6-Br. R[2] =H, Me R[3] =aryl, heterocyclic

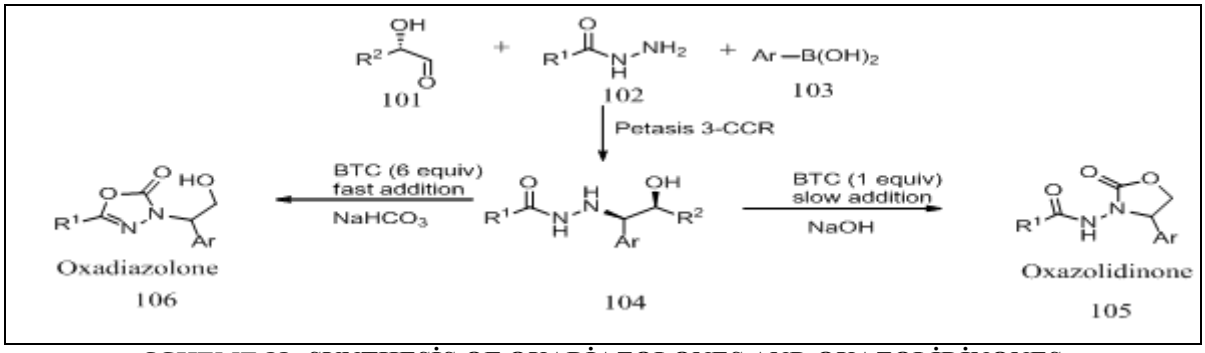
SCHEME 21: SYNTHESIS OF INDOL-3-YL-ARYL-ACETIC ACID

Synthesis of Oxadiazolones and Oxazolidinones: The **(**1 equiv**.)** hydrazides **97**, **(**1 equiv**.)** glycolaldehyde 98 and **(**1**.**2 equiv**.)** trans-phenylvinylboronic acid 99 when heated in the mixture of MeOH and Hexafluoroisopropanol **(**HFIP**)** solvent at 65°C, results in final product 100 shown in **Scheme 22.**



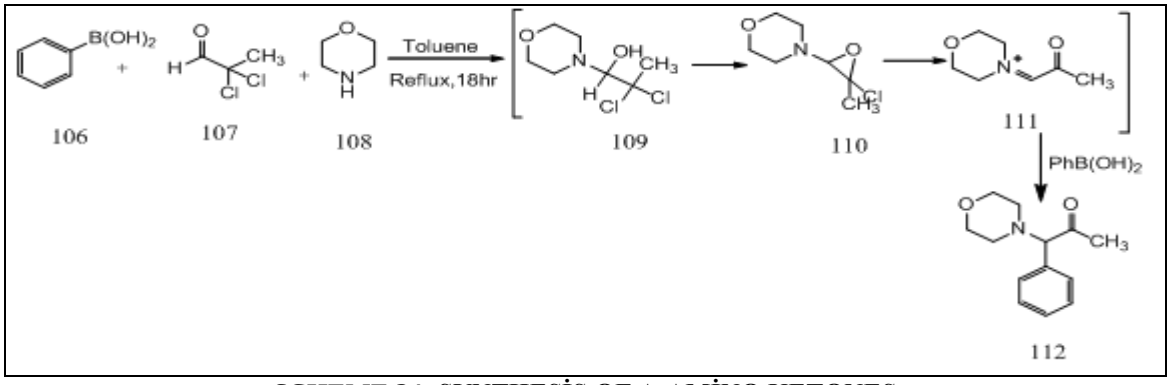
SCHEME 22: SCOPE OF HYDRAZİDE İN PETASİSREACTİON

The reaction of α-hydroxy aldehyde 101, amines **(**primary or secondary**)** 102, and substituted vinyl or aryl boronic acids103 gives amino alcohols 104**.** Additional amounts of bis **(**trichloromethyl**)** carbonate **(**1 equiv**)** and strong basic workup results in desired oxazolidin-2-one**(**oxazolidinone**)** 105**.** When **(**6 equiv**)** bis**(**trichloromethyl**)** carbonate given by fast addition results in another desired product which is 1,3,4-oxadiazol-2-**(**3H**)**-one **(**oxadiazolone**)** 106 given in scheme 23**.**[57]



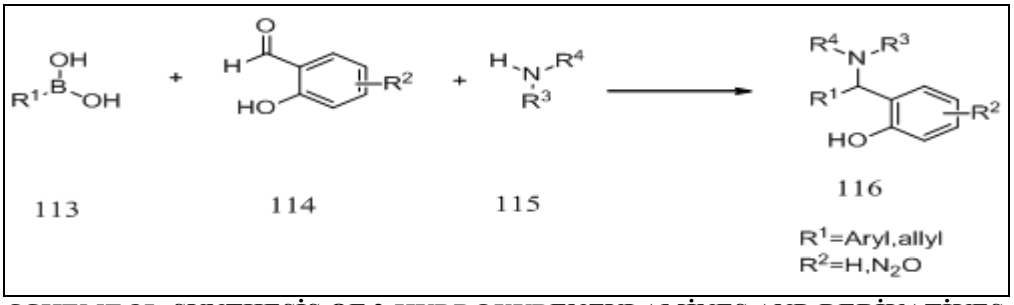
SCHEME 23: SYNTHESİS OF OXADİAZOLONES AND OXAZOLİDİNONES

Preparation of α-Amino Ketones: Instead of the boronic acid Mannich product, the reaction of α, α –dichloropropanal 107 with three equivalents of morpholine 108 and two equivalents of phenylboronic acid 106 in toluene at reflux for 18 hours yields 1-morpholinyl-1-phenylpropanone 112**. Scheme 24** [58].



SCHEME 24: SYNTHESİS OF A-AMİNO KETONES

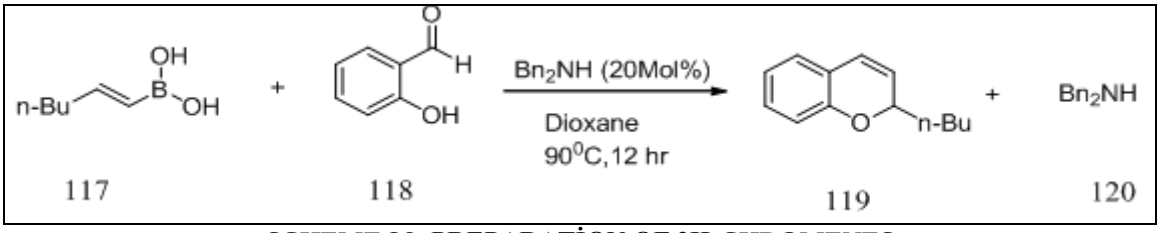
Synthesis of 2-Hydroxybenzylamines and Derivatives: The reactions of substituted 2-hydroxy aromatic aldehydes **(**substituted salicylaldehydes**)** 114, amines 115 and aryl, 1-alkenyl, or allyl boronic acids 113 can easily produce 2-hydroxybenzylamine derivatives 116 **Scheme 25** [59-60].



SCHEME 25: SYNTHESİS OF 2-HYDROXYBENZYLAMİNES AND DERİVATİVES

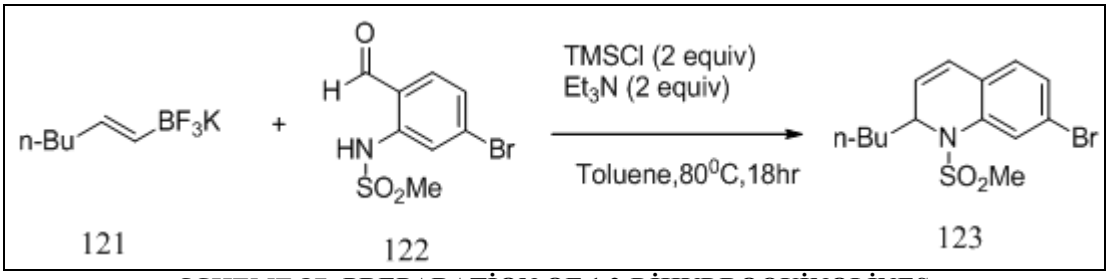
Preparation of Heterocycles:

Preparation of 2H-Chromenes: 2H-chromene derivatives **119** can be efficiently synthesized using 2-hydroxy aromatic aldehydes **(**substituted salicylaldehydes**)** 118, amines, and 1-alkenyl boronic acids **117 Scheme 26** [61].



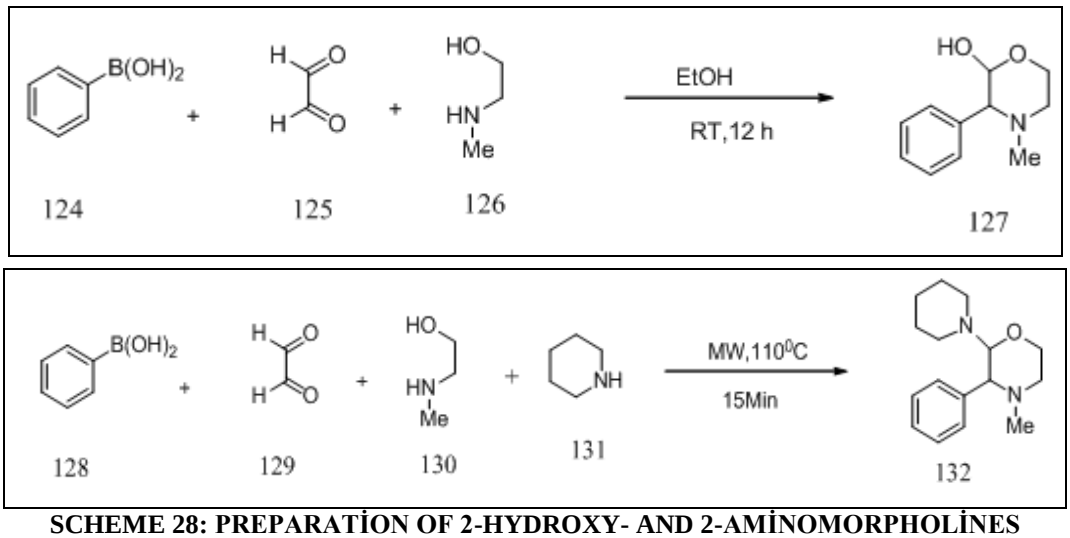
SCHEME 26: PREPARATİON OF 2H-CHROMENES

Preparation of 1,2-Dihydroquinolines: In the presence of 2 equivalents of trimethylamine and 2 equivalents of trimethylsilyl chloride in toluene, reactions of potassium 1-alkenyltrifluoroborates 121 and 2-sulfamidobenzaldehyde 122 derivatives yield 1,2-dihydroquinoline derivatives 123 shown in **Scheme 27** [62].



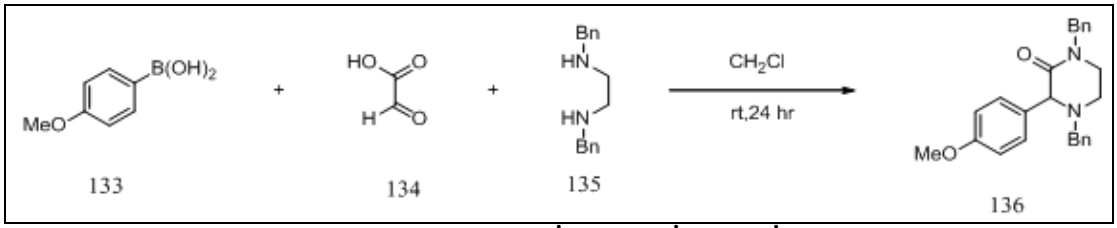
SCHEME 27: PREPARATİON OF 1,2-DİHYDROQUİNOLİNES

Preparation of 2-Hydroxy- and 2-Aminomorpholines: When glyox11al **125** react with boronic acids **124** and 1,2-amino alcohols **126** to form 2-hydroxymorpholines **127 (**Scheme 28 a**).**[63] The inclusion of a secondary amine**131** as the fourth reaction component, on the other hand, results in 2-aminomorpholines**132** shown in **(**b**)** [64]**.**



SCHEME 28: PREPARATİON OF 2-HYDROXY- AND 2-AMİNOMORPHOLİNES

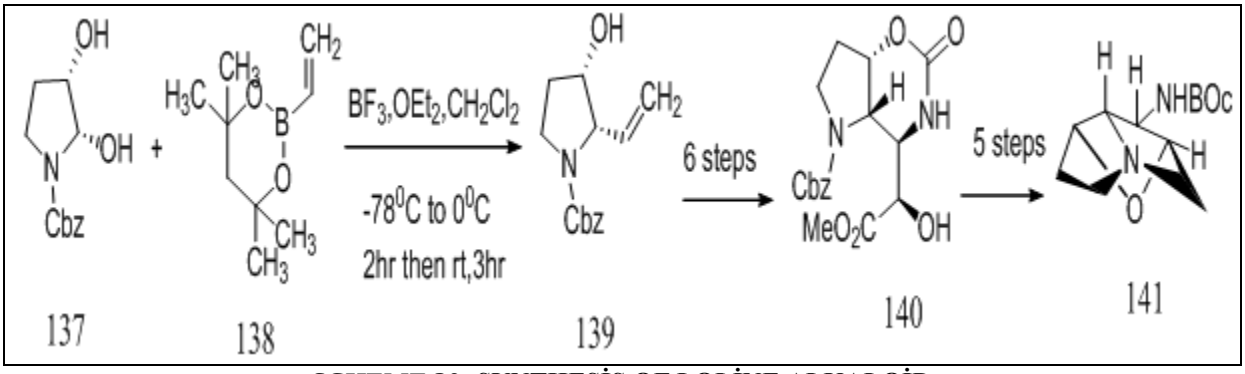
Preparation of Piperazinones: Piperazinones 136 are formed when boronic acids 133, glyoxylic acid 134 reacts with 1,2-diamines135 **(**scheme 29**)** [65].



SCHEME 29: PREPARATİON OF PİPERAZİNONES

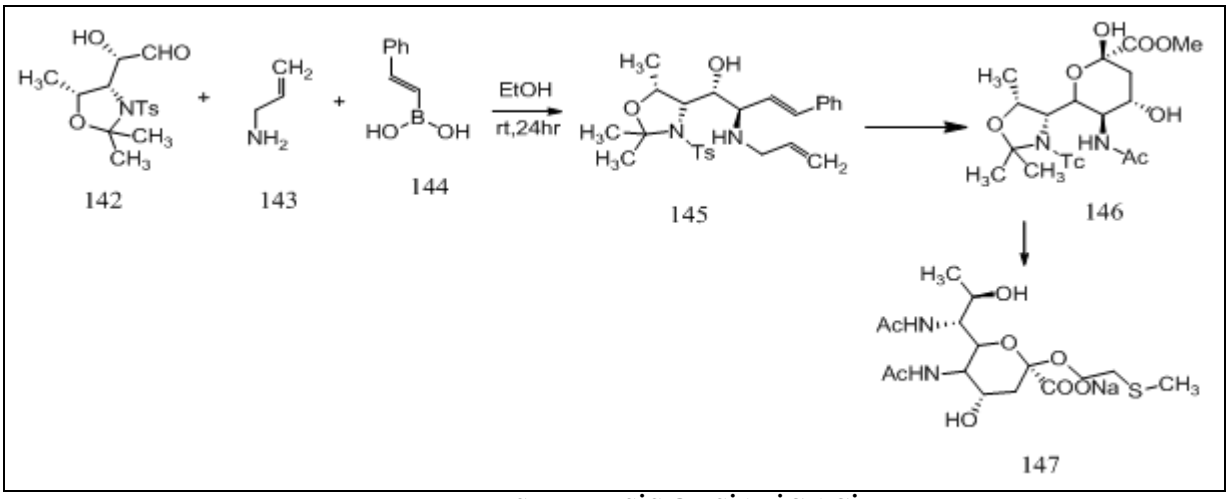
In the Synthesis of Natural Chemicals:

Loline Alkaloid: A loline alkaloid is a member of 1-amino pyrrolizidines with a tricyclic ring system 66 has been shown much interest in synthetic works [67.] The loline alkaloid was synthesized using a two-component Petasis-like process. The reaction of dihydroxypyrrolidine 137 and tetra-methyipentanediol boronates 138 to givevinylpyrrolidinol 139 which was after six steps forms pyrrolooxazinone 140. Pyrrolooxazinone 140 in another five steps gives the N-Boc norlodine 141 as a lonine alkaloid**.** Scheme 30**)** [68]**.**



SCHEME 30: SYNTHESİS OF LOLİNE ALKALOİD

Sialic Acid: Legionaminic acids, which are analogues of N-acetylneuraminic acid, are diamino monosaccharides that belong to the nonulosonic acid family and are important components in Legionnaires' disease [69]. Seeberger and colleagues used chelation-controlled organometallic additions and the PR to synthesise orthogonally enclosed legionaminic acids starting with D-threonine, which was employed as the aldehyde compound's precursor**.**The PR of α-hydroxyl aldehyde 142, **(**E**)**-styrylboronic acid 144, and monoallylamine 143 yield aminol 145. These can result in orthogonally covered legionaminic acid, which was then used to make a linker-equipped legionaminic acid 147 given in scheme 31 [70-71].



SCHEME 31: SYNTHESİS OF SİALİC ACİD

CONCLUSION: The Petasis reaction has been shown to be a useful MCR for accessing physiologically active compounds and performing synthetically interesting transformations. Through a systematic assessment of examples, we highlight the types of petasis reaction such as two-component, three-component, and four-component petasis type reactions. The quick, microwave-assisted methodology for carrying out the petasis reaction yields consistent results with a shorter reaction time. The microwave-assisted process works well with aryl boronic acids, but only when secondary amines are used. This review highlights on different solvent used for better result. The petasis reaction used to obtain various synthetic products along with the natural product synthesis are also highlighted**.**

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CONFLICT OF INTEREST: We declares that we have no conflict of interest**.**

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