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Review Article

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Multi component reactions and non-steroidal anti-inflammatory drugs

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ABSTRACT

Multicomponent reactions (MCR's) are attracting attention of chemist as one of the most powerful synthetic tools for the development of molecular diversity and complexity. It is also useful in synthesis of various heterocyclic compounds. Many of the heterocyclic compoundshave been reported to possess anti-inflammatory activity. This review provides readers with an overview of the exploitation of multicomponent reactions for the synthesis of non-steroidal anti-inflammatory drugs. Multicomponent reactions are more efficient, cost effective and economical than traditional methods. Literature survey reveals that various multicomponent reactions are exploited for the synthesis of new non-steroidal anti-inflammatory drugs like Biginelli reaction, Ugi reaction, Kabachnik field reaction, Hantzsch reaction, Petasis reaction, Mannich reaction etc.

Keywords: Non steroidal anti-inflammatory drugs, Analgesic, Multi component reactions.

INTRODUCTION

Multicomponent reactions (MCRs) are chemical reactions in which three or more compounds react to form a single product. The reaction gives highly selective products that retains majority of atoms present in the starting material. MCRs provide great possibility for getting molecular diversity and complexity in few steps within less time.

The various advantages of MCR can be summarized as follows:
1. Utilization of simple and readily available starting materials.
2. Wide range of possibilities for the efficient construction and development of highly complex molecules in single step.
3. Favourable economic factors, including the cost of raw materials, energy and human resources.
4. Low environmental impact, use of environmentally friendly solvents, atom economy.
5. Simple work-up procedure, efficient recovery and recycling of catalyst.
6. Experimental simplicity.
7. Product having high stereo selectivity and high yield.
8. Saves energy and time.
9. Avoids several steps.
10. Green synthetic approach.
11. Avoid hazardous by products.
12. Possibility of automation.
13. Intermediate separation and purification steps.
14. Open possibilities for the use of mono and bifunctional catalysts for achieving fully green processes.

Multicomponent reactions are more beneficial than conventional linear-type synthesis because it provides creation of several bonds in one single step [1]. Therefore MCR's are gaining more importance in organic chemistry and medicinal [2]. Conventional multi-step reactions produces waste by-products, it also utilises hazardous, toxic,

expensive solvents. MCR's is efficient synthetic procedure for effective and quick organic transformation because the target molecule is obtained in one pot, single step so molecular diversity and complexity can be obtained by just changing the reacting components [3, 4].

Inflammation

Inflammation is part of the body's immune response. It is the response of organism to the pathogens. Inflammation is a local reaction of the vascular and supporting elements of a tissue to injury leading into the formation of protein-rich exudates. It is a protective response from nonspecific immune system to localize, neutralize, or to destroy an injurious agent in preparation for the process of healing. Symptoms of inflammation are calor (heat), dolor (pain), tumor (swelling), rubor (redness) and function laesa (loss of function). It is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. The symptoms of pain are redness, swelling, heat, and loss of function. By the help of inflammation the organism gets rid of the injurious stimuli and to initiate the healing process. Inflammation is caused by physical agents, chemical agents, immunological reactions and infection by pathogenic organism [5]. Anti-inflammatory refers to the property of a substance to treat and reduce inflammation. Non steroidal anti-inflammatory drugs (NSAIDs) are useful tools in the treatment of acute and chronic inflammation [6], pain [7] and fever [8]. Long-term usage of anti-inflammatory drugs leads to side effects such as gastrointestinal lesions, bleeding and nephrotoxicity [9, 10].

Importance of anti-inflammatory drugs

Anti-inflammatory drugs reduce pain caused by inflammation. It inhibits or blocks the effect of (COX) enzymes. (COX) enzymes known as called cyclo-oxygenase. COX enzymes are produces the chemical called prostaglandin. At the side of injury or damage some prostaglandins are produce. These drugs block the production of prostaglandin and reduce pain. There are two types of COX enzymes - COX-1 and COX-2. COX-2 enzyme is responsible for the production of prostaglandins. Anti-inflammatory painkillers are sometimes classified into two main groups:

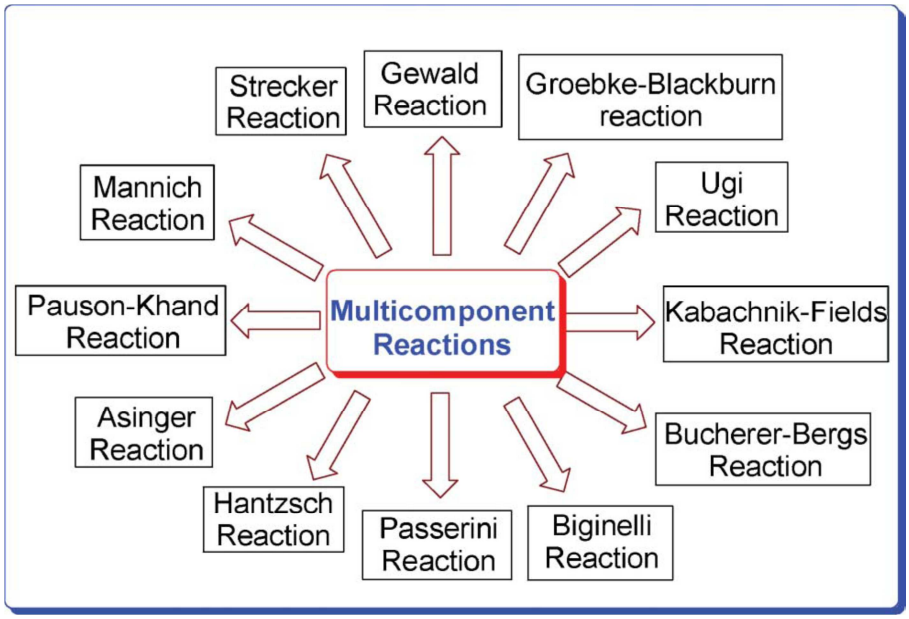
- Nonselective or standard NSAIDs. Most fall into this group, including diclofenac, ibuprofen, indometacin, and naproxen. They block both COX-1 and COX-2 enzymes.
- Coxibs. For example, celecoxib and etoricoxib. These mainly (selectively) block just the COX-2 enzyme.

Based on their chemical structure or mechanism of action NSAIDs are classified. New substances are mostly classified by mechanism of action. Eg: **Salicylates**: Aspirin (acetylsalicylic acid), Diflunisal, Salsalate. **P-amino phenol derivatives**: Paracetamol, phenacetin. **Propionic acid derivatives**: Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen. **Acetic acid derivatives**: Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone. **Enolic acid (Oxicam) derivatives**: Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam. **Fenamic acid derivatives (Fenamates)**: Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid. **Selective COX-2 inhibitors (Coxibs)**: Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Lumiracoxib, Etoricoxib, Firocoxib. **Sulphonanilides**: Nimesulide.

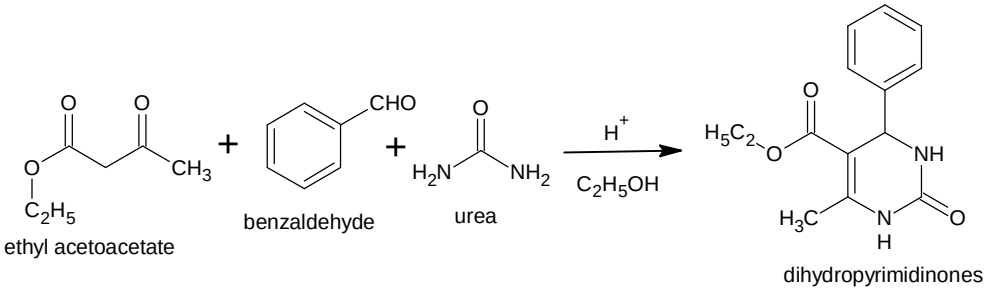
Anti-inflammatory painkillers have two main uses: **To reduce pain**. Anti- inflammatory compounds are used to ease up pain in various situations, including osteoarthritis, rheumatoid arthritis, joint pains, muscle and ligament pains (strains and sprains), dysmenorrhoea (period pain), postoperative pain, headaches, migraines etc.

To reduce inflammation. Inflammation is also reduced. This can further reduce pain and stiffness that occurs with inflammation condition such as rheumatoid arthiritis.

Various types of multicomponent reaction



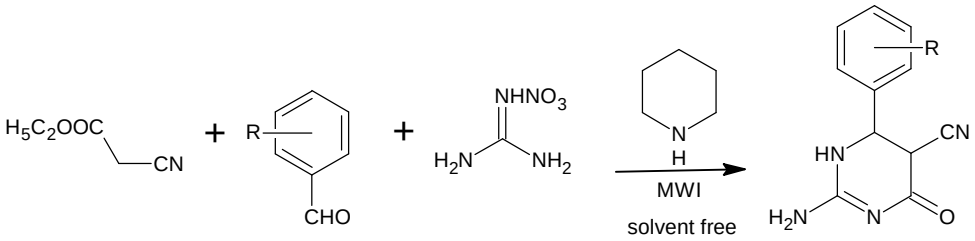
1. Biginelli reaction



Scheme 1. General scheme for Biginelli reaction.

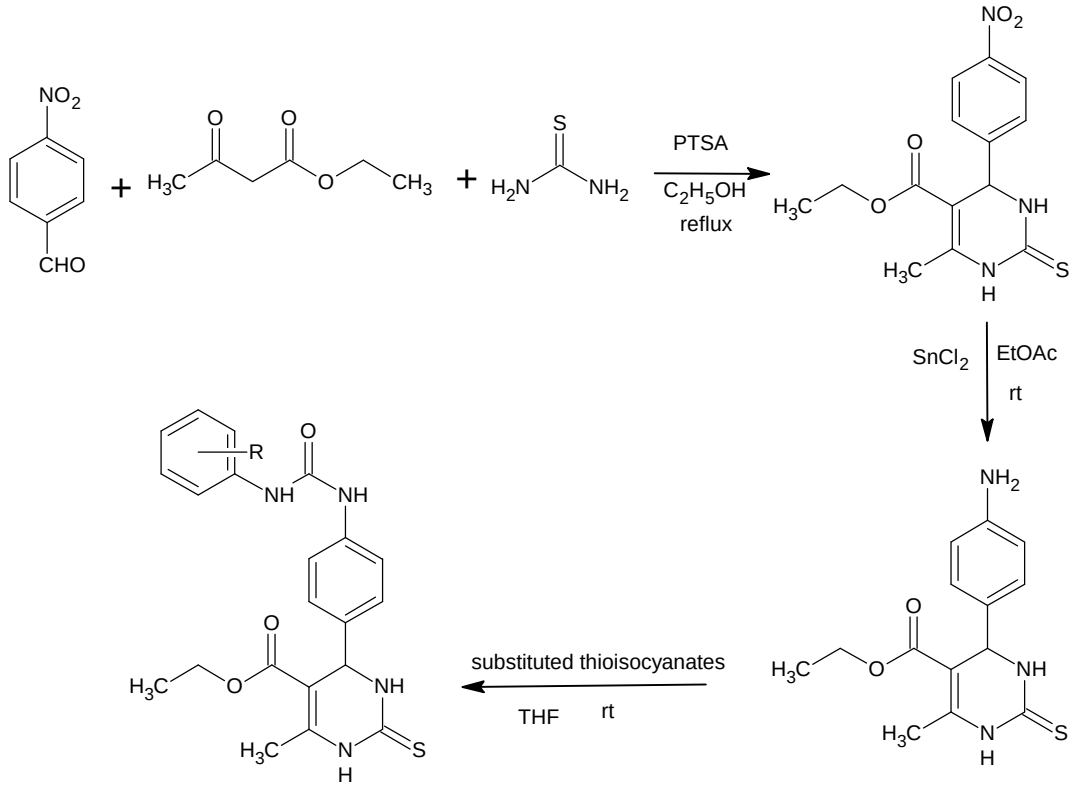
The Biginelli reaction [11] is one of the common multicomponent reaction that produces 3,4-dihydropyrimidin-2(1H)-ones from aldehyde, ethyl acetoacetate, urea. This reaction is named by Italian chemist Pietro Biginelli in 1891. The product Dihydropyrimidinones obtained from the reaction is used in the pharmaceutical industry.

- **Biginelli reaction used for synthesis of anti-inflammatory drugs**

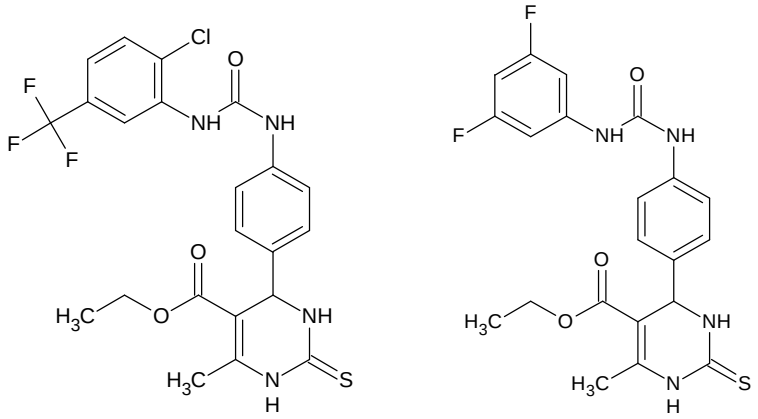


Scheme 2. Synthesis of 2-amino dihydropyrimidinone derivatives

Anjna *et al*. [12] reported a synthesis of 2-amino dihydropyrimidinone derivatives by three-component condensation of aldehydes, ethyl cyanoacetate, and guanidine nitrate in presence of 2-3 drops of piperidine under microwave irradiation. The synthesized compounds were screened for their anti-inflammatory activity using carrageenan-induced rat paw edema method. Most of the compounds were reported to have significant anti-inflammatory activity. The synthesized compounds were produced in excellent yield within short period of time. The author observed that by increasing microwave power up to 600 watts, there was an increase in the yield and shortened reaction time, but beyond 600 watts there was no significant change in reaction time and yield.

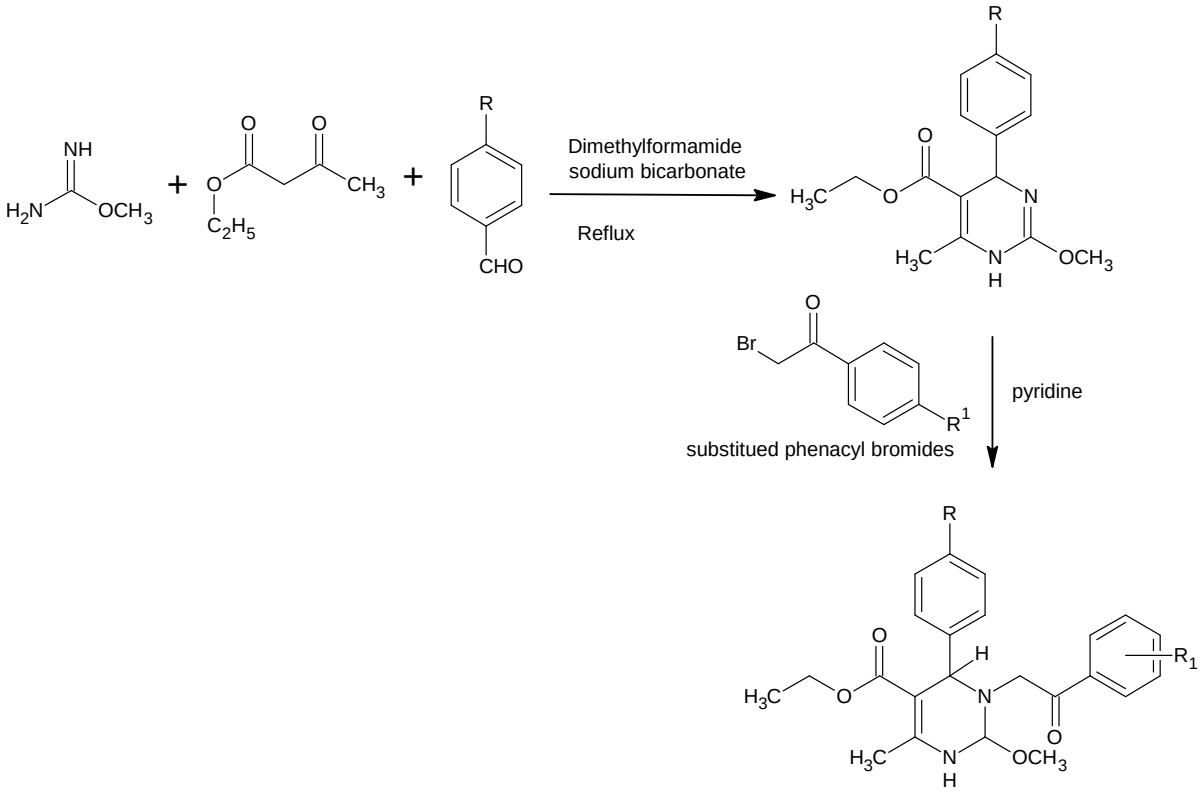


Scheme 3. Synthesis of 3,4-dihydrothiopyrimidin-2(1H)-one urea derivatives.



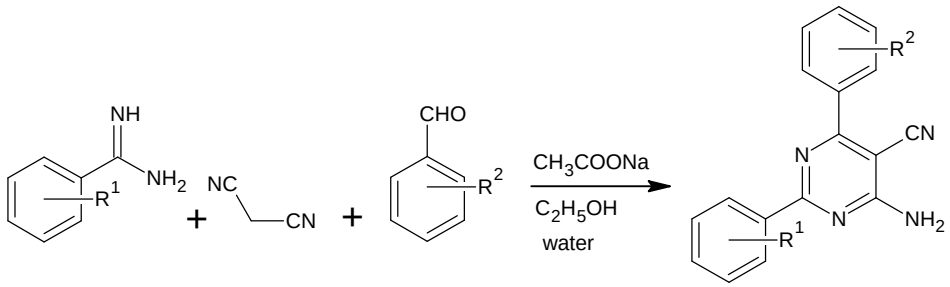
Compound A Compound B

R. H. Tale *et al*. [13] has synthesized a series of novel 3,4-dihydropyrimidin-2(1H)-one urea derivatives of biological importance using Biginelli reaction. An intermediate ethyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was synthesized by heating a mixture of p-nitrobenzaldehyde, ethylacetoacetate and thiourea in ethanol at 80^0C for 8 h using catalytic amount of PTSA. Reduction of nitro group was carried out by using $SnCl_2$ in ethyl acetate at room temperature. Resulting amine was then subjected to react with different substituted isocynates in THF. The author observed that a majority of the analogues of the series was found to be active and exhibited the good (68% and 62%) TNF-a and IL-6 (92% and 86%) inhibitory activity. The author observed that the position of the substituent on terminal benzene ring of urea moiety has profound effect on the activity. The 2- and 5-positions on the terminal benzene ring are the favourable site for the higher potency. Evidently, the compound A with Cl and CF_3 at 2- and 5-positions, respectively, exhibiting highest TNF-a and IL-6 inhibitory activity, while presence of Cl at 2-position and CF_3 group at 6-position exhibits no TNF-a activity or low IL-6 inhibitory activity. The compound B with fluoro group at 3- and 5-position of terminal benzene ring showed better TNF-a (62% at 10 lM) and IL-6 (86% at 10 lM) inhibitory activity. Biological activity evaluation study revealed that among all the compounds screened, compounds 12 and 17 found to have promising anti-inflammatory activity (68–62% TNF-a and 92–86% IL-6 inhibitory activity at 10 lM).



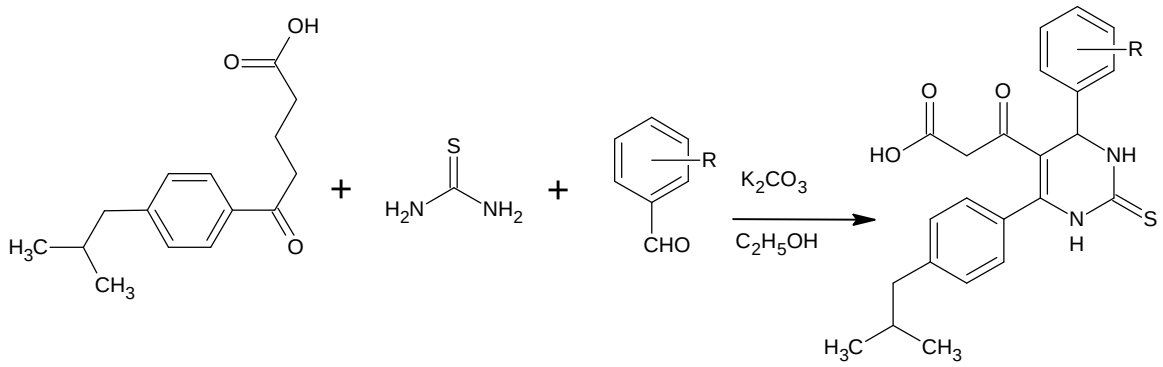
Scheme 4. Synthesis of 3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3,4-tetrahydropyrimidine-5-carboxylates

R.V. Chikhale *et al*. [14] have presented the one-pot synthesis of a series of ethyl 6-methyl-2-methoxy-3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates via Biginelli-type condensation of aromatic aldehydes with urea (or thiourea) using as a catalyst. Anti-inflammatory activity was carried out by carrageenan induced rat-paw edema method.



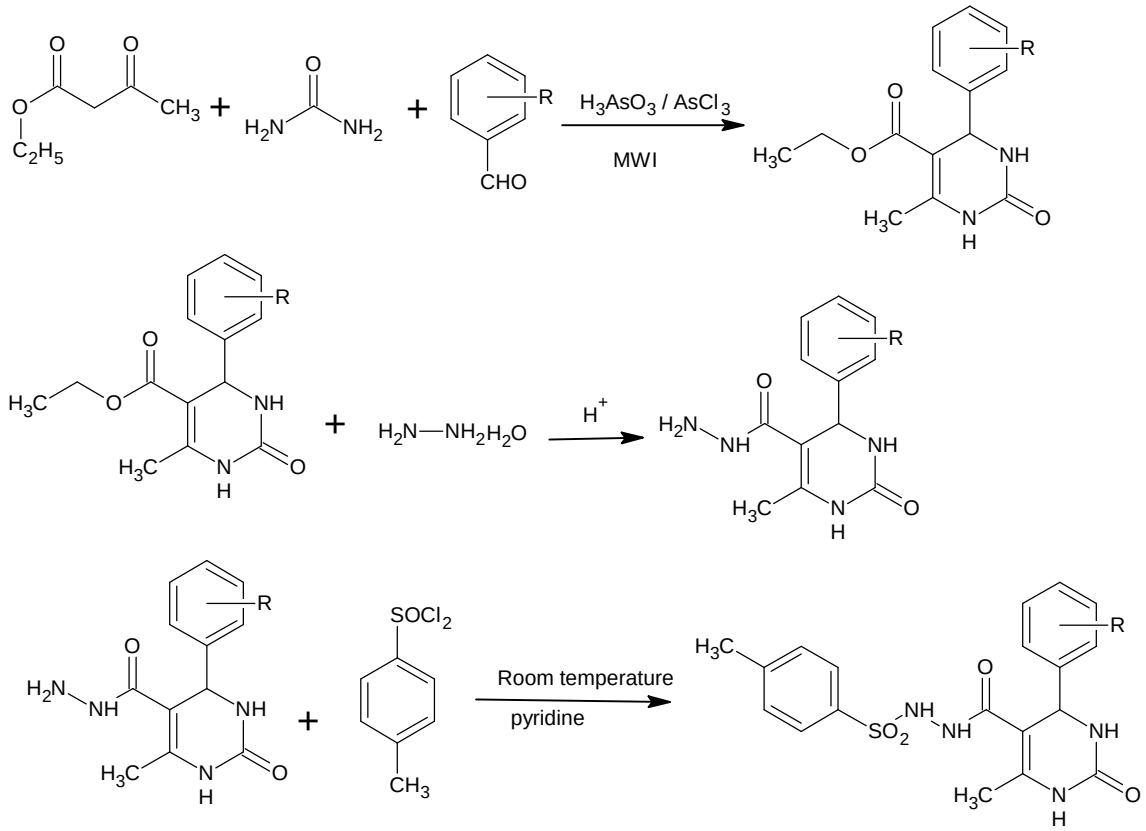
Scheme 5. Synthesis of 3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3,4-tetrahydropyrimidine-5-carboxylates

Kapupara P. P. *et al*. [15] has discovered the synthesis and pharmacological screening of 4-amino-5- pyrimidine carbonitriles as potential anti-inflammatory agents. The target molecule was synthesized by adding aldehydes, malononitrile, amidine hydrochloride and sodium acetate in water and ethanol and refluxed with stirring for 6hrs. The obtained compounds were evaluated for their anti-inflammatory activities as well as gastric ulcerogenic effects. Results showed that the compound with (-Cl and -CH_3) group on benzene ring showed potent anti-inflammatory activity in carrageenan-induced rat paw edema test with low gastric ulcerogenicity compared with etoricoxib.



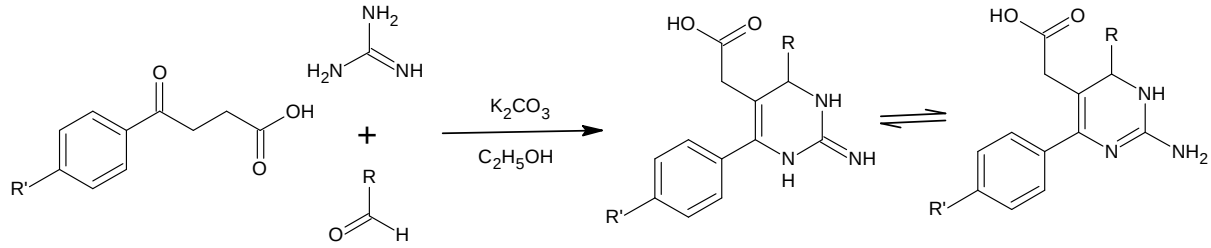
Scheme 6. Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid

Hassan. A. Osman *et al*. [16] reported synthesis of 3-(4, 6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives. The compounds was synthesized by using Biginelli reaction, a condensation of thiourea, 5-(4- isobutylphenyl)-5-oxopentanoic acid and substituted aldehydes. Aryl acetic acid or propanoic acid derivatives have found to have major contribution in non-steroidal anti-inflammatory agents. Acid side chain was frequently used to have more potent anti-inflammatory agent. The synthesized compounds were obtained in good yield. All the newly synthesized compounds demonstrated anti-inflammatory activity comparable to that of ibuprofen at the same dose.



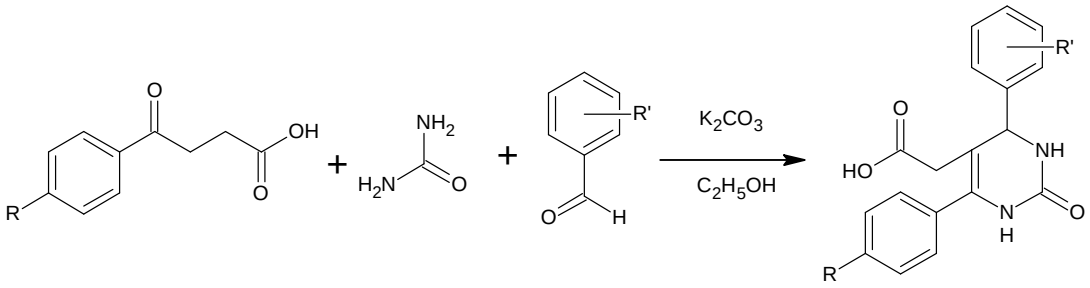
Scheme 7. Synthesis of 3,4-Dihydropyrimidine-2(1H)-one Derivatives

P.A. Patil *et al*. [17] has discovered new 4-Substituted aryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazides by synthesizing in a three step reaction. In first step 5-(ethoxy carbonyl)-6-methyl-4-substitutedaryl-3,4-dihydropyrimidin-2(1H)- ones was obtained. Second step consist of synthesis of 4-substituted aryl-6-methyl-2-pyrimidinone-5-carbohydrazides. Third step involves synthesis of 4-substituted aryl-6-methyl-2-pyrimidinone-5-(N-p-tosyl) carbohydrazides. The tested compound showed anti-inflammatory and analgesic activity.



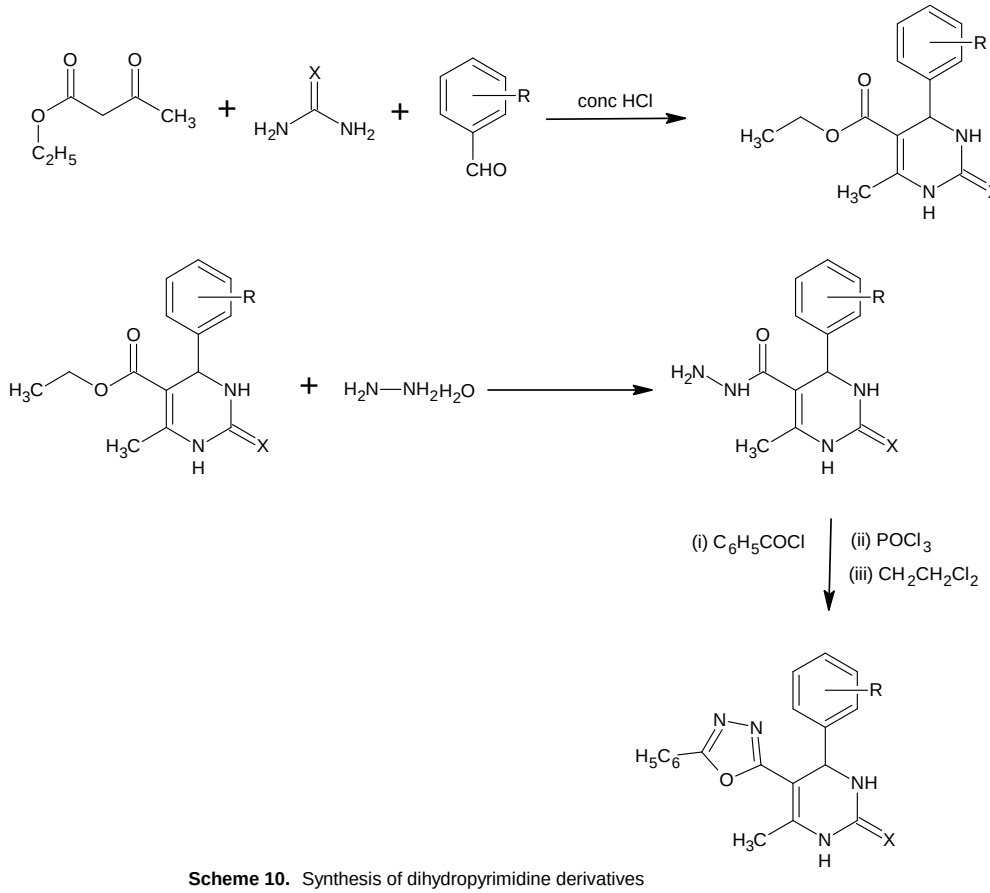
Scheme 8. Synthesis of 2-amino-6-(4-substituted aryl)-4-(4-substitutedphenyl)-1,6-dihydropyrimidine-5-yl-acetic acid derivatives

Sushilkumar S. Bahekar *et al*. [18] has discovered a synthesis of series of 2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl-acetic acid derivatives by condensation reaction of aroylpropanoic acid, guanidine nitrate and aromatic aldehydes in presence of K_2CO_3 as a catalyst.



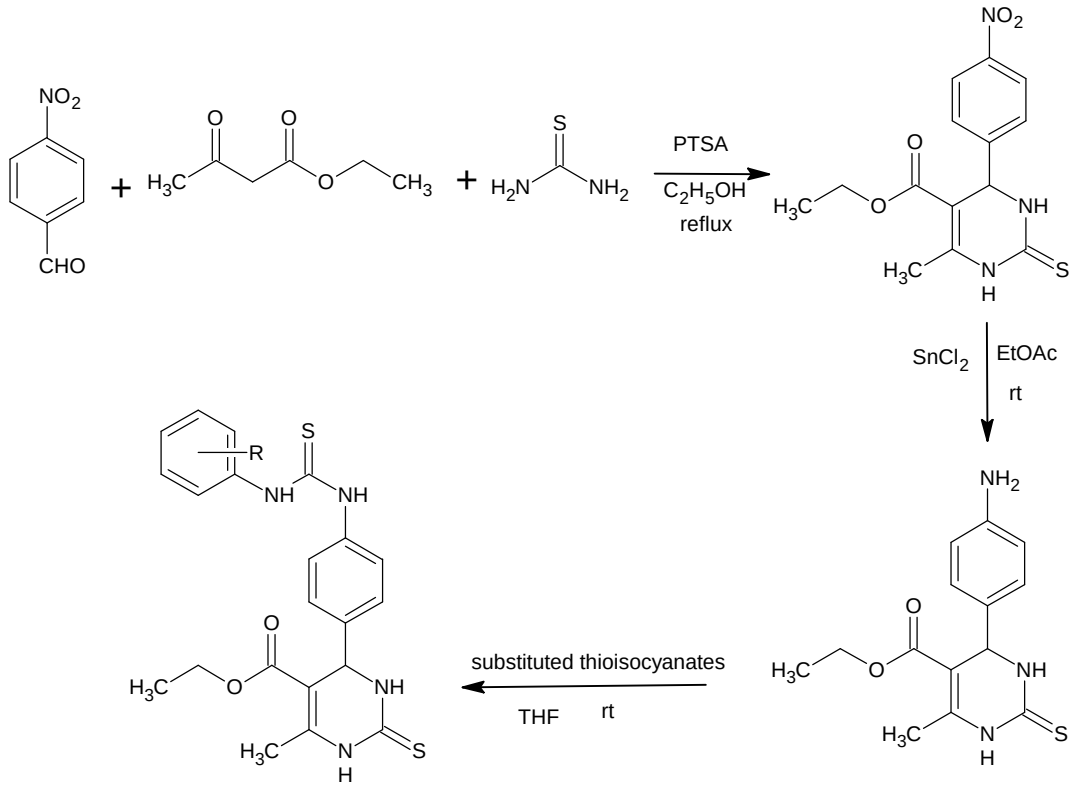
Scheme 9. Synthesis of [4, 6-(4 substituted aryl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidin- 5-yl]-acetic acid derivatives

Santosh N. Mokale *et al*. [19] has investigated synthesis of A series of [4,6-(substituted aryl)-2-oxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid has been synthesized by the base catalyzed condensation of 4-(4-substituted phenyl)-4-oxo butanoic acid, urea with aldehyde in ethanol. The synthesized compound was evaluated for anti-inflammatory activity.



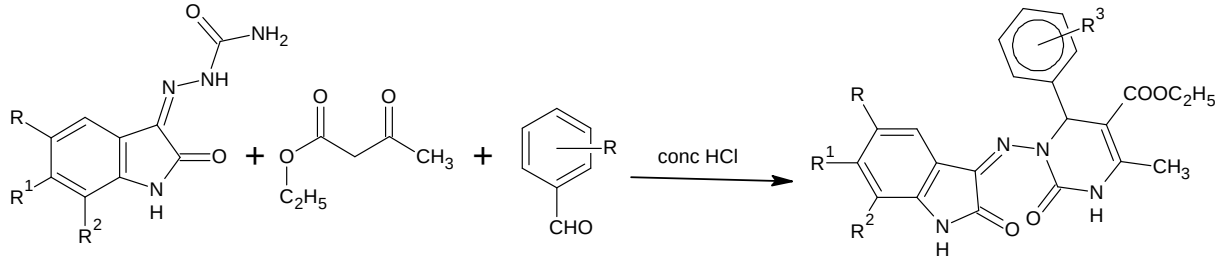
Scheme 10. Synthesis of dihydropyrimidine derivatives

Manish Kumar Mishra *et al*. [20] has synthesized and evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method for a series of 6- methyl- 2 - oxo N- (4- oxo- 2- substituted phenyl- 1, 3- thiazolidin- 3- yl)- 4- substituted phenyl- 1, 2, 3, 4- tetrahydropyrimidine- 5- carboxamide. The reaction was carried out simply by heating a mixture of three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature.



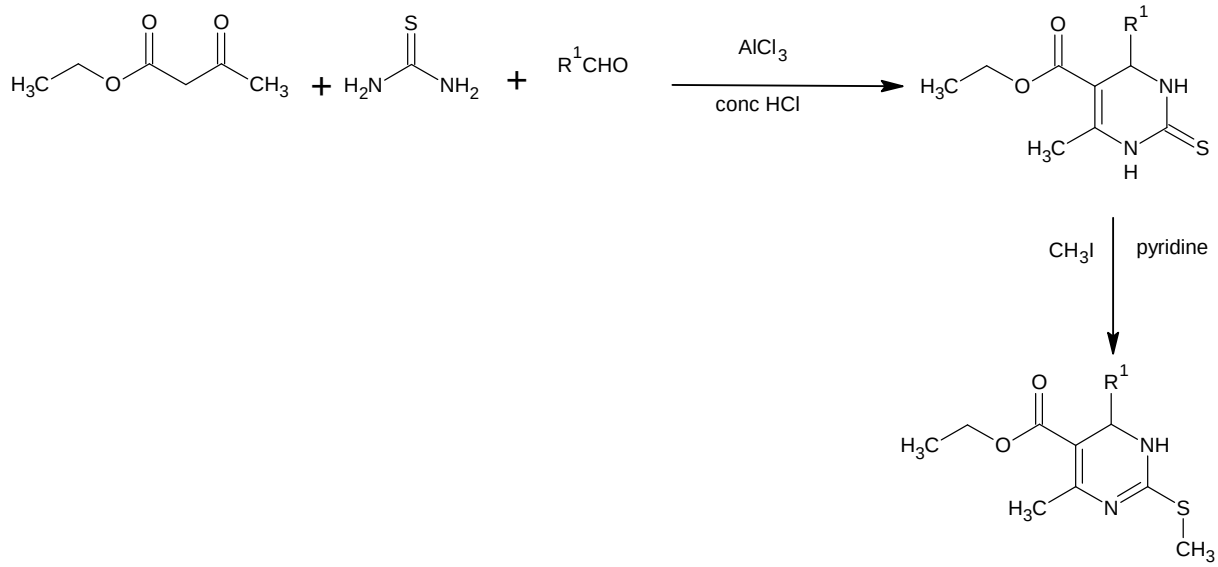
Scheme 11. Synthesis of 3,4-dihydrothiopyrimidin-2(1H)-one derivatives of N-aryl urea

Rajesh H. Tale *et al*. [21] has developed synthesis of novel thioanalogs of 3,4-dihydrothio pyrimidin-2(1H)-one derivatives of N-aryl urea by sequential Biginelli's reaction, reduction followed by reaction of resulting amine with different arylisothiocynates. The synthesized compounds were screened and found to have promising anti-inflammatory activity.



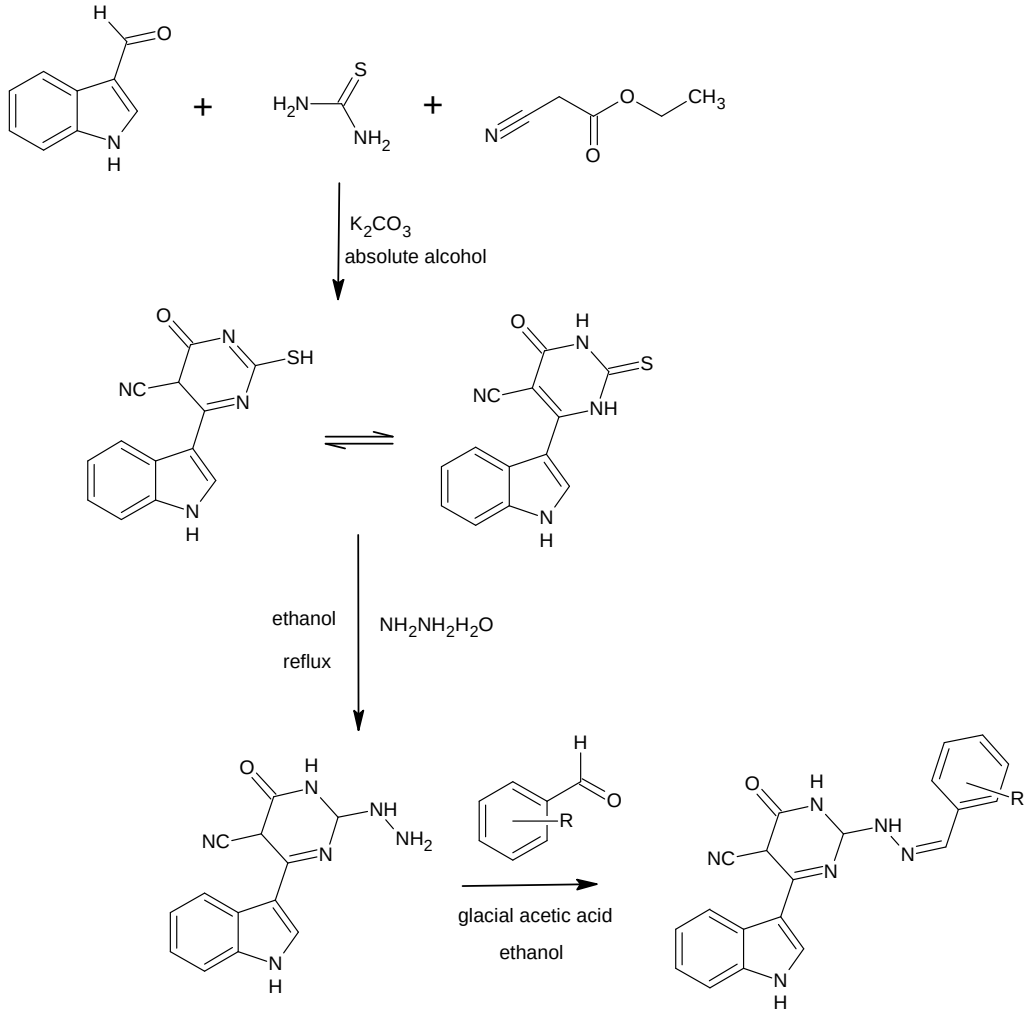
Scheme 12. Synthesis of 3-substituted [3, 4-dihydropyrimidinones]-Indolin-2-ones

M. Ajitha *et al*. [23] has investigated the anti-inflammatory activity [22] and analgesic activity [23] of new 3-substituted [3, 4-dihydropyrimidinones]-Indolin-2-ones, ethylacetoacetate and aromatic aldehydes, in dry methanol and a concentrated hydrochloric acid as a catalyst was condensed by multicomponent one pot condensation by named Biginelli's reaction for 10 to 12 hours on a water bath. The synthesized compounds were tested for anti-inflammatory activity by carrageenan induced rat paw method.



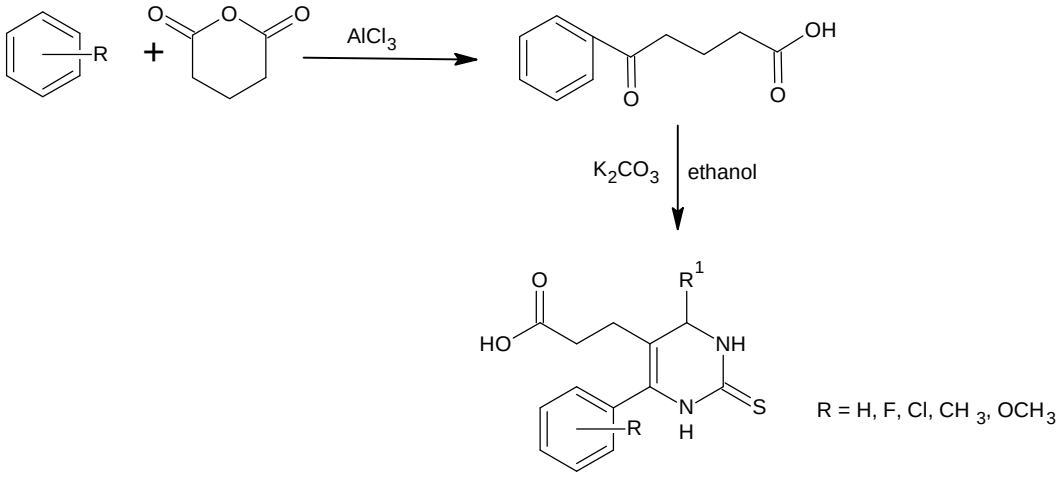
Scheme 13. Synthesis of 2-methylthio-1,4-dihydropyrimidines

Ramesh Sawant and Varsha Sarode [24] a series of 2-methylthio-1,4-dihydropyrimidine derivatives were synthesized in good yields by alkylation of 1,2,3,4-tetrahydropyrimidines (I) with methyl iodide in the presence of pyridine. The synthesized compounds were tested for analgesic activity.



Scheme 14. Synthesis of 4,5-dihydropyrimidine-5-carbonitrile derivatives.

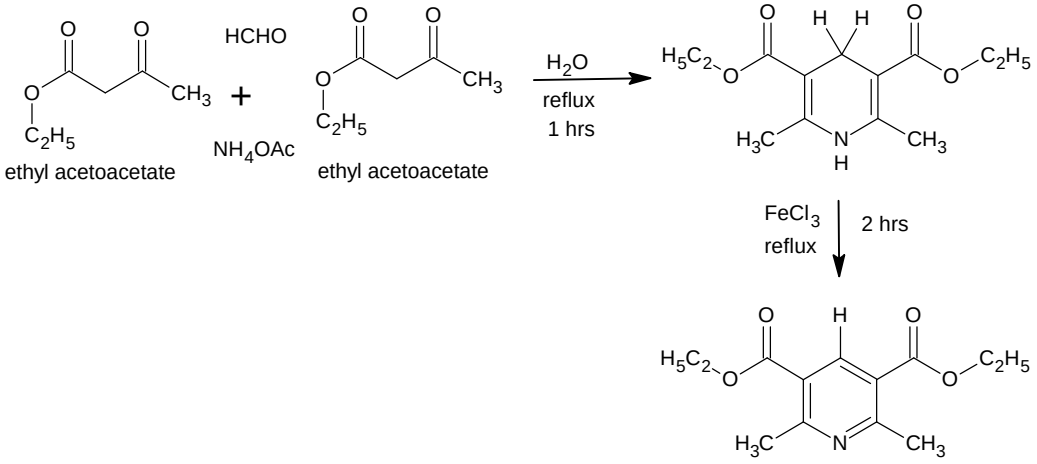
Mohammad Mumtaz Alam *et al*. [25] has reported potassium carbonate catalysed synthesis of dihydropyrimidine-5-carbonitriles followed by reaction with hydrazine hydrate, aromatic aldehydes. The synthesized compounds were found to have anti-inflammatory and analgesic properties. The compounds were also tested for ulcerogenic activity and showed superior GI safety profile.



Scheme 15. Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives

Santosh N. Mokale *et al*. [26] investigated synthesis of a series of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives synthesized by condensation of thiourea, 5-(4-subtituted phenyl)-5-oxopentanoic acid and substituted aldehydes. The synthesized compounds were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant ($p < 0.05$) anti-inflammatory activity.

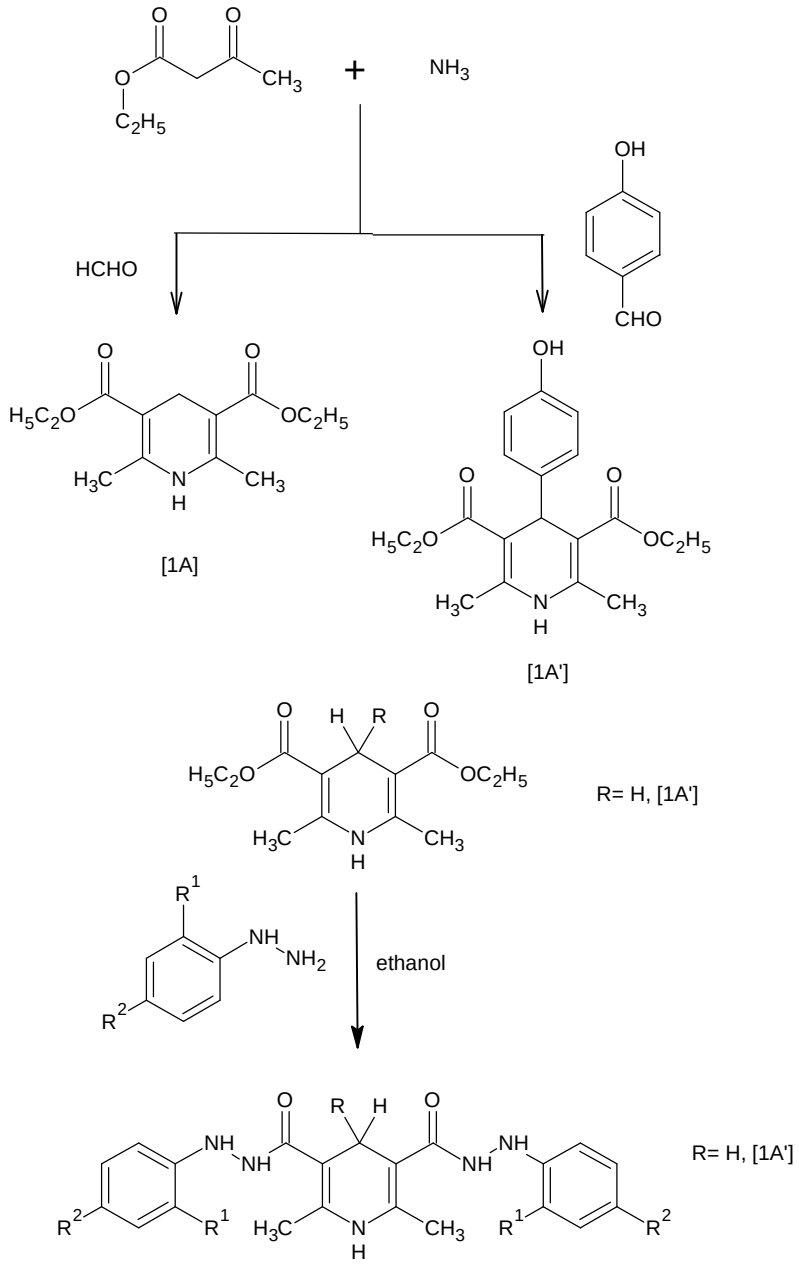
2. Hantzsch reaction



Scheme 16. General scheme for Hantzsh reaction.

The Hantzsch pyridine synthesis [27] also called as Hantzsch dihydropyridine synthesis is a multi-component organic reaction where aldehyde such as formaldehyde, β-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia reacts to form product. Initially dihydropyridine is formed as a product which oxidizes in next step to to produce pyridine. Aromatization is the main driving force for the reaction. This reaction was reported in 1881 by Arthur Rudolf Hantzsch.

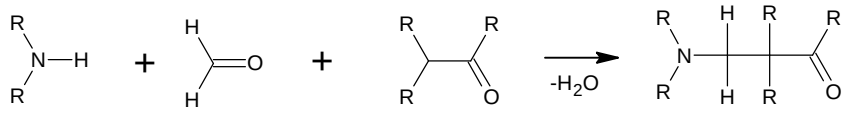
▪ **Hantzsch reaction used for synthesis of anti-inflammatory drugs**



Scheme 17. Synthesis of 2,6-dimethyl-N $_3$,N$_5$-diphenyl-1,4-dihydropyridine-3,5-dicarbohydrazide

A.Asma Samaunnisa *et al*. [28] reported a hantszch reaction for the synthesis of a series of new 2,6-dimethyl-N$_3$,N$_5$-diphenyl-1,4-dihydropyridine-3,5-dicarbohydrazide and its derivatives were synthesized from Diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates and Diethyl-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates were prepared by the condensation of ethyl acetoacetate with aldehydes in presence of ammonia.

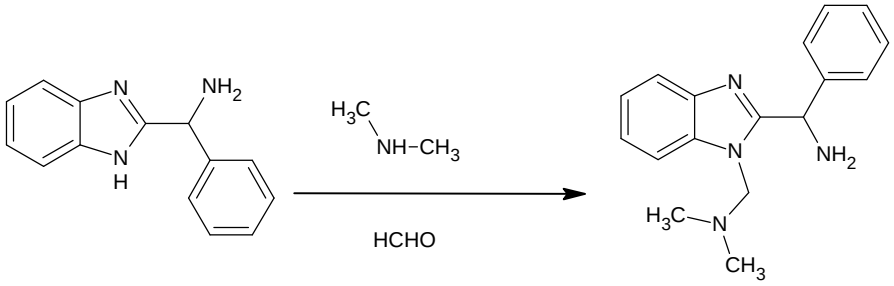
3. Mannich reaction



Scheme 18. General scheme for Mannich reaction

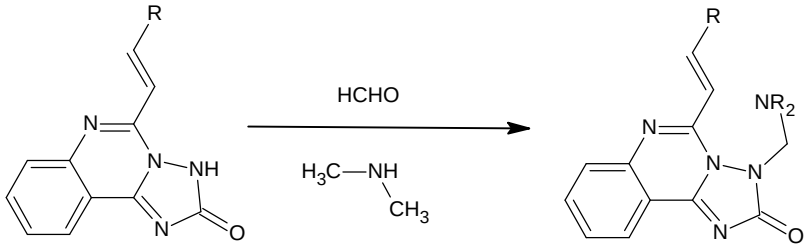
The Mannich reaction [29] is an example of multicomponent reaction which involves reaction of carbonyl functional group with formaldehyde and ammonia with primary or secondary amine to obtain β-amino-carbonyl compound known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.

- **Mannich reaction used for synthesis of anti-inflammatory drugs**



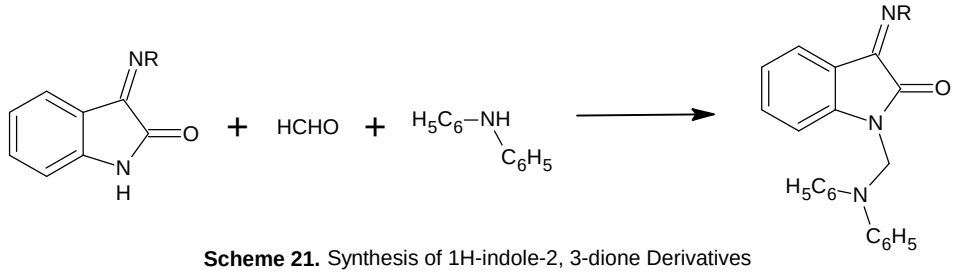
Scheme 19. Synthesis of benzamidazole using mannich base

B. Anil Reddy [30] has synthesized 1, 2-disubstituted benzimidazole derivatives using mannich bases. It was obtained by reacting 2-(1-amino benzyl) benzimidazole, secondary amine and formaldehyde the reactants were refluxed with stirring at 70-75 °C. The synthesized compound was evaluated for anti-inflammatory activity by using carrageenan induced paw edema.



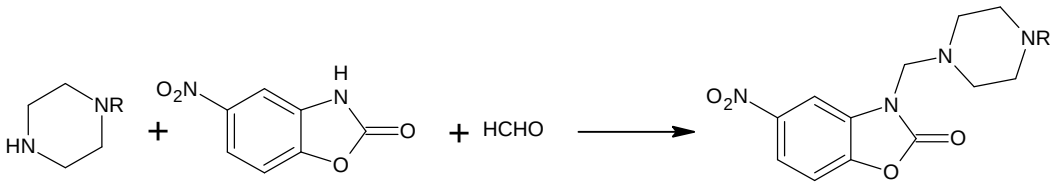
Scheme 20. Synthesis of substituted quinazolinone derivatives

Meenu Chaudhary *et al*. [31] has reported synthesis of a series of novel substituted-[1,2,4]triazolo[1,5c] quinazolino ne derivatives, by using mannich reaction. Quinazolinone is a compound made up of two fused six member simple aromatic rings-benezene and pyrimidine ring and have been reported to posses versatile type of biological activities such as anticancer, anticonvulsant, anti-inflammatory, antihelminthic, antimicrobial activities. The compound was synthesized by mannich reaction using formamide and different secondary amines. All synthesized compounds were screened for anti-inflammatory activity.



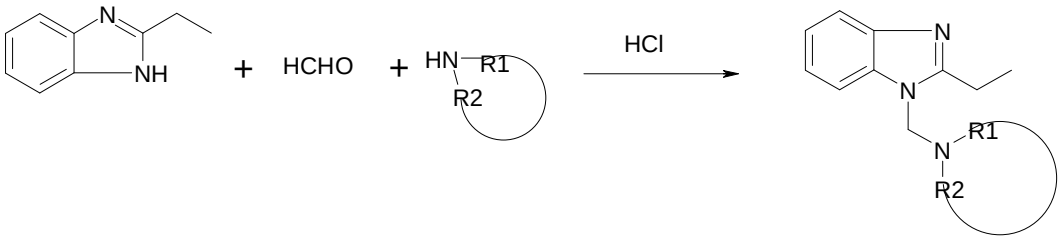
Scheme 21. Synthesis of 1H-indole-2, 3-dione Derivatives

Panda J *et al*. [32] has discovered synthesis of some 1H-indole-2, 3-dione derivatives. The starting compound 1H-indole-2,3-dione on reaction with different substituted anilines formed the Schiff bases. The corresponding N Mannich bases have been prepared by the reaction of the Schiff bases with diphenylamine in the presence of formaldehyde. The synthesized Mannich bases were screened for their antibacterial, analgesic and anti-inflammatory activities by the standard methods. According to author the compound containing chloro group showed the most favorable activity.



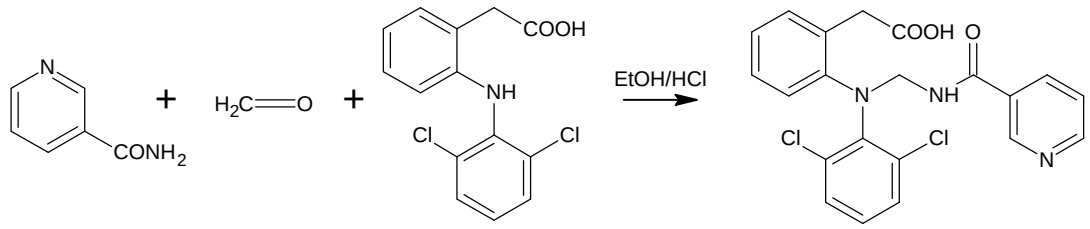
Scheme 22. Synthesis of 5-nitro-3-piperazinomethyl-2-benzoxazolinones

Meric Koksal *et al*. [33] has prepared new Mannich Bases of 5-Nitro-2-Benzoxazolinones. The target compounds were prepared by vigorously stirring a solution of the substituted piperazine derivative, 5-nitro-2-benzoxazolinone in methanol, formaline was added and then mixture refluxed in a water bath for 1 h. The synthesized compounds were examined for their in vivo anti-inflammatory and analgesic activities in two different bioassays, namely, carrageenan-induced hind paw edema and p-benzoquinone-induced abdominal constriction tests in mice and also ulcerogenic effects were determined. Among the tested derivatives most promising results were obtained for the compounds bearing electron-withdrawing substituents (F, Cl, -$COCH_3$) in the ortho/para position of the phenyl nucleus on the piperazine ring at 3 position of benzoxazolinone moiety. The analgesic activities of all compounds are higher than their anti-inflammatory activities.

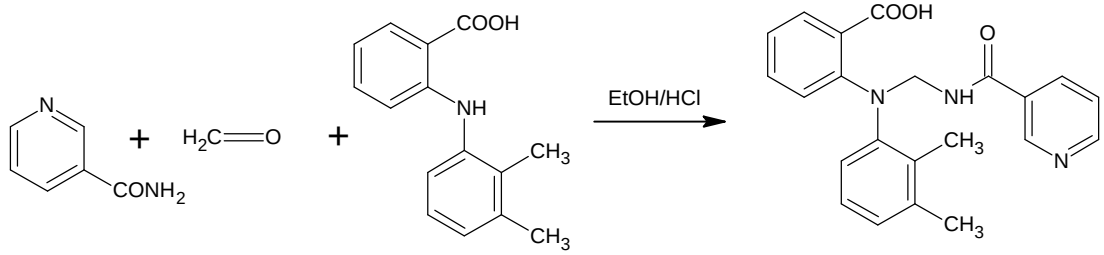


Scheme 23. Synthesis of 2-ethyl benzamidazole derivatives.

G. Mariappan *et al*. [34] has developed one pot synthesis of [1-(N-substitued amino) methyl]-2-ethyl benzamidazole derivatives that has been synthesized by condensation of 2-ethyl benzamidazole with substituted primary and secondary amines. Analgesic activity has been carried out on mice by using tail flick method.

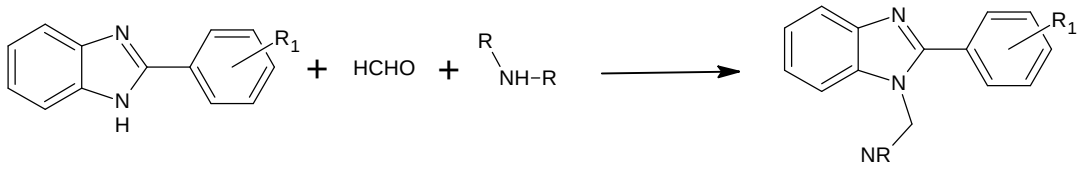


Scheme 24. Synthesis of mannich base nicotinamide with diclofenac MND



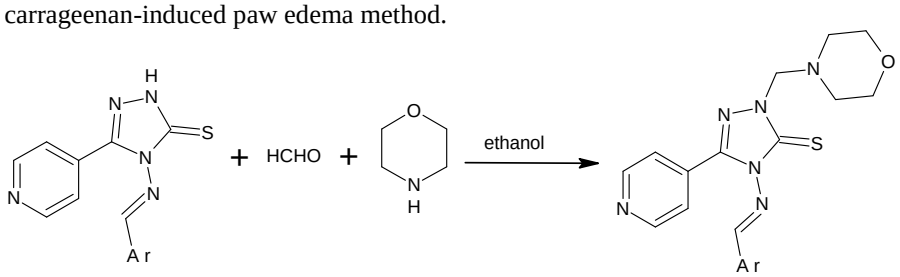
Scheme 24. Synthesis of mannich base nicotinamide with mefenamic acid MNM

Ritchu Babbar *et al*. [35] has proposed Mannich bases of Nicotinamide with diclofenac and mefenamic acid. The compound was tested for their anti-inflammatory activity. Nicotinamide on reaction with secondary amine, i.e., diclofenac and mefenamic acid in presence of formaldehyde and hydrochloric acid lead to the formation of target molecule. The molecules were evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema method and exhibited significant activity.



Scheme 25. Synthesis of N-Mannich bases of 2-(substitutedphenyl)benzimidazole.

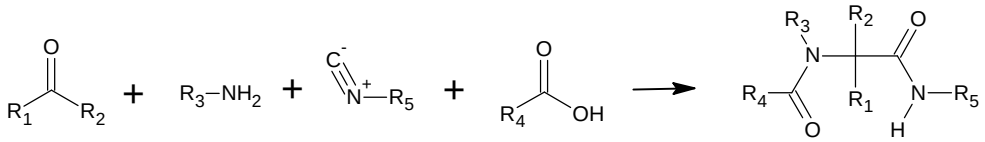
J.T Leonard *et al*. [36] has demonstrated synthesis of 1-(substituted methyl)-2-(substituted phenyl) benzimidazoles. The compounds were evaluated for anti-inflammatory and anti-bacterial activities. The author observed that the compounds having methoxy substituent at phenyl ring produce better activity than nitro substituent. The compounds with morpholine, piperazine, piperidine, 4-methyl piperazine and 4-ethyl piperazine substitution at amine position produce good anti-inflammatory activity. The synthesized compound was subjected for anti-inflammatory activity using carrageenan-induced paw edema method.



Scheme 26. Synthesis of 4-[1-4-substitutedphenyl methylidene]amino-1-(morpholinomethyl)-3-(4-pyridyl)-4, 5-dihydro-1H-1, 2, 4-triazole-5-thione

Mostafa A. Hussein *et al*. [37] has designed the synthesis 4-[1-4-substituted phenyl methylidene] amino-1-(morpholinomethyl)- 3-(4-pyridyl)-4, 5-dihydro-1H-1, 2, 4-triazole-5-thione. Compounds were synthesized in a one pot reaction involving formaldehyde, and morpholine. All compounds were evaluated for their anti-inflammatory activity and analgesic activity using indomethacin as a reference drug. The author observed compounds carrying Cl, Br, and NMe_2 moieties, respectively revealed maximum activity at 4 h post-injection and showed ~84-100% of the inhibition exhibited by indomethacin a result that could be attributed to the structural similarities to that moieties in indomethacin.

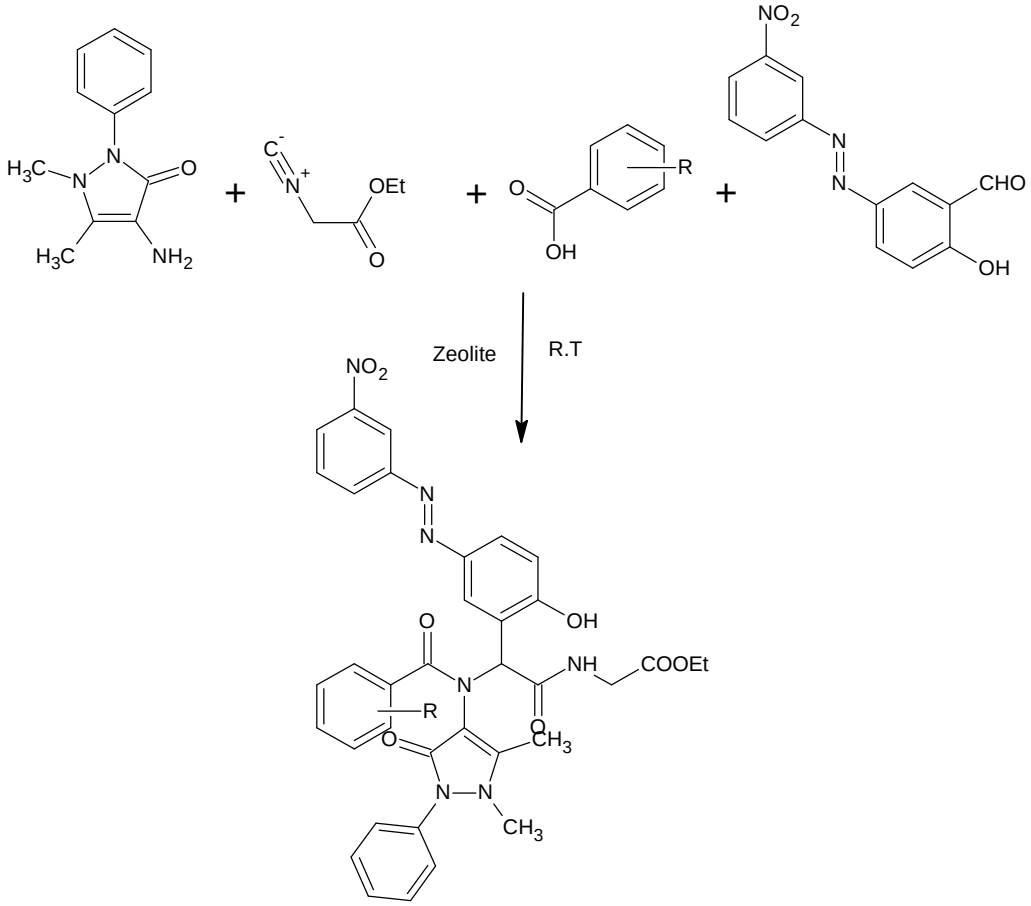
4. Ugi reaction



Scheme 27. General scheme for Ugi reaction.

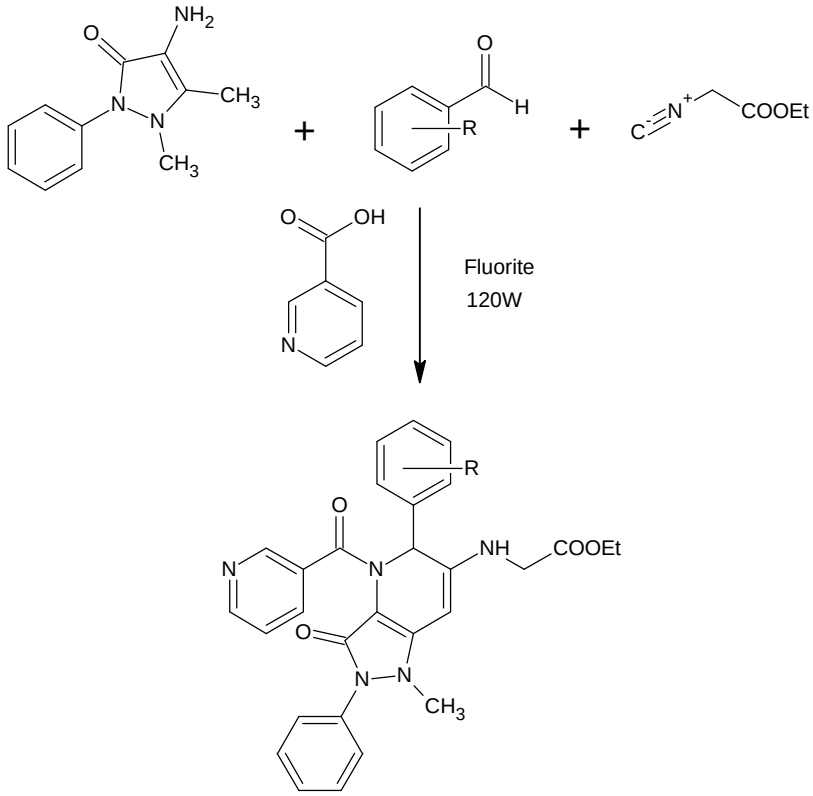
The Ugi reaction [38] is a multi-component reaction where a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid reacts together to form a bis-amide. The reaction is named after Ivar Karl Ugi in 1959. As Ugi reaction is exothermic in nature the reaction usually completes within few minutes.

- **Ugi reaction used for synthesis of anti-inflammatory drugs**



Scheme 28. Synthesis of UGI 4CR derivatives

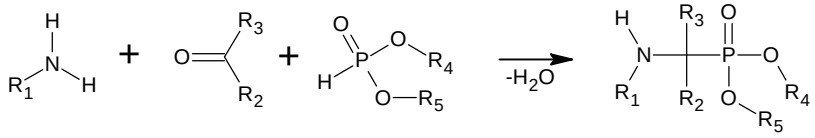
Ipsita Mohanram, *et al*. [39] has synthesized Ugi 4 CR by adding a mixture of 2-hydroxy-4-((3-nitrophenyl)diazenyl)benzal dehyde, 4-aminoantipyrine, ethyl isocyanoacetate, substituted carboxylic acid in ethanol and Zeolite in one-pot and stirred at room temperature. The synthesized compound was tested for analgesic and anti-inflammatory activities. Analgesic activity was evaluated by Eddy hot plate method using Morphine Sulfate as a standard reference drug. Anti-inflammatory activity was evaluated by mercury displacement method using Diclofenac as standard reference drug.



Scheme 29. Synthesis of Ugi 4CR

Ipsita Mohanram *et al*. [40] has developed an efficient and rapid synthesis of novel anti-inflammatory and antimicrobial agents using 4-aminoantipyrine, nicotinic acid, ethylisocyanoacetate and substituted aldehydes via Ugi four component reactions (Ugi-4CR) protocol under microwave irradiation in presence of Fluorite as a catalyst.

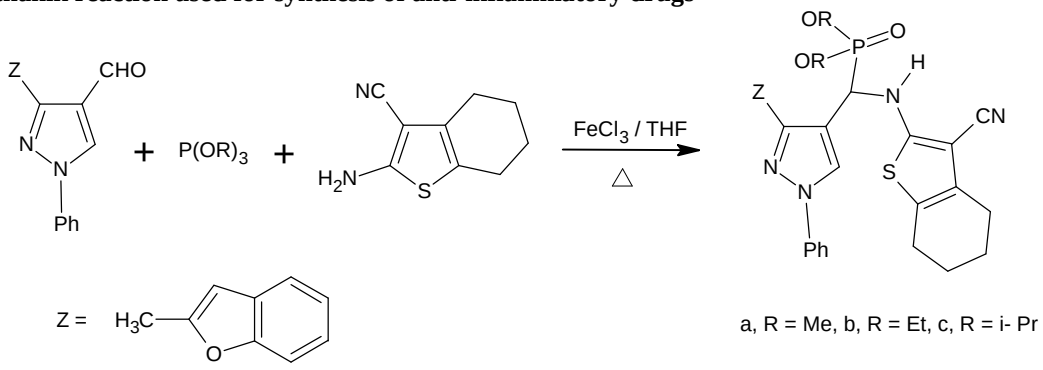
5. Kabachanik field reaction



Scheme 30. General scheme for the Kabachnik - Fields reaction

Kabachnik–Fields reaction [41] is a multicomponent reaction which involves formation of an α-amino phosphonate from an amine, a carbonyl compound and a dialkyl phosphonate. This multicomponent reaction was independently discovered by Martin Izrailevich Kabachnik and Ellis K. Fields in 1952. This reaction involves firstly the formation of an imine followed by an addition reaction of the phosphonate P-H bond into the C=N double bond. The reaction is accelerated by using dehydrating reagent and Lewis acid.

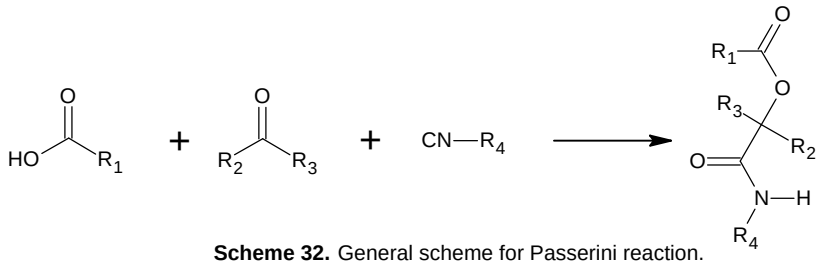
- **Kabachanik reaction used for synthesis of anti-inflammatory drugs**



Scheme 31. Synthesis of alpha-aminophosphonates

Wafaa M. Abdou *et al*. [42] has demonstrated synthesis of alpha-aminophosphonates and alpha-aminophosphonic diamides with anti-inflammatory properties. Schiff-base Kabachnik–Fields intermediates generated in situ from substituted pyrazole-4-carbaldehyde and 2-aminothiophene derivatives were trapped by dialkyl phosphites to produce the corresponding alpha-aminophosphonates in moderate yields. Some of the new compounds exhibited considerable anti-inflammatory properties.

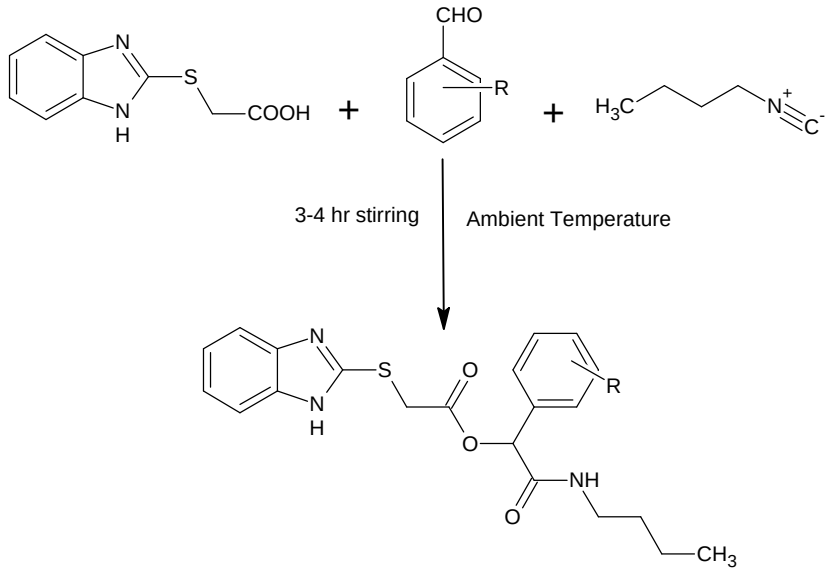
6. Passerini reaction



Scheme 32. General scheme for Passerini reaction.

The Passerini reaction [43] is a multicomponent reactionused for the formation of α-acyloxy amide from an aldehyde (or ketone), an isocyanide and a carboxylic acid. This organic reaction was discovered by Mario Passerini in 1921. This reaction is the first isocyanide based multi-component reaction.

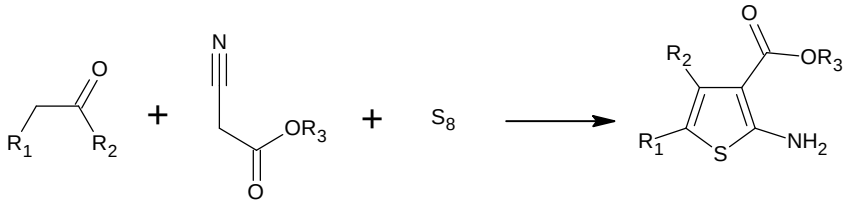
- **Passerini reaction used for synthesis of anti-inflammatory drugs**



Scheme 33. Synthesis of benzimidazole derivative

Irfan N. Shaikh *et al*. [44] has discovered synthesis of a series of carbonyl-amide linkage based new benzimidazole derivatives from acid, aldehydes and isocyanide at ambient temperature via Passerini reaction. All the compounds synthesized were screened for their potential anti-inflammatory, antidiabetic and anticonvulsant properties.

7. Gewald reaction

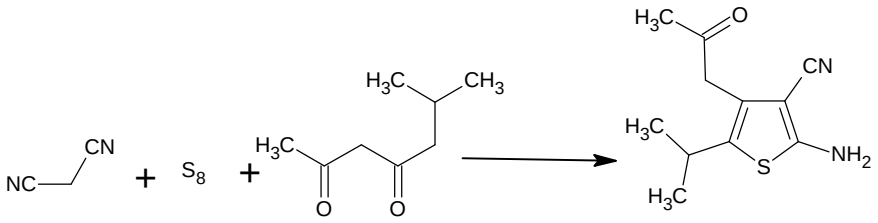


Scheme 34. General scheme for Gewalds reaction

The Gewald reaction [45] is multicomponent reaction which involes the condensation of a ketone or aldehyde with a α-cyanoester in the presence of elemental sulfur and base to give a poly-substituted 2-amino-thiophene.

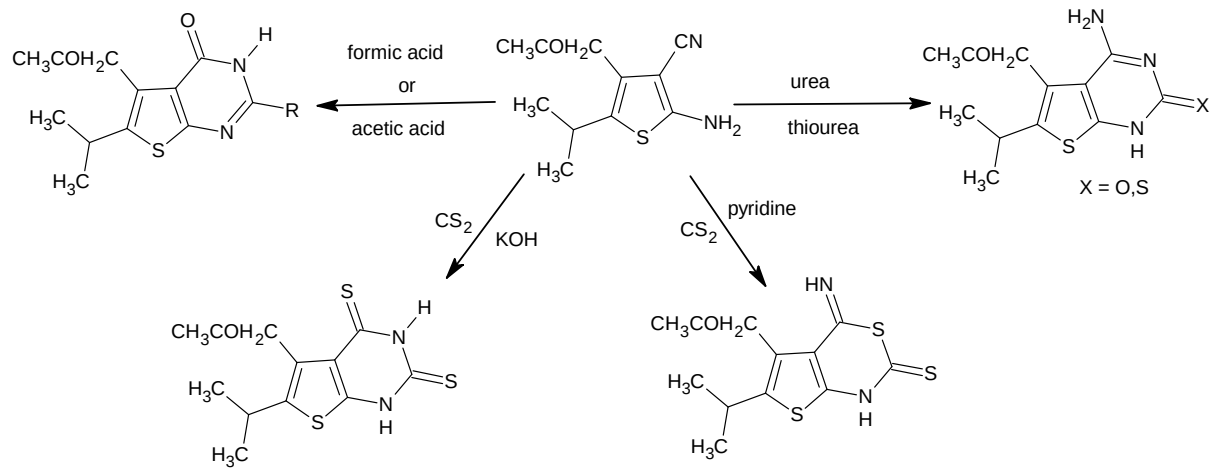
- **Gewald reaction used for synthesis of anti-inflammatory drug**

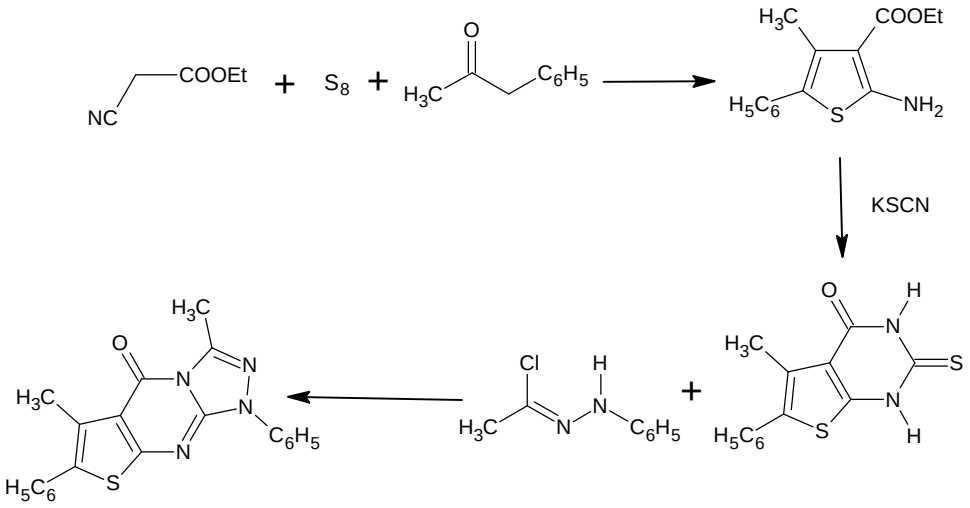
Step 1



Scheme 35. Synthesis of acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile derivative

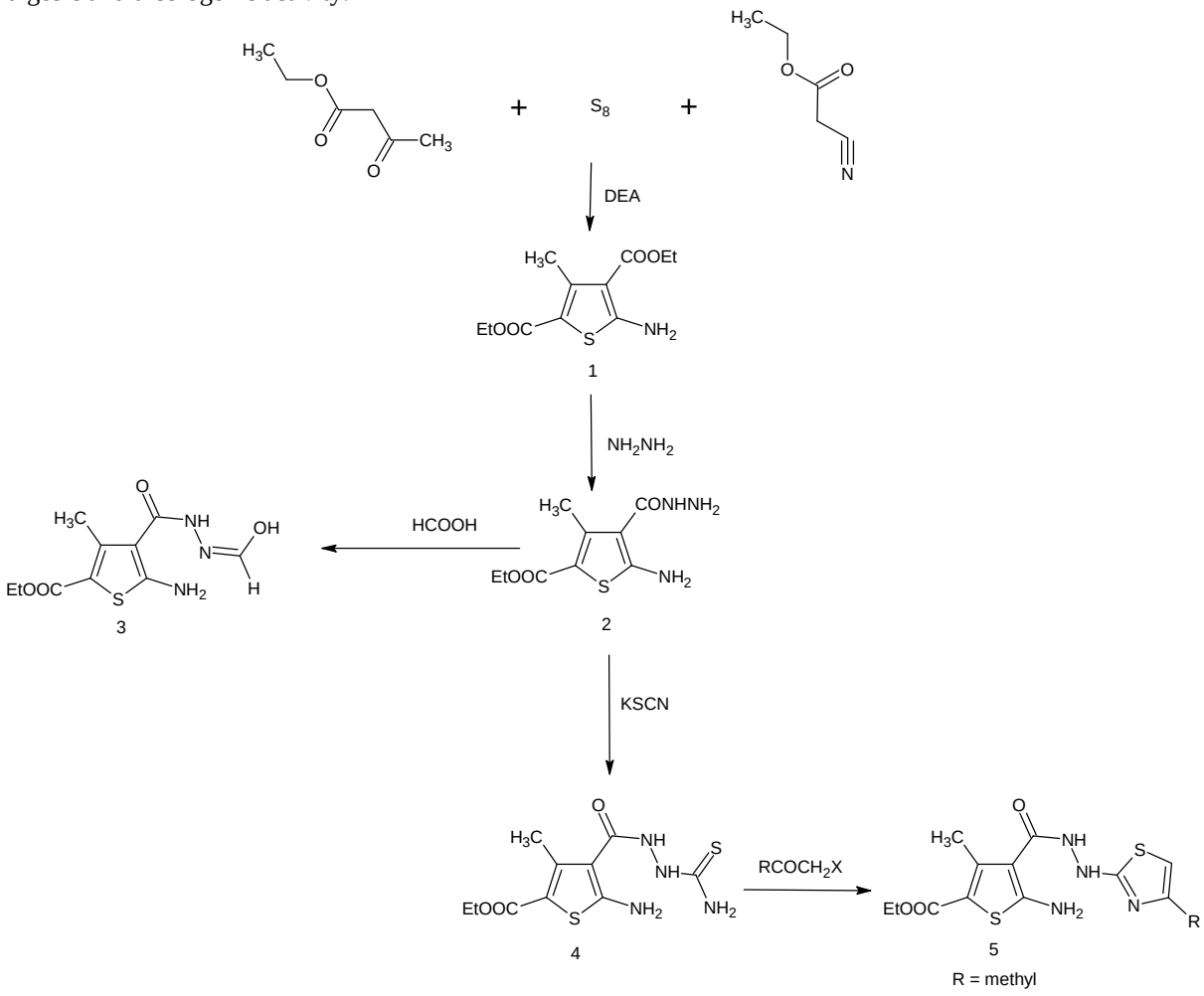
Step 2

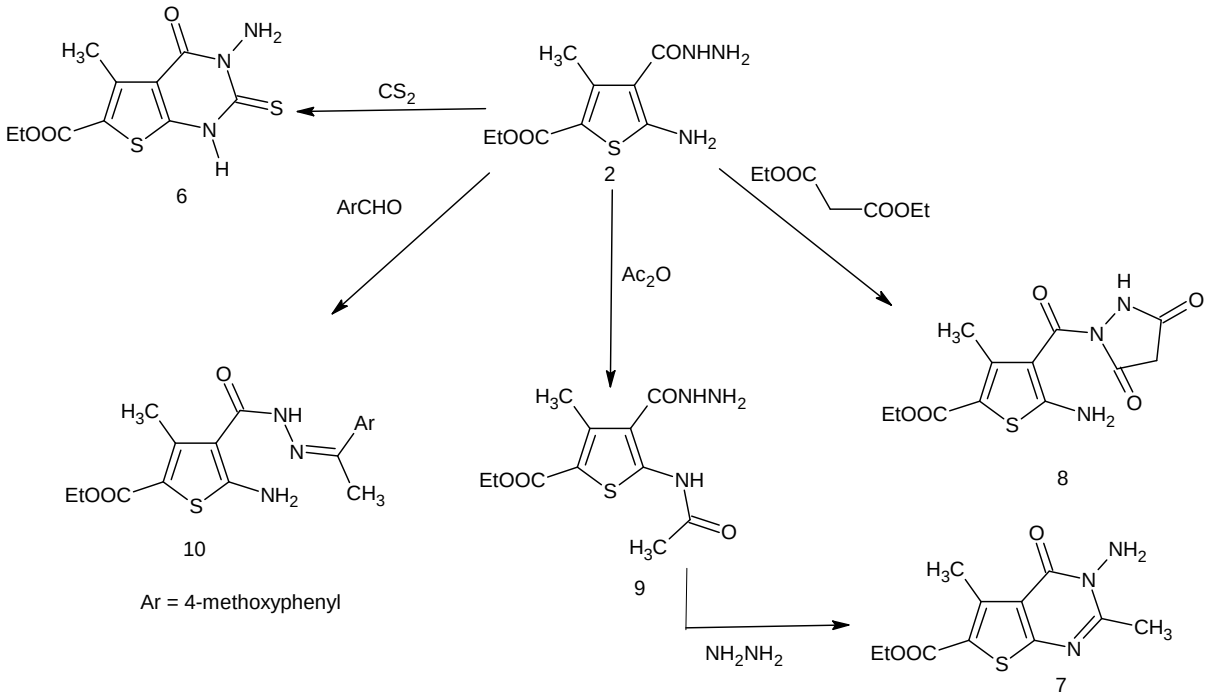




Scheme 35. Synthesis of 5-methyl-6-phenyl-2-thioxo--thieno[2,3-d]pyrimidine derivative

Abdel-Rahman B *et al*. [46] reported synthesis of thieno[2,3-d]pyrimidine derivatives which was obtained from reacting acetone-1-(2-amino-5-isopropyl-thiophene-3-carbonitrile by reacting 6-methyl-heptane-2,4-dione, malononitrile, sulfur and diethylamine. The synthesized compound obtained was evaluated for anti-inflammatory, analgesic and ulcerogenic activity.

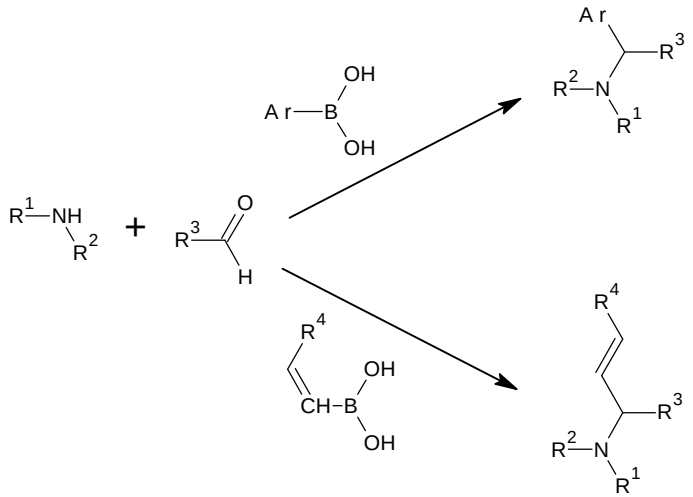




Scheme 36. Synthesis of 3-Pyrazolyl-thiophene and thieno[2,3-d]pyrimidines

H. N. Hafez, A. El-Gazzar *et al*. [47] has reported synthesis of two series of 5-ethyl-2-amino-3-pyrazolyl-4-methylthiophenecarboxylate and 2-thioxo-N3-aminothieno[2,3-d]pyrimidines were prepared from 3,5-diethyl-2-amino-4-methylthio-phenecaboxylate and evaluated for anti-inflammatory, analgesic and ulcerogenic activities.

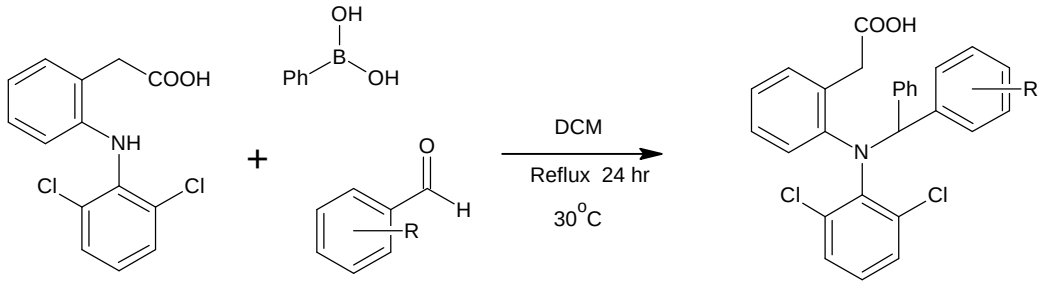
8. Petasis Reaction



Scheme 37. General scheme for Petasis Reaction

Petasis reaction [48] is a multicomponent reaction involving an amine, aldehyde, and vinyl- or aryl-boronic acid to form substituted amines. In the Petasis reaction, the vinyl group of the organoboronic acid serves as the nucleophile. The Petasis reaction is mild reaction and also useful in generating α-amino acids.

- **Petasis reaction used for synthesis of anti-inflammatory drug**



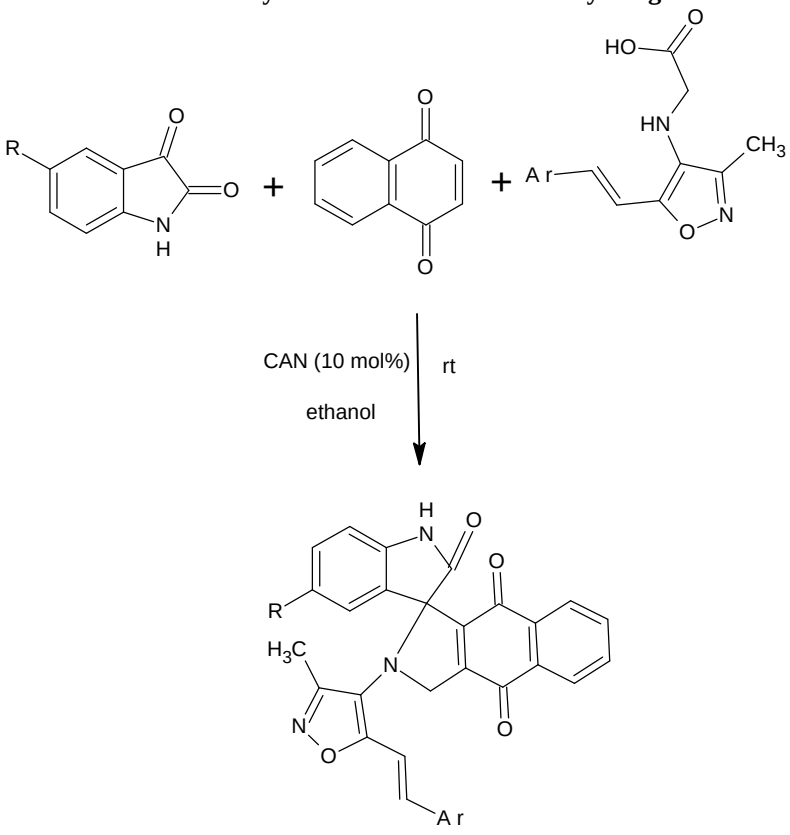
R = H, -OH, -NO $_2$, -OMe, -Cl

Scheme 38. Synthesis of diclofenac analogue.

Hassan A. Osman and G. M. Nazeruddin [49] has reported synthesis of a series of diclofenac derivatives obtained from petasis reaction involving aldehyde, diclofenac and phenyl boronic acid into 1:1:1 molar ratio in 15 ml Dichloromethane stirring at 30^0C. The synthesized compound was subjected for anti-inflammatory activity using carrageenan-induced paw edema method.

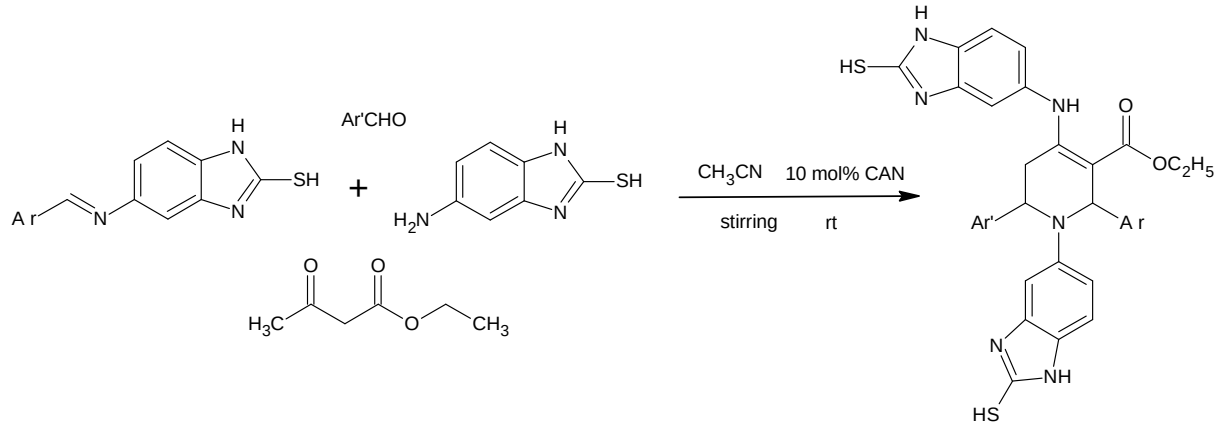
9. Miscellaneous reactions

- **Miscellaneous reaction used for synthesis of anti-inflammatory drugs**



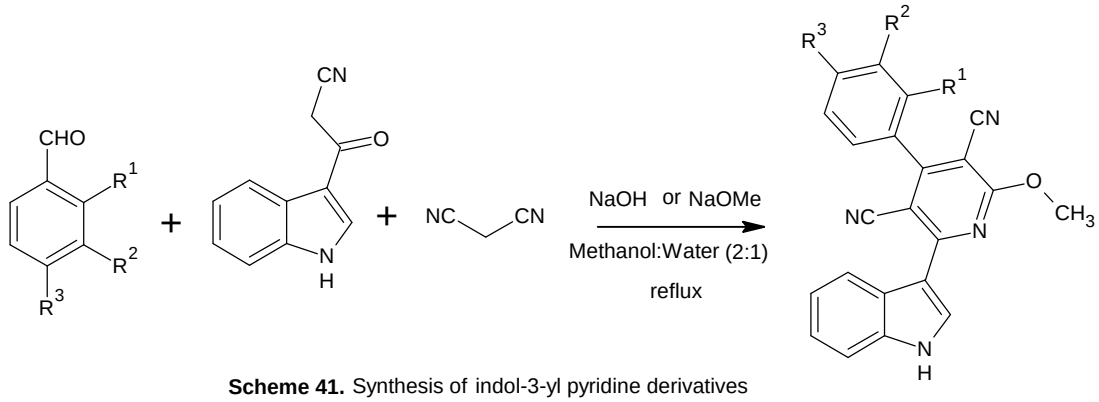
Scheme 39. Synthesis of isoxazolyl-2,3-dihydrospiro[benzo(f)isoindole-1,3-indoline]-2',4,9-triones

E. Rajanarendar *et al.* [50] has prepared isoxazolyl-2,3-dihydrospiro[benzo[f]isoindole-1,3'-indoline]-2',4,9-triones by reacting 4-amino-3-methyl-5-styrylisoxazole with chloroacetic acid followed by a three component reaction with substituted isatins and 1,4-naphthoquinone using Ceric ammonium nitrate (CAN) catalyst under aerial oxidation condition.



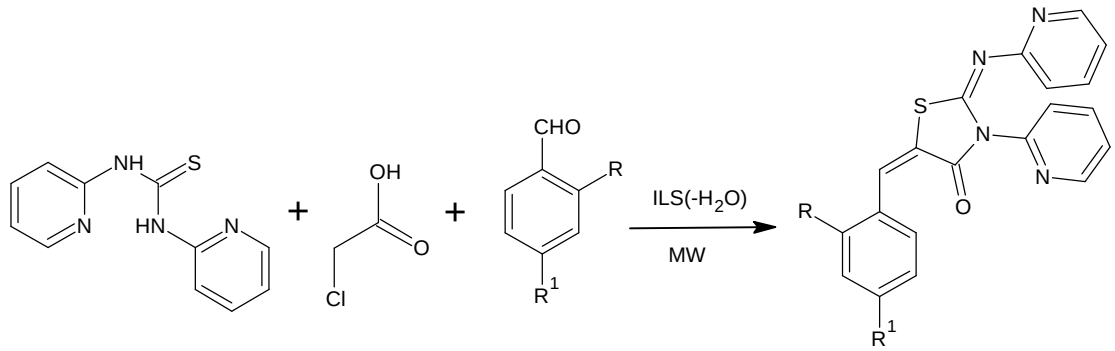
Scheme 40. Synthesis of benzo[d]imidazolyltetrahydropyridine carboxylates

Anisetti Ravindernath *et al*. [51] synthesized a series of novel benzo[d]imidazolyltetrahydro pyridine carboxylates by one-pot multi-component reaction of (E)-5-(benzylidene amino)-1H-benzo[d]imidazole- 2-thiol 3, 5-amino-2-mercapto-benzimidazole 4, aromatic aldehyde 5, and ethyl acetoacetate in acetonitrile using ceric ammonium nitrate (CAN) as Lewis acid catalyst, and evaluated for their anti-inflammatory, antioxidant, antibacterial and antifungal activities.



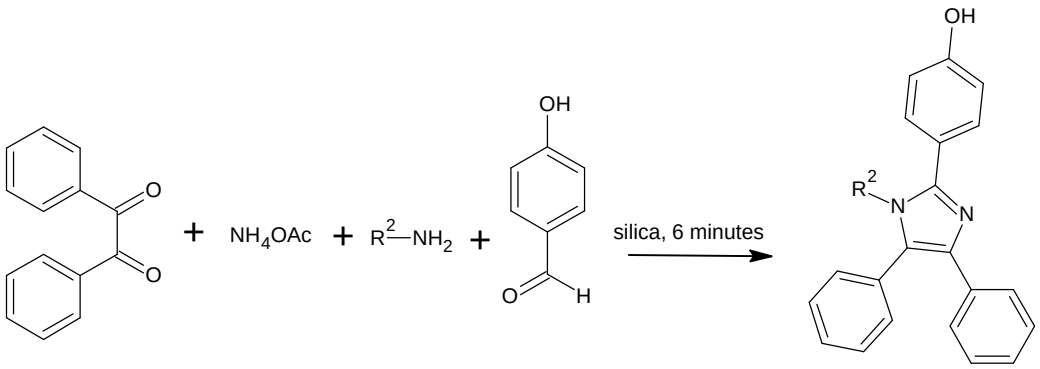
Scheme 41. Synthesis of indol-3-yl pyridine derivatives

Prakasam Thirumurugan *et al*. [52] has synthesized 2-(1H-Indol-3-yl)-6-methoxy-4-arylpyridine-3,5-dicarbonitrile through one-pot multi component reaction. The synthesized compounds showed a good anti-inflammatory activity. Also a series of bis-Hantzsch dihydropyridine derivatives were synthesized and they exhibit analgesic activity. The molecule was obtained by reacting 3-cyanoacetyl indole, aldehyde, malononitrile and freshly prepared sodium methoxide, sodium hydroxide in methanol and water in reflux condition.

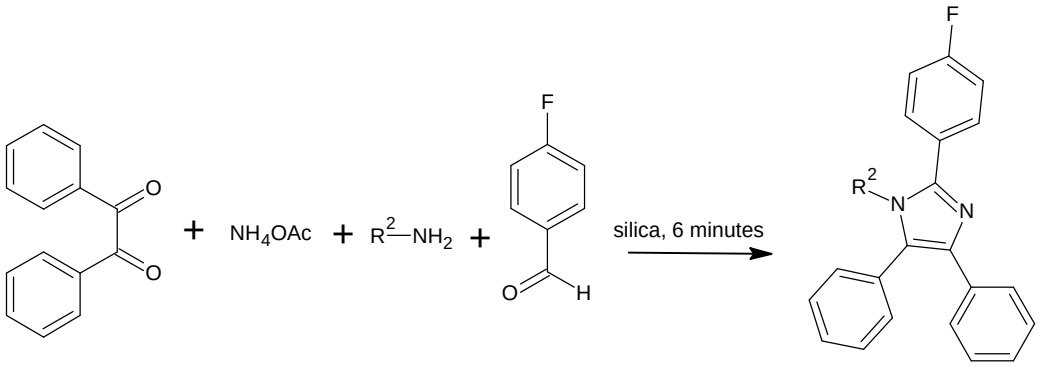


Scheme 42. Synthesis of 4-thiazolidinone derivatives

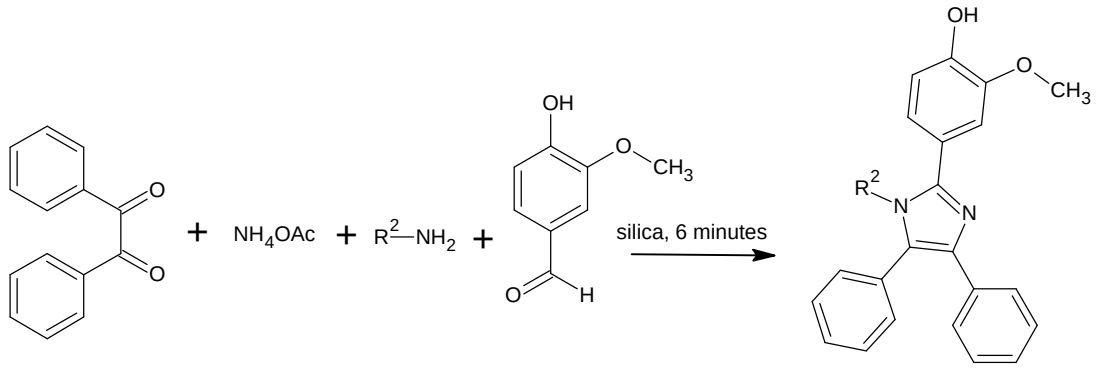
Muhammad Naeem *et al*. [53] has prepared 4-thiazolidinone derivatives by using 1,3-dipyridin-2-ylthiourea, chloroacetic acid, substituted benzaldehyde, and ionic liquids in water and irradiated under microwave irradiation. The compound were synthesized and evaluated for anti-inflammatory activity.



Scheme 43. Synthesis of N-substituted 4,5 diphenyl-2-(4-hydroxyphenyl)imidazole derivatives

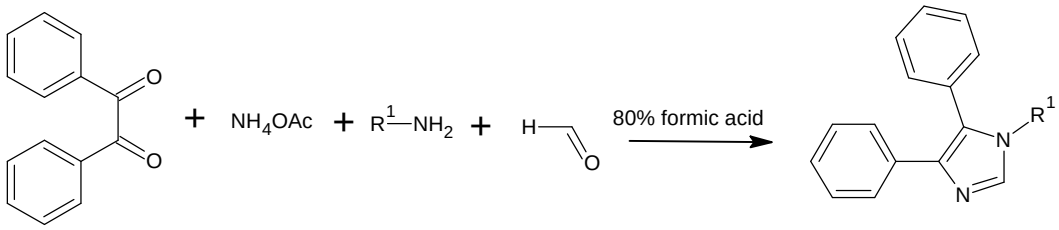


Scheme 43. Synthesis of N-substituted 4,5 diphenyl-2-(4-fluorophenyl) imidazole derivatives



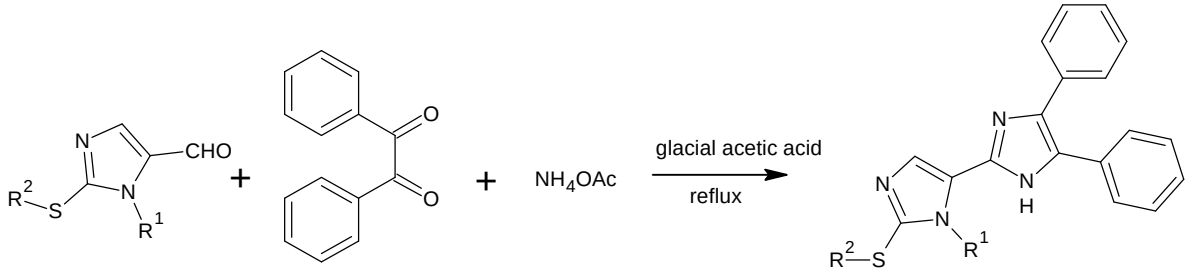
Scheme 43. Synthesis of N-substituted 4,5 diphenyl-2-(4-hydroxy-3- Methoxy phenyl) imidazole derivatives

Harsha Tripathy *et al*. [54] had demonstrated one pot synthesis of 1,2,4,5 - tetra-substituted imidazoles by single step four-component condensation reaction wherein the cyclization occurs to form imidazole ring . The target molecule was obtained from Benzil, ammonium acetate, aldehydes and amine were triturated with silica under microwave irradiation. The synthesized compound was screened for anti-inflammatory activity by rat paw edema method.



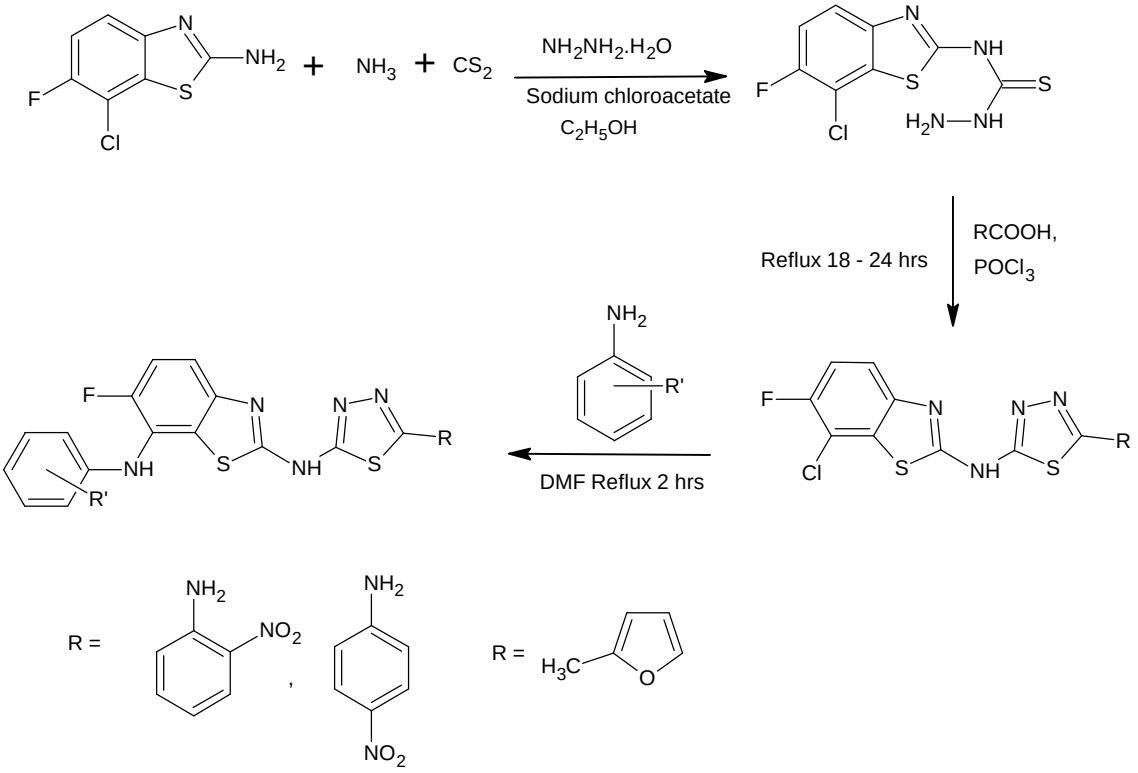
Scheme 44. Synthesis of 1,4,5-Tri Substituted Imidazoles

Harsha Tripathy *et al*. [55] has synthesized tri substituted imidazoles using synthetic microwave oven, which showed significant reduction in reaction time, increased yield and synthesis of library of compounds in a very short time. The synthesized compounds were screened for anti-inflammatory activity by rat paw edema method and they showed good activity.



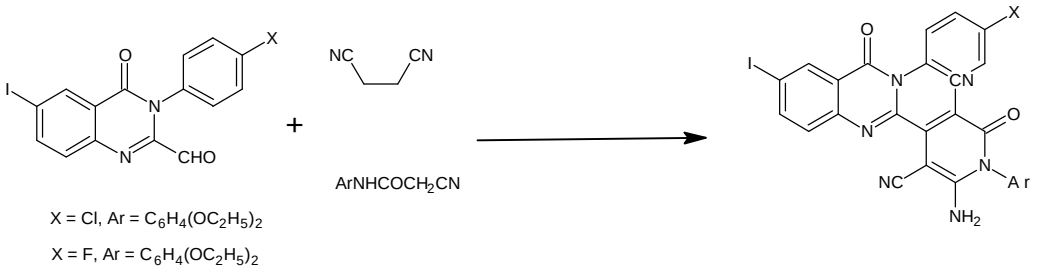
Scheme 45. Synthesis of 4,5-Diaryl-2-(2-alkylthio-5-imidazolyl) Imidazoles

Mohammad Reza Saberi *et al*. [56] has synthesized of 4, 5-diaryl-2-(2-alkylthio-5-imidazolyl) imidazole derivatives and their anti-inflammatory and antinociceptive activities were evaluated. 2-(2-Alkylthio-5-imidazolyl)-4,5-diphenylimidazole compounds were obtained by the reaction of benzyl with 2-alkylthio-1-benzylimidazole-5-carbaldehyde, in the presence of ammonium acetate. More potent compounds were aimed to achieve by the author with moderate selectivity for COX-2.



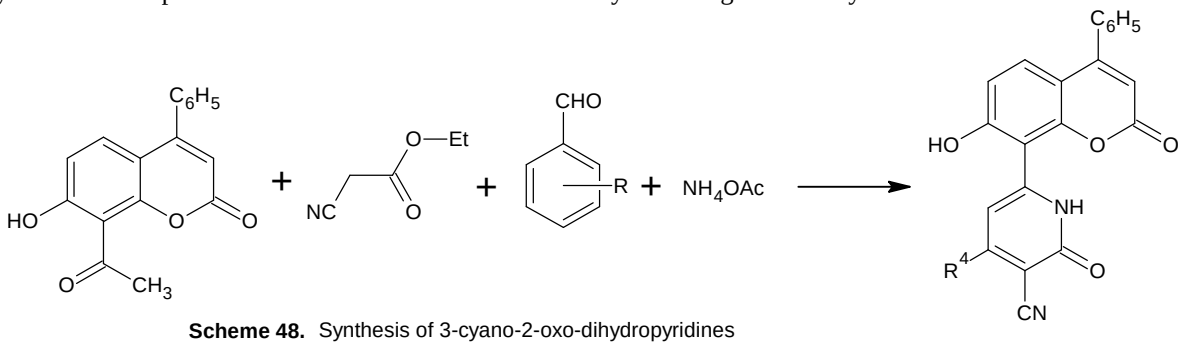
Scheme 46. Synthesis of 7-Aryl-6-Fluoro-N- (5- Aryl -1, 3, 4 -Thiadizol-2-yl) 1-3-benzothiazol-2-amine

M. Sugumaran *et al*. [57] has synthesized a new series of flurobenzothiazole incorporated 1, 3, 4 - thiadiazole compounds and evaluated for the anti-inflammatory activity by carrageenan-induced paw oedema method.

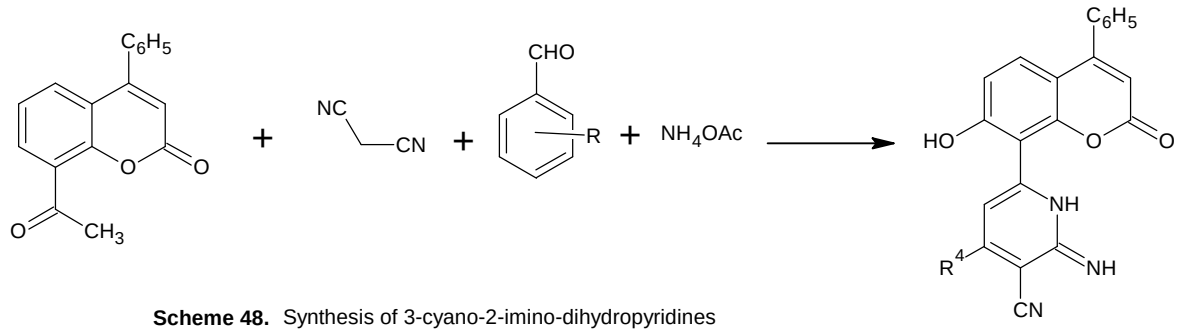


Scheme 47. Synthesis of pyridinone derivatives

Awatef A. Farag *et al*. [58] reported a one-pot methodology for the synthesis of pyridinone derivatives. The synthesized compound was evaluated for anti-inflammatory and analgesic activity.

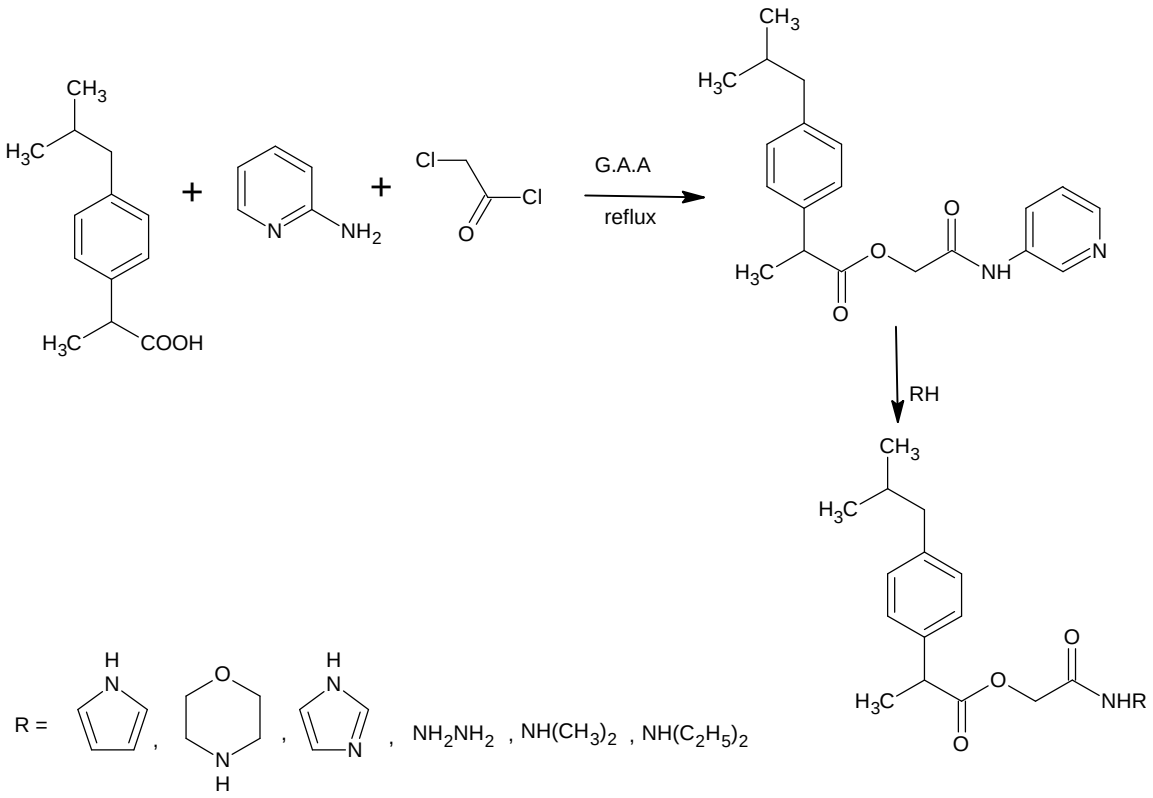


Scheme 48. Synthesis of 3-cyano-2-oxo-dihydropyridines



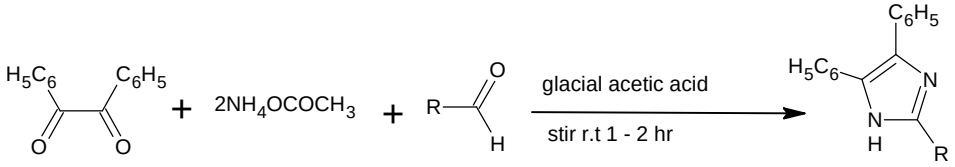
Scheme 48. Synthesis of 3-cyano-2-imino-dihydropyridines

Amal A. M. Eissa *et al*. [59] has demonstrated synthesis of 8-Acetyl-7-hydroxy-4-phenyl-2H-benzopyran-2-one using this as starting material 3-cyano-2-oxo-dihydropyridines and 3-cyano-2-imino-dihydropyridines has been synthesized compound showed significant anti-inflammatory, analgesic and antipyretic activities.



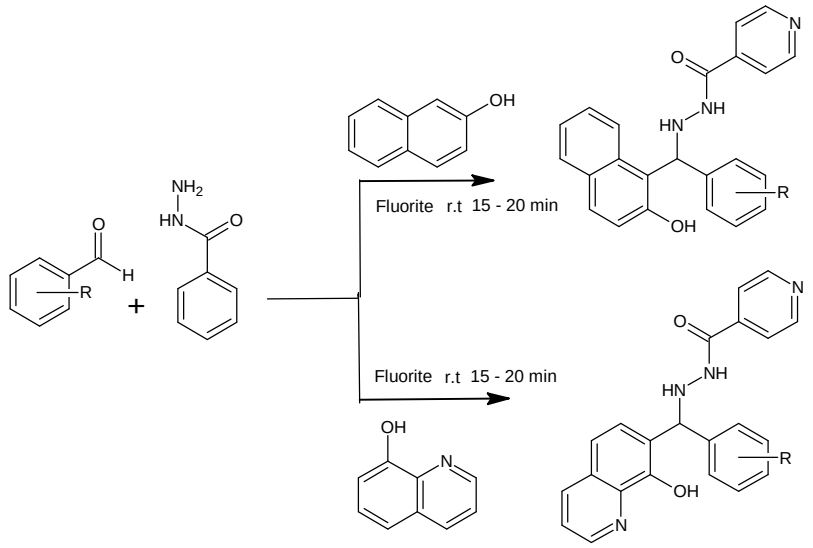
Scheme 49. Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid pyrrolidin-2-ylcarbamoyl methyl ester derivatives

Richa Gupta *et al.* [60] has reported synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-ylcarbamoyl methyl ester by refluxing Ibuprofen with 2-amino pyridine in chloroacetyl chloride in presence of glacial acetic acid gave 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-yl-carbamoyl methyl ester, which can be used as a prodrug for ibuprofen with enhanced anti-inflammatory potential. Derivatives were then treated with various cycloamino moieties such as morpholine, pyrrolidine, hydrazine hydrate. The synthesized compounds have shown significant anti-inflammatory activity.



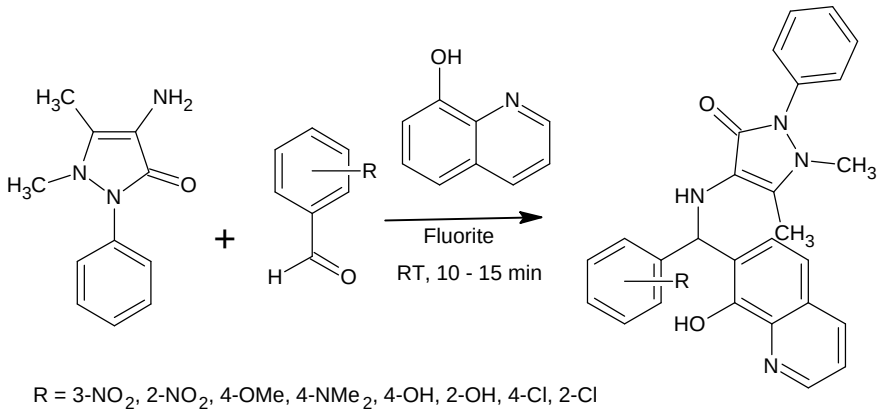
Scheme 50. Synthesis of 2-substituted-4,5-diphenyl-1 H-imidazoles.

A. Puratchikody and Mukesh Doble [61] have demonstrated synthesis of imidazoles by condensation of benzil, aldehydes, ammonium acetate. The anti-inflammatory activity and QSAR studies of the compound has been carried on 2-substituted-4, 5-diphenyl-1H-imidazoles. Compounds with phenyl substitution with –F, –Cl, $–NH_2$, $–N(CH_3)_2$, –OH and $–OCH_3$ at the p-position showed higher activity than the other substitutions in the studies. The author observed electron-donating groups and hydrophilicity play an important role in the biological activity. Lowering of activity was observed with hydrophobic groups.



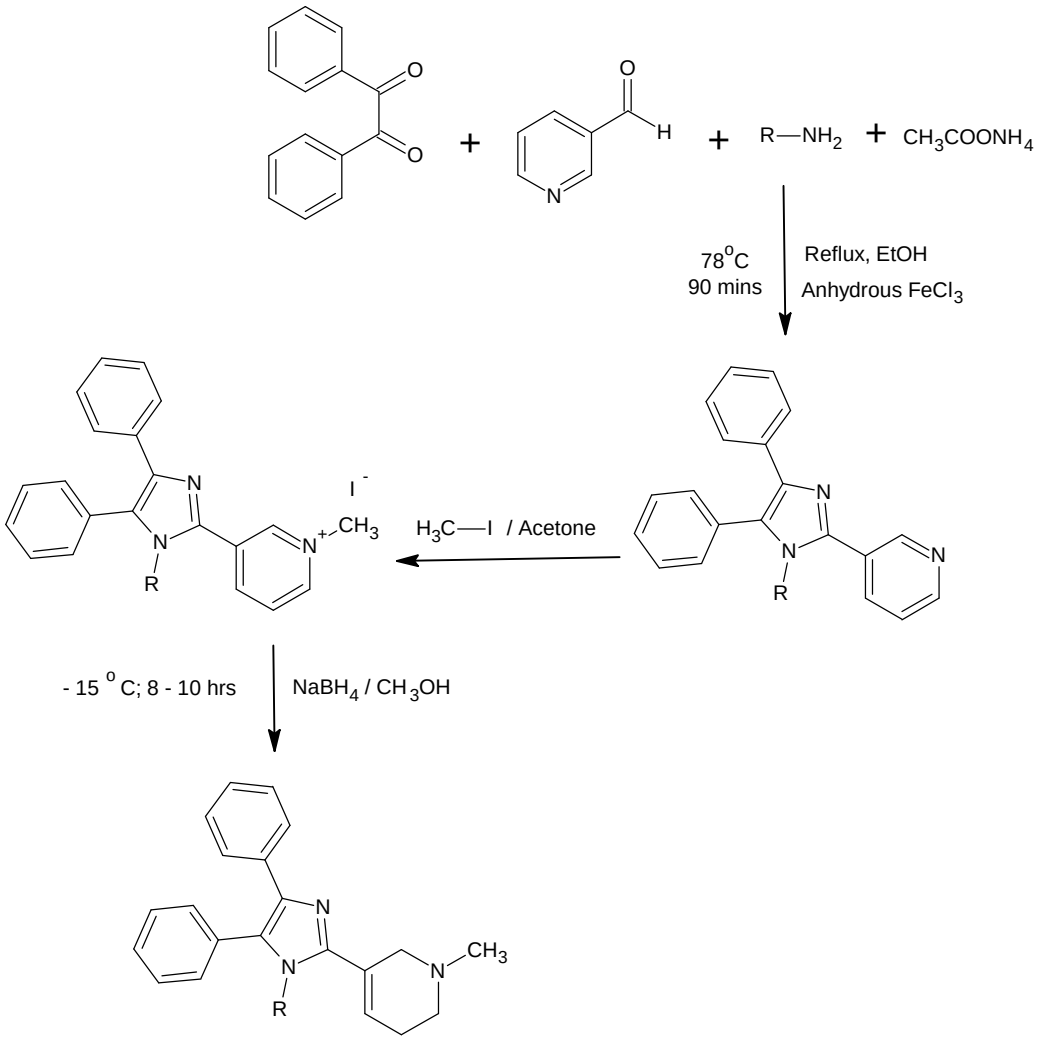
Scheme 51. Synthesis of isoniazid derivatives

Ipsita Mohanram *et al*. [62] has discovered a novel synthesis of isoniazid derivatives that has been achieved by the condensation of aldehydes, isoniazid, and phenols via Betti reaction has been described. The reactions were carried out at room temperature using fluorite as catalyst. The compound was investigated for in vivo anti-inflammatory activity on Wistar albino rats using a standard reference drug diclofenac.



Scheme 52. Synthesis of 4amino antipyrine derivatives via betti reaction

Ipsita Mohanram and JyotsnaMeshram [63] has reported the synthesis and biological evaluation of 4-aminoantipyrine derivatives prepared from a three-component Betti reaction. The synthesis was initiated by the condensation of aromatic aldehyde, 4-aminoantipyrine, and 8-hydroxyquinoline in presence of fluorite as catalyst in a simple one-step protocol. All the synthesized derivatives were screened *in vivo* anti-inflammatory activity against a reference drug, Diclofenac respectively. The results show that compounds having 4-OMe, 4-NMe_2, 4-Cl, 2-Cl substituent were found to possess potential anti-inflammatory activity when compared with reference drugs, respectively. The bioactivity of these derivatives has also been evaluated with respect to Lipinski's rule of five using molinspiration cheminformatics software.



Scheme 53. Synthesis of 1-methyl-3-(1,4,5-trisubstituted-1H-imidazol-2- yl)-1,2,5,6-tetrahydropyridine

Manal Mohammed *et al*. [64] has discovered the synthesis of 1-methyl-5-(1-alkyl/aryl-4,5-diphenyl-1H-imidazol-2-yl)-1,2,5,6-tetrahydropyridine. Synthesis of the target molecule was achieved by firstly subjecting to multicomponent, one-pot synthesis for achieving substituted imidazole with pyridine incorporated in the five-membered ring then successive N-methylation of pyridine using methyl iodide that resulted to methyl iodide salt. The author reduced the salt to get novel N-alkyl/aryl substituted imidazol-2-yl arecolines. The compounds were evaluated for *in vitro* anti-inflammatory by Human Red Blood Cell (HRBC) membrane stabilization method using Diclofenac as standard. The author also performed molecular docking for anti-inflammatory activity. It has been concluded that the computational values obtained after docking are in good agreement with the experimental values.

CONCLUSION

MCR have great relevance in synthesis of many medicinally important compounds. We hope to have shown that multicomponent reactions are an excellent, multipurpose approach to the synthesis of non steroidal anti-inflammatory drugs. Besides the development of new reactions or improved conditions for the classical ones, future developments in this field will probably involve the application of multicomponent-based strategies to target-oriented synthesis. Moreover, long-term clinical usage of NSAIDs is associated with significant side effects. Therefore new and safer anti-inflammatory drugs represent a challenging goal for such a research area. As resistance to anti-inflammatory drugs is widespread, there is an increasing need for identification of novel structures that may be of use in designing new, potent and less toxic anti-inflammatory agents. We hope that this review will serve to stimulate research in this fascinating and very useful area of organic synthesis. This critical review describes developments in multicomponent reaction have been used for the synthesis of non steroidal anti-inflammatory drugs reported since 2003. Significantly broadened scopes, new techniques, more environmentally benign methods and entirely novel MCRs reflect the increasingly inventive paths that synthetic chemist follow may in this field. The author regrets any omissions that may have occurred in this review.

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