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SYNTHETIC PROGRESS OF DIVERSE HETEROCYCLIC SCAFFOLDS BY MULTI-COMPONENT REACTION (MCR) STRATEGIES: A REVIEW

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Abstract: A general view of our study aimed towards the recent and efficient synthesis of structurally diverse heterocyclic skeletons by combinatorial methodologies is presented. Multi-component Reactions (MCRs) assumes a critical part in procuring a greener approach in synthetic chemistry of the fact that these responses are eco-friendly, inexpensive, and systematically synthesis in the facets of reaction time, number of steps, yield, work-up procedure, atom-economy and mild conditions. When combined with the one-pot procedure, MCRs provide an efficient synthetic methodology for a variety of highly complex molecules. These responses are broadly utilized by synthetic chemists to make heterocyclic motifs with altogether extended varieties having different advantages to the society. The current review surveys recent developments and advances of MCRs in the entire synthesis of N, S, and O bearing diverse heterocyclic scaffolds.

Keywords: Heterocyclic motifs, multicomponent reactions, combinatorial synthesis, synthetic protocols

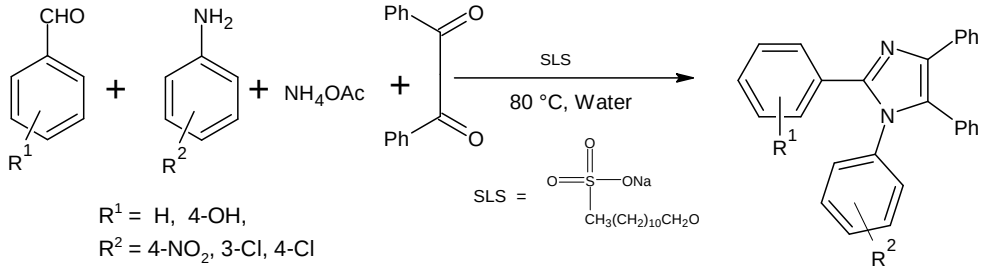
Introduction

The recent drug discovery development depends on the ability of synthetic chemical science to provide huge libraries of small molecules with increasing structural complexity and diversity. Multicomponent reaction (MCR) sequencing with elaboration or cyclization way provides an efficient strategy to generating libraries of heterocyclic motifs [i]. Recent attractiveness of the combinatorial approach for three component (3-CR) & four component (4-CR) in synthetic organic chemistry that allow fast access to various functionalized heterocyclic scaffolds with high selectivity and yield by using minimum synthetic requirements. MCRs have progressed

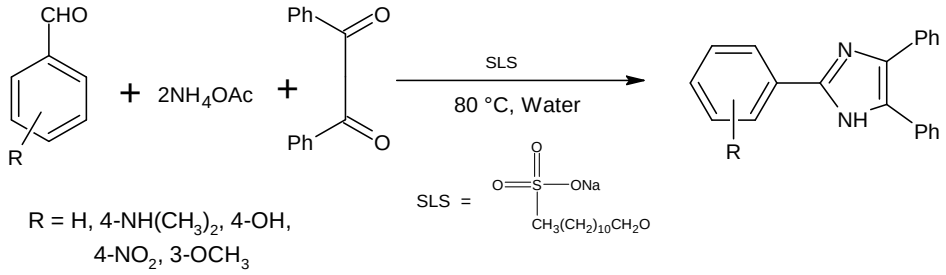
from being a substance interest towards a vibrant tool for synthetic chemists over the most recent couple of years. In the modern heterocyclic chemistry, MCRs a strong and target-situated synthetic strategy, has widely been utilized and applied for the quick development of heterocyclic skeletons, and interest from different parts of science is developing continuously [ii, iii]. MCRs enable the efficient, facile, automated, and high throughput making of various hetero-organic motifs. The interest in MCRs lies not only in their green synthesis but also in the medicinal properties usually found for the molecules prepared straight from its strategies. The endeavour of new combinatorial approaches has turned into a more proficient area of exploration, yielding new potent motifs for drug design and discovery. The numerous efforts by which different heterocyclic rings are deployed in the synthesis and MCRs is illustrative of their adaptability. Although the greater part of the MCRs are known for quite a while (Strecker (1850), Biginelli (1893), Mannich (1912), Passerini (1921)…), [iv] these protocols regain interest for the plan and design of different heterocycles of pharmacological & therapeutically interest as well with respect to material science applications. A benefit of combinatorial science is the extremely enormous chemical space, most likely the biggest available synthetic space for drug discovery and medicinal & pharmaceutical chemistry purposes [v]. The present review article intended to show the straightforward methodologies, commitments and worth that combinatorial science could bring towards drug design plan disclosure endeavours directed at heterocycles. Its process on a lot more extensive scale will fundamentally depend upon expanding the ongoing information based on reasonable response conditions and beginning materials. At long last, current survey review article is well eminent with wide utilizations of MCRs (3-CR, 4-CR) and they serve as expected approaches for the synthesis of novel heterocyclic scaffolds. The potential uses of this conventional and green synthetic protocols in organic medicinal and pharmaceutical chemistry might be significant.

Synthetic aspects of MCRs

Bansal *et al* [vi]. reported the synthesis of tetrasubstituted and trisubstituted imidazoles up to 95% yields **(Scheme 1a** & **1b)** utilizing sodium lauryl sulfate (SLS) as a catalyst *via* one-pot MCR from generally available starting material. The benefits of SLS catalyst found in MCR are its versatility, low cost, environment friendly, easily available and reusable. The reaction was performed in universal solvent water and under the mild reaction conditions.

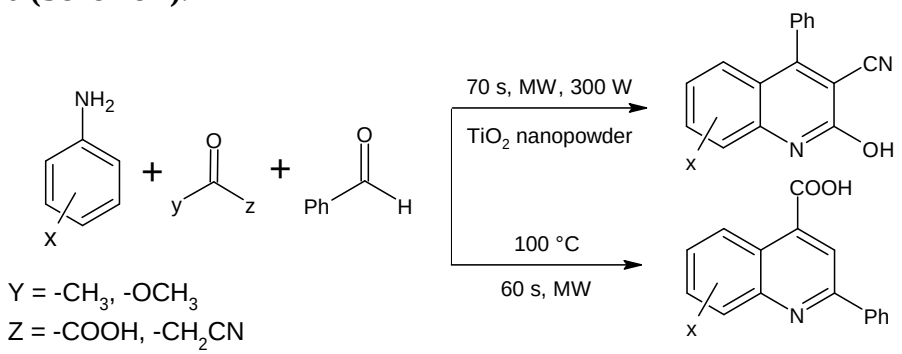


Scheme 1a. Synthesis of tetrasubstituted Imidazole derivatives.



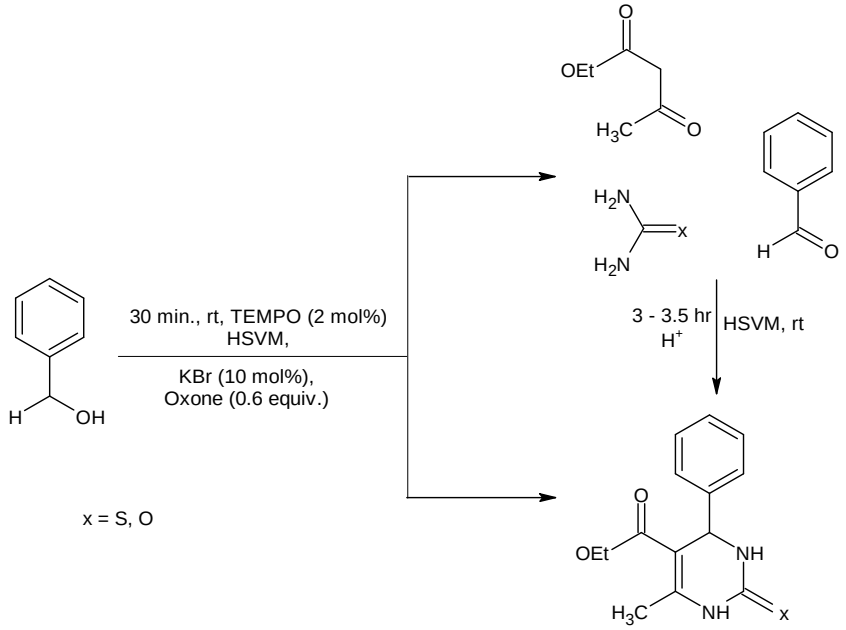
Scheme 1b. Synthesis of trisubstituted Imidazole derivatives.

Batista *et al.* [vii] synthesized a combinatorial protocol for substituted quinolines under microwave irradiations without any catalyst. The fast green reaction and low-cost available reagents made this synthesis appealing for further exploitation. In this MCR, TiO_2 nano-catalyst in powder form has proven excellent photo-catalytic activity towards a similar synthesis which provided an efficient synthetic approach to hydroxyquinoline derivatives with 75-88% yield **(Scheme 2)**.



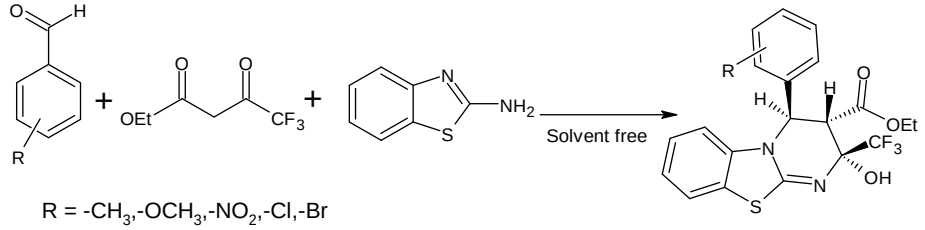
Scheme 2. Eco-friendly synthesis of substituted quinolines

Mal *et al.* [viii] performed the coupling of the Biginelli protocol with one of the starting reactants and *in-situ* synthesis of the catalyst and they found that bromonium catalyzed oxidation of benzyl alcohols, achieved by their treatment with combination of Oxone, KBr and TEMPO, followed by addition to a one pot of active methylene (ethyl acetoacetate) and urea, thiourea, afforded the cost of pyrimidines in excellent yields **(Scheme 3)**. The starting material upon its oxidation and the proton freed was expected to act as a catalyst.



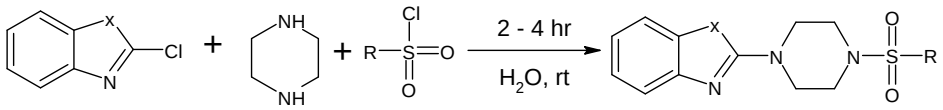
Scheme 3. Mechanochemical Biginelli synthesis

Chadegani *et al.* [ix] developed MCR protocol for pyrimidobenzothiazoles which was performed easily under solvent & catalyst free environments followed by consequent annulations with higher bond-forming efficiency in very good yields. **(Scheme 4)**.



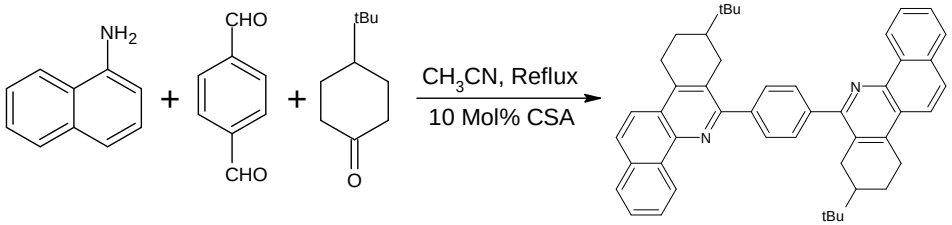
Scheme 4. Solvent free synthesis of pyrimidobenzothiazole derivatives

Dileep *et al.* [x] designed an efficient & facile protocol for the synthesis of Benzothiazole/Benzoxazole/Benzimidazole linked substituted piperazine scaffolds by a one pot combinatorial approach, of 2-chlorobenzdiazole/2-chlorobenzoxazole/2-chlorobenzothiazole, piperazine, and a substituted arylsulfonyl chloride in green solvent (H_2O) and catalyst-free conditions in acceptable yields. **(Scheme 5)**.



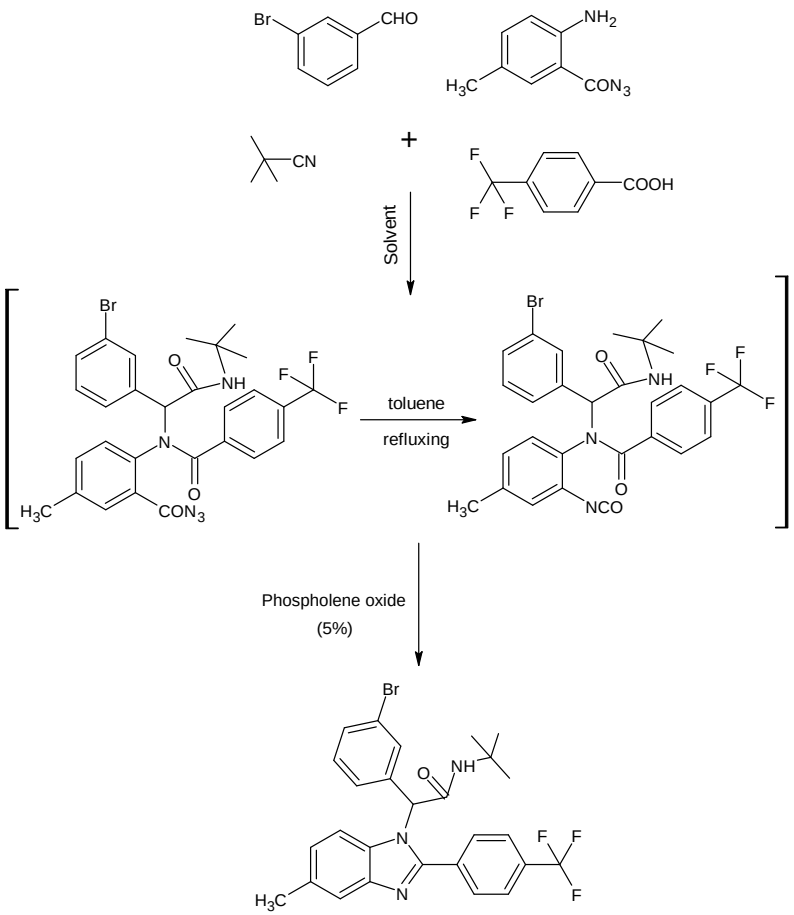
Scheme 5. Synthesis of Benzothiazole/Benzoxazole/Benzimidazole based substituted piperazines

The synthesis of fused bis-benzoquinolines by utilizing naphthylamine, terephthalaldehyde, and 4(^{t}Bu)cyclohexanone in the presence of 10 mol % camphor sulfonic acid (CSA) as catalyst were studied [xi] (**Scheme 6**). The reported protocol offered some benefits, for example, easily available inexpensive catalyst, less response time, gentle reaction conditions, basic isolation methodology, an extensive variety of substrate scope, and eco-friendly with high atom economy in one pot with two C−C bond developments.



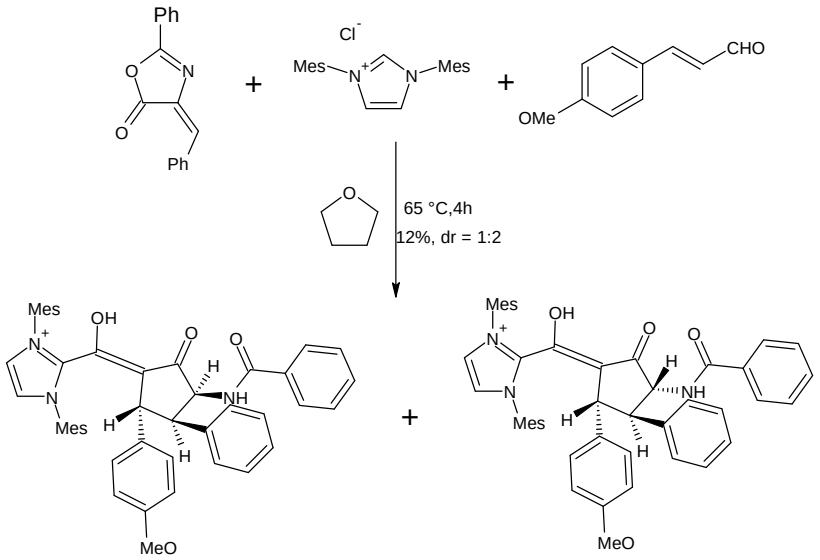
Scheme 6. Synthesis of fused bis-benzoquinolines

A one pot straightforward approach was developed [xii] using consecutive Ugi /catalytic aza-Wittig protocol cyclizing to combine multi-substituted benzimidazole moieties, starting from 3-bromobenzaldehyde, 2-amino-5-methylbenzoyl azide, t-butylisocyanide and 4-trifluoromethylbenzoic acid by utilizing catalytic amount of phospholene oxide in respectable yield **(Scheme 7)**. The revealed catalytic aza-Wittig development demonstrated high atom economy within the presence of catalytic measure of organophosphorus reagents contrasted and the regular aza-Wittig reaction.



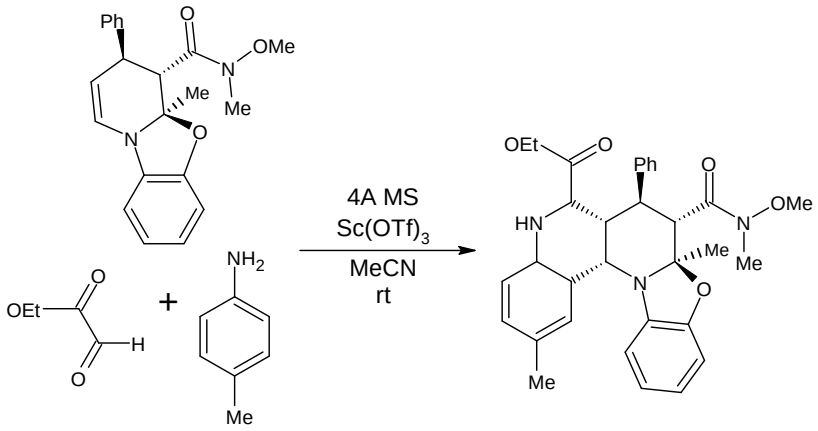
Scheme 7. Synthesis of multi-substituted benzimidazole derivatives

Krishnan *et al.* [xiii] performed a MCR including arylidene oxazolone, enal and NHC, leading to the combination of highly substituted cyclopentanones in very good yields. The product was synthesized by using 4-methoxycinnamaldehyde, imidazolium chloride (20 mol%) and benzylidene phenyloxazolone in THF in DBU (25 mol%) under the mild condition **(scheme 8)**. This is the first combinatorial approach reported which involved NHC and enal occurring *via* homoenolate.



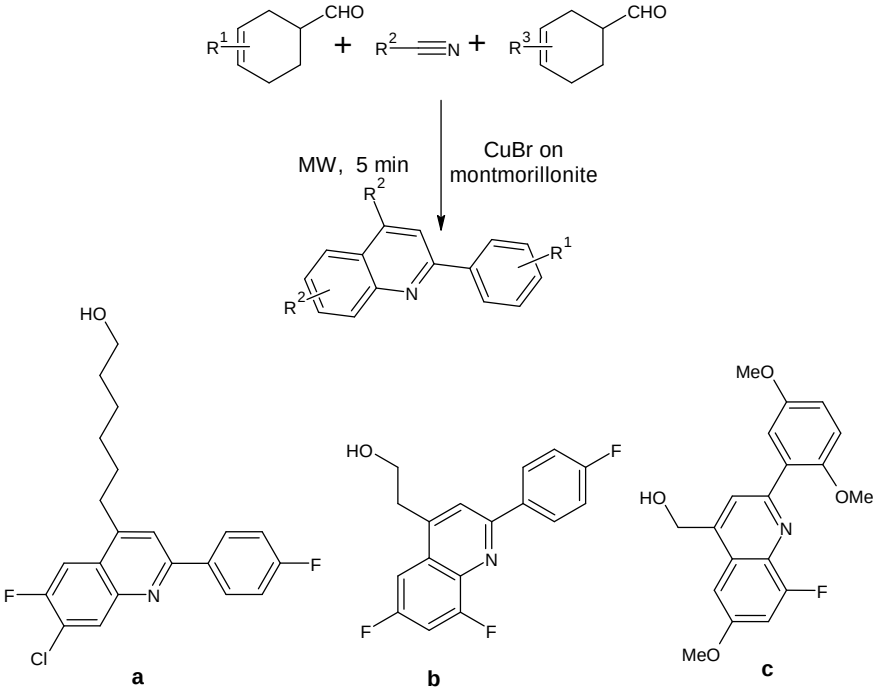
Scheme 8. Synthesis of highly substituted cyclopentanone scaffolds

The combinatorial reaction of enamines with the *in-situ* created 2-azadienes was known as the Povarov response. The synthetic strategies of substituted tetrahydropyridines by combining enamine with ethyl glyoxylate and p-toluidine using a catalytic amount of scandium (III) triflate in good yield were reported [xiv] **(Scheme 9)**.



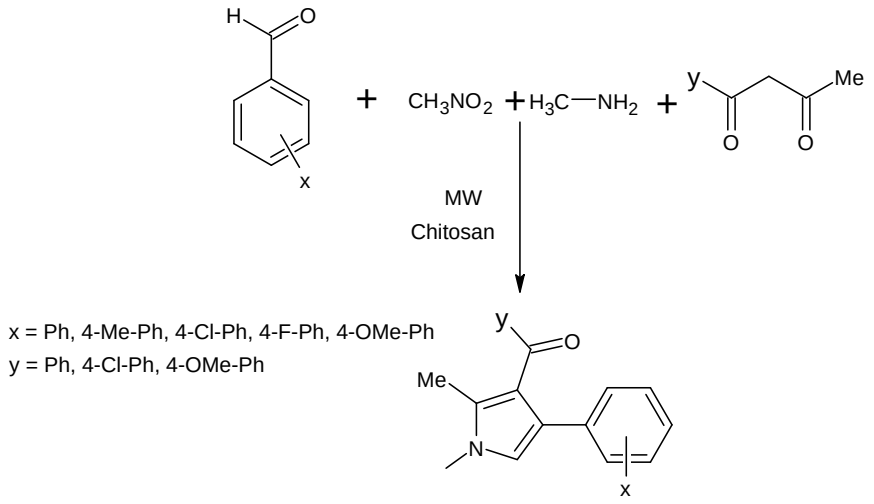
Scheme 9. Synthesis of tetrahydropyridine derivative

Yadav *et al.* [xv] performed the combinatorial synthesis of disubstituted quinoline scaffolds by using aldehydes, alkynes and anilines utilizing montmorillonite clay doped with CuBr under the microwave irradiation (MW) in acceptable yields **(Scheme 10)**. In synthesis, they were expected to underwent amino-alkylation of the terminal alkyne followed by a cyclic isomerization and an oxidative-aromatization.



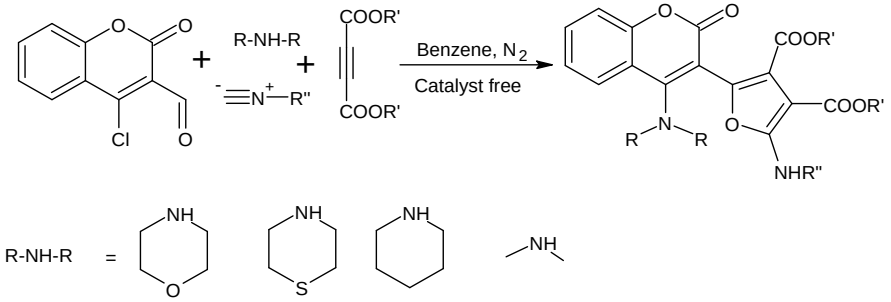
Scheme 10. Synthesis of Cu catalysed disubstituted quinolines

Recently, a facile and eco-friendly methodology were developed [xvi] for the preparation of muti-substituted pyrrole moieties *via* a one-pot 4-CR protocols of amines, aldehydes, bi-carbonyls, & nitromethane by utilizing chitosan as a heterogeneous and environmentally benign, reusable, and cost-effective catalyst **(Scheme 11)**. First attempt was reported by utilizing chitosan in its native structure in a 4-CR under microwave irradiation (MW).



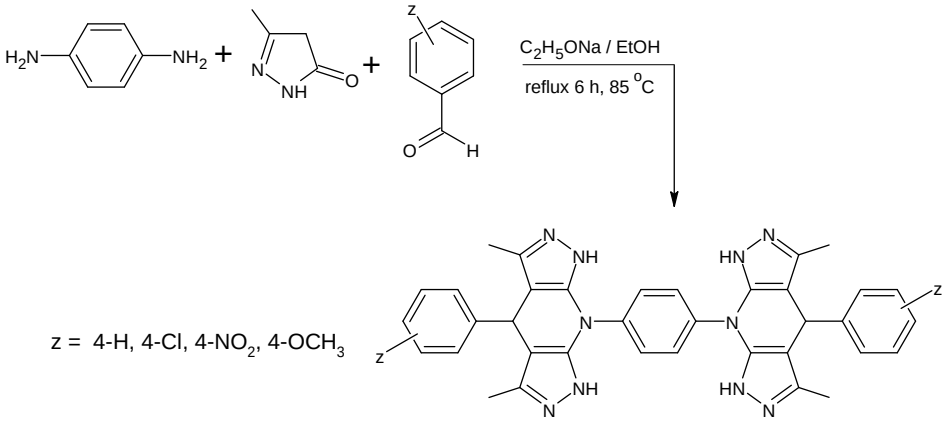
Scheme 11. Combinatorial synthesis of substituted pyrrole derivatives

Jalli *et al*. [xvii] envisaged an efficient one-pot 4-CR protocol for the synthesis of 3-furyl coumarin derivatives by utilizing 4- chloro-3-formyl coumarin, secondary amines, dialkyl acetylene dicarboxylate, and isocyanides under the catalyst free conditions. All the synthesized 3-furylcoumarin molecules were obtained as yellow color solids subsequently by column chromatography in good to excellent yields. **(Scheme 12)**.



Scheme 12. Synthesis of 3-furyl coumarinS

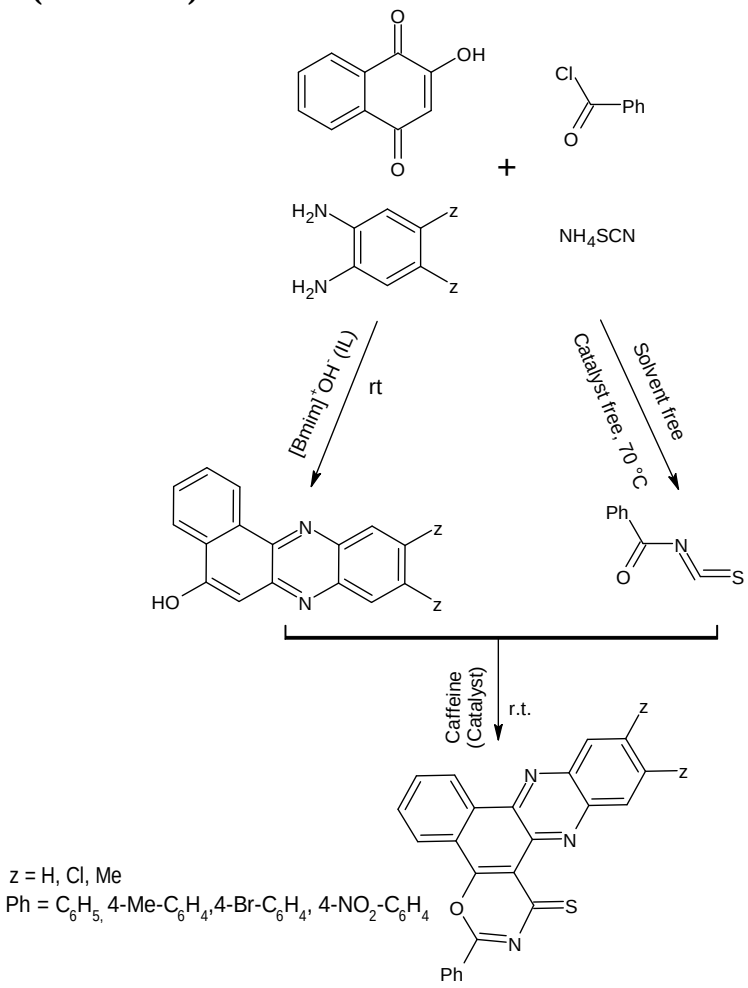
A method was reported [xviii] for the preparation of bis- bipyrazolopyridines by one-pot 3-CR reaction of methyl substituted dihydropyrazoleone, with substituted aldehydes and p-phenylenediamine by utilizing ethanol as a reaction medium. The synthesized scaffolds were obtained *via* aldol condensation and Michael addition reactions **(Scheme 13)**.



Scheme 13. Synthesis of bis- bipyrazolopyridine derivatives

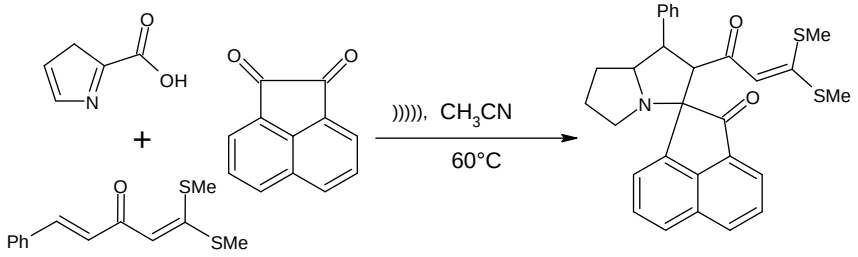
Mohebata and co-workers [xix] developed a straightforward protocol for the facile preparation of several potentially pharmacologically active polyfunctionalized benzooxazinophenazines, by using one-pot MCR between hydroxy-naphthoquinone, diamines, ammonium thiocyanate

and acid chlorides catalysed in butyl-methylimidazolium hydroxide ([bmim]+OH^- = ionic liquid). This protocol was achieved by using caffeine as a natural available, inexpensive, non-toxic, and solid catalyst. This protocol has the benefits of mild reaction conditions, cost effective, eco-friendly, easy workup procedure, higher yields and useful in preparation of complex heterocycles **(Scheme 14)**.



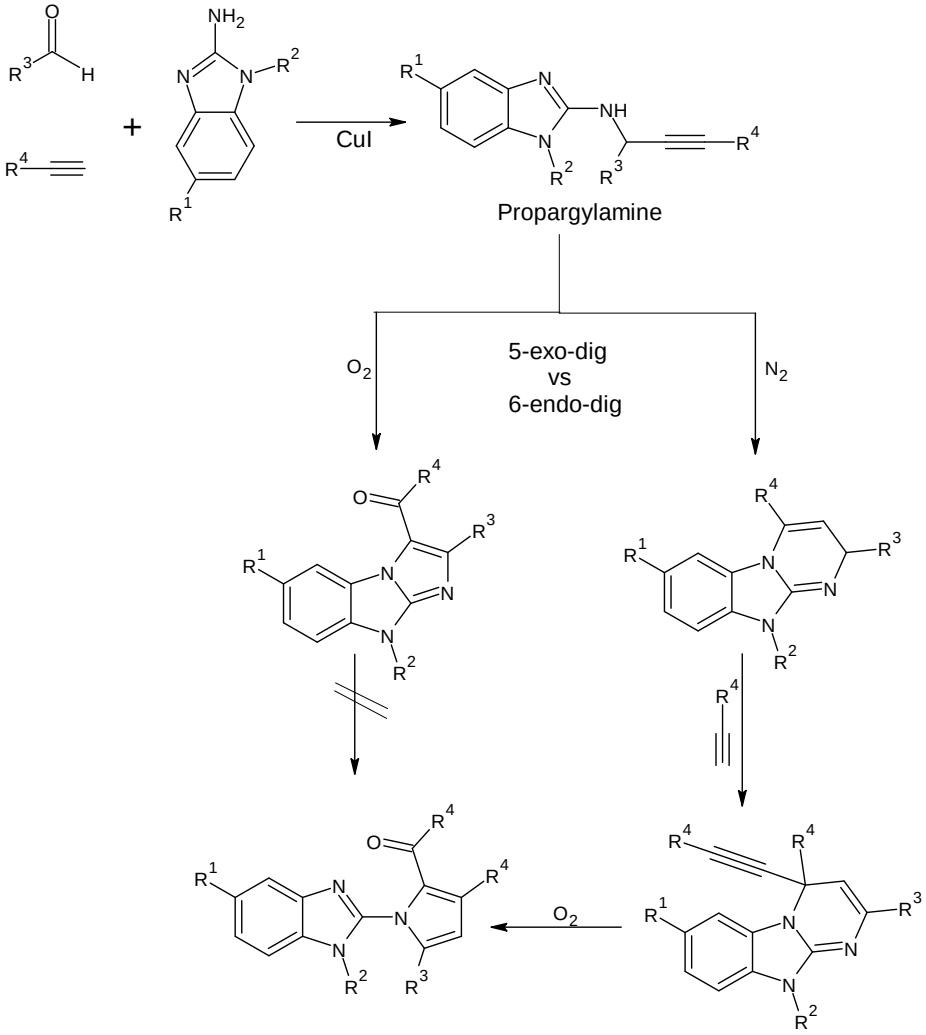
Scheme 14. Synthesis of benzooxazinophenazine moieties

Recently, a protocol has investigated for various spiro-acenaphthylene fused pyrrolizines/pyrrolothiazolines in single step by combinatorial approach. By this protocol, a variety of spiroacenaphthylenes was rapidly synthesized with excellent regio-/stereoselectivity under catalyst free condition, easy work-up procedure, affording the desired motifs from readily available reactants. The prepared spiroacenaphthylene- S, S-acetal motifs were further converted into pharmacologically and optically active pyranone type of polyheterocycles. This reported MCR involved α- aroylidineketene dithioacetals (AKDTAs), L-proline/S-proline and acenaphthenequinone to the synthesis of spiro-acenaphthylene-pyrrolizino/pyrrolo-thiazolinone derivatives under ultrasound irradiation condition [xx] (**Scheme 15**).



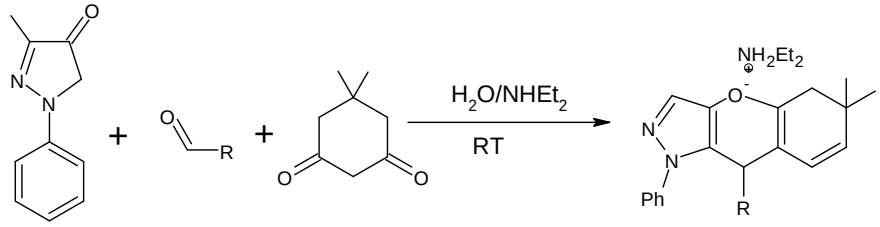
Scheme 15. Synthesis of spiro- pyrrolizine derivative

An effective combination of benzoimidazoimidazolone through oxidative 5-exo-dig cycloisomerization of 2-aminobenzimidazole aldehyde, and terminal alkyne under oxygen consuming circumstances were accounted. Sun *et al.* [xxi] found a copper-catalyzed tandem synthesis of benzimidazole-connected 2-ketopyrroles from readily accessible 2-aminobenzimidazole, aldehydes, and alkynes. The cascade reaction was depicted to include regioselective 6-endo-dig cyclization to deliver benzimidazopyrimidine which underwent through oxidative ketonization by utilizing copper and molecular oxygen through a helpful catalytic framework. **(Scheme 16)**.



Scheme 16. Synthesis of benzoimidazoimidazolones

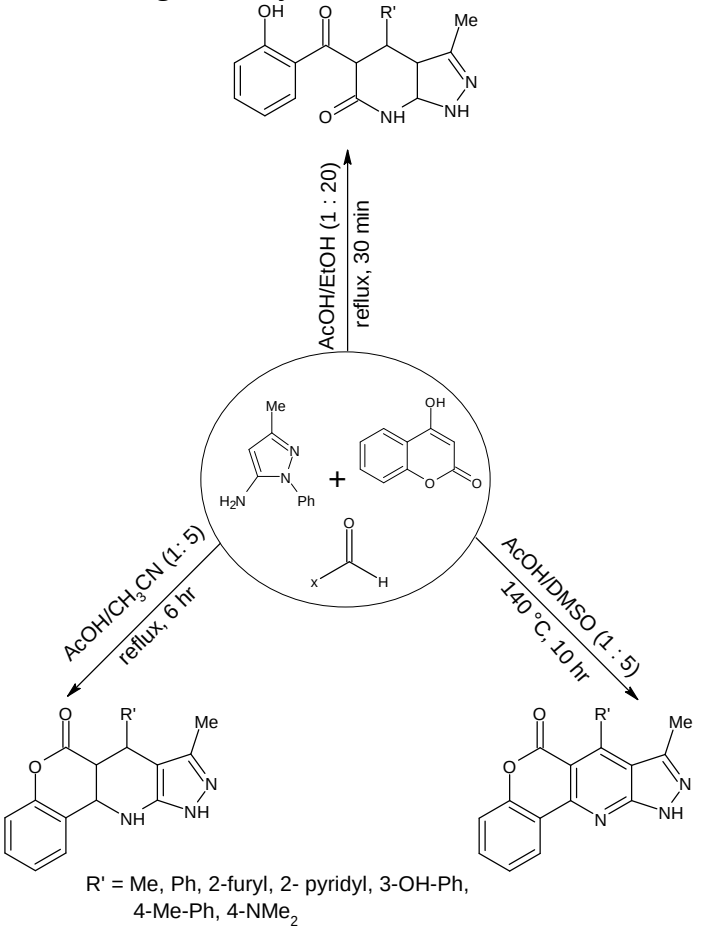
Similarly, pyrazole-dimedone derivatives were designed and prepared *via* single pot Knoevenagel condensation and Michael addition of methyl and phenyl substituted pyrazolone, dicarbonyl compound (dimedone) and various araldehydes by using H_2O-$NHEt_2$ as reaction medium. This one pot MCR green protocol reported the final products as hybrid frameworks in good yields with substrate tolerance of pyrazole-dimedones [xxii] **(Scheme 17)**.



R = *p*-CH_3-Ph, *p*-Br-Ph, Ph, *p*-F-Ph, Thiophene, *m*-Br-Ph

Scheme 17. Synthesis of pyrazole-dimedones derivatives

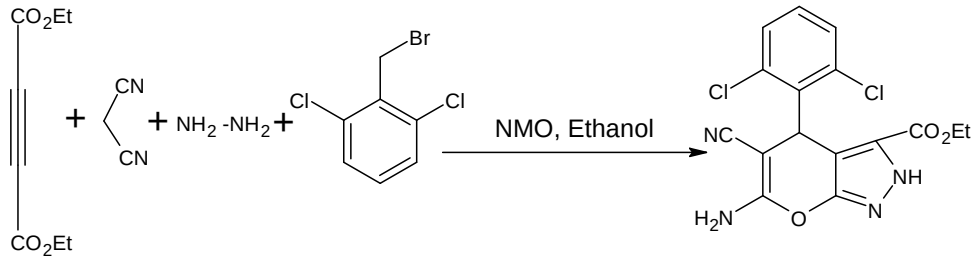
A combinatorial protocol was studied for aminopyrazole, hydroxycoumarin and aldehydes in different solvents like DMSO, toluene, dichloromethane, and acetonitrile by use of catalysts like $ZrCl_4$, $InCl_3$, $FeCl_3$, L-proline *etc.* by Liu *et al*. [xxiii] **(Scheme 18)**. Whereas the reaction in CH_3CN / CH_3COOH (1:5) provided dihydropyrazolopyridines, acetic acid /dimethyl sulfoxide (5:1) yielded the corresponding aromatized pyrazolopyridines exclusively. In ethanol/acetic acid combination an unexpected product dihydropyrazolopyridinone was formed due to C–O bond cleavage from cyclic ester**.**



R' = Me, Ph, 2-furyl, 2- pyridyl, 3-OH-Ph, 4-Me-Ph, 4-NMe_2

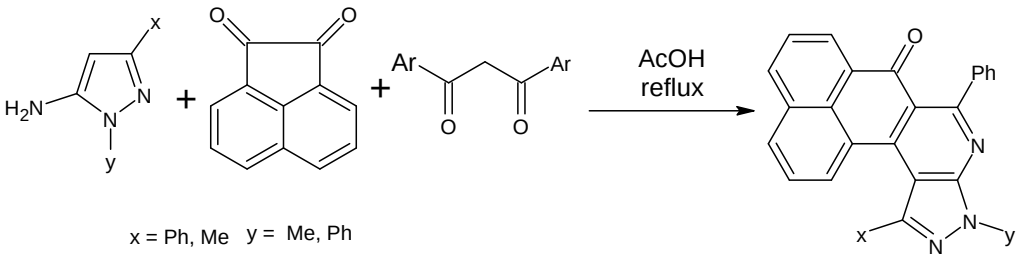
Scheme 18. Synthesis of pyrazolopyridine derivatives.

Shivashankar *et al.* [xxiv] performed an efficient protocol for the preparation of pyrano-pyrazoles through a MCR from benzyl halides, cyano-acetonitrile, and hydrazine by utilizing NMO–Ag_2O catalyst. This domino protocol implied Knoevenagel condensation, Michael addition, intra-molecular cyclization and tautomerization. The mild reaction conditions, simple operational, broad functional group tolerance and excellent yields are the main benefits of this synthesis **(Scheme 19)**.



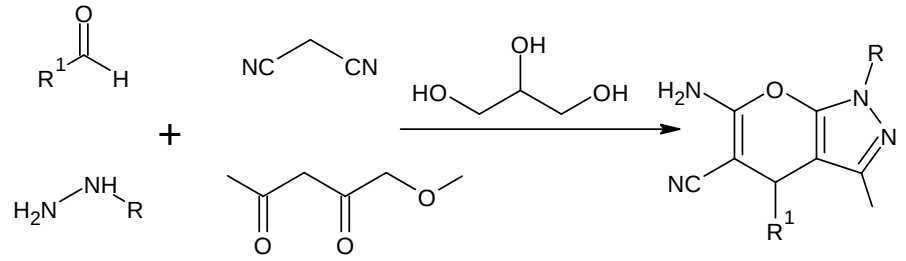
Scheme 19. Synthesis of pyrano-pyrazole derivative

Beerappa and co-workers studied [xxv] the insertion based combinatorial protocols of acenaphthylenedione with diaroylmethanes and electron-rich pyrazoloamines that led to structures of the multi-functionalized pentacyclic pyrazole-fused naphthoisoquinoline skeleton with high regioselectivity. This work provided an attractive synthetic efficiency for the structurally diverse naphthoisoquinolines **(Scheme 20)**.



Scheme 20. Synthesis of pentacyclic pyrazolo fused naphthoisoquinolines

Sohal *et al.* [xxvi] described an MCR protocol for dihydropyranopyrazoles from the condensation of EAA, hydrazine hydrate, different aryldehydes and active methylene compound (malononitrile) by using glycerol, as environmentally benign, economical catalyst in acceptable yields **(Scheme 21)**.

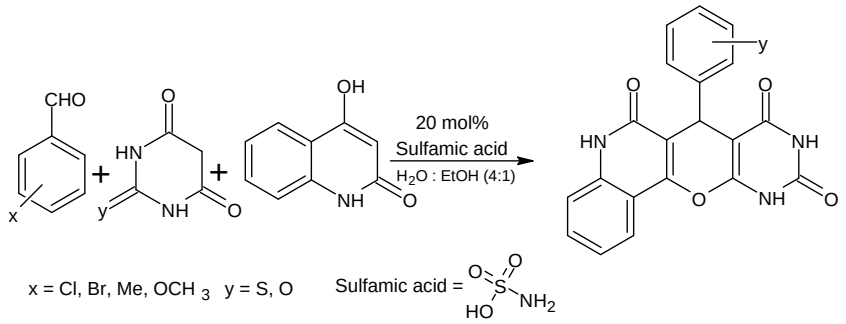


R = H, Ph

R^1= 4-MeC_6H_5, 2-$NO_2C_6H_5$, 4-$NO_2C_6H_5$

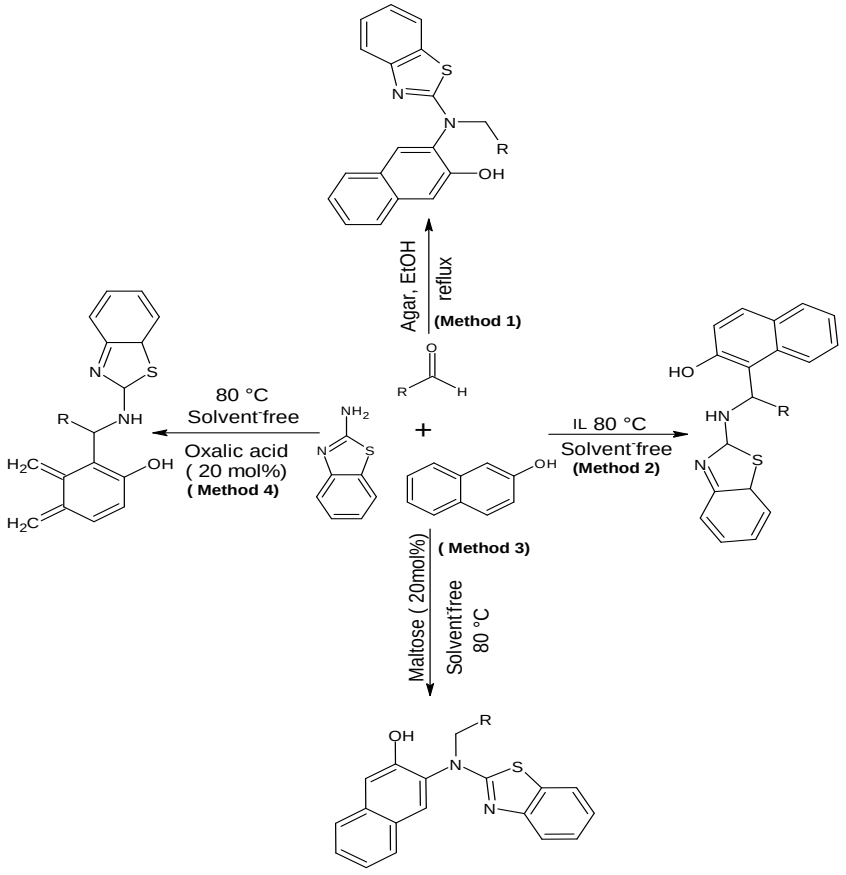
Scheme 21. Synthesis of dihydropyranopyrazoles

Deshmukh and co-workers [xxvii] demonstrated a cheap, atom-economic, and eco-friendly protocol for the preparation of fused pyranoquinolines by utilizing sulfamic acid (H_3NSO_3) in aq. Ethanol (4:1) media as a reusable green catalyst through the MCR condensation. The strategy has major benefits including its simple operation, greener route, simple workup procedure, selectivity, and excellent yields **(Scheme 22)**.



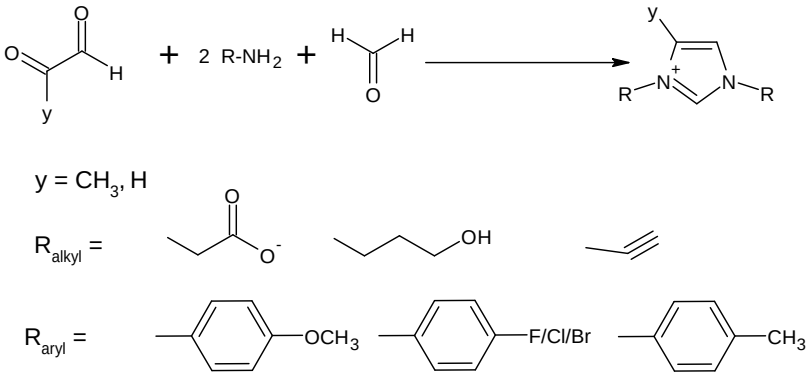
Scheme 22. Synthesis of pyranoquinoline derivatives

Balwe *et al*. [xxviii] performed Fe-catalyzed coupling of aminobenzothiazole with nitroalkane & aldehydes in air to form benzoimidazothiazole. This conversion occurs through reaction of substituted aminobenzothiazole, naphthol and benzaldehyde using agar under the reaction condition (**Scheme 23, method 1)**. One of the protocol also studied for benzothiazolyl-amino-phenyl-methyl-naphthols by using a newly synthesized acidic catalyst succinimidinium hydrogensulfate ([H-Suc]HSO_4) (IL) as an effective and recyclable catalyst with excellent yield in less time. **(Scheme 23, method 2)** The MCR protocol of naphthol, aminobenzothiazole, and benzaldehyde using 20 mol % maltose at 80 ^oC were studied by Adrom *et al*. In all protocols, higher yields were observed in less time period of reaction **(Scheme 23, method 3)**. Taher *et al.* developed a one pot facile and efficient protocol of substituted benzothiazolyl-naphthols under solvent free environments through MCR condensation of aryldehydes, naphthol and amino-benzothiazole using oxalic acid as an organo-catalyst. This reported combinatorial approach offers few advantages like high yields, clean reaction profiles, simple operation, eco-friendly, lacking the use for column-chromatography and easy work up procedure **(Scheme 23, method 4).**



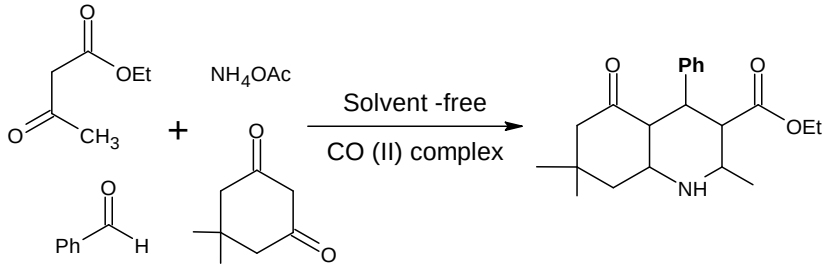
Scheme 23. Multi-component reactions of 2-aminobenzothiazole

Esposito *et al*. [xxix] designed and performed the synthesis of various symmetric bifunctional imidazolium compounds by direct Debus-Radziszewski multi-component reaction from several aliphatic amines in good yields **(Scheme 24)**.



Scheme 24. One-pot protocol of bifunctional imidazolium-bearing derivatives

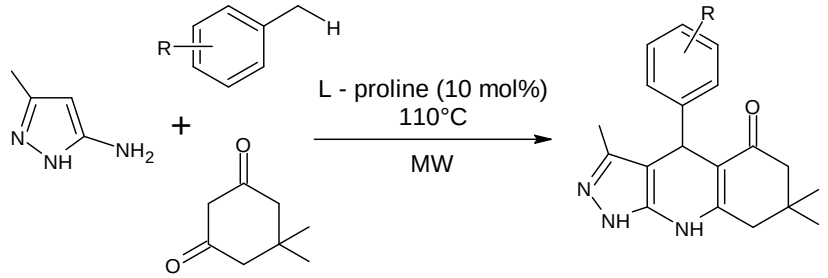
The protocol for the preparation of polyhydroquinolines was performed using high-yielding, efficient, versatile and environmentally benign method. In continuation of efforts in the improvement of new ways for the preparation of heterocyclic frameworks using green catalysts, Allamah and co-workers reported an efficient Hantzsch synthesis by using catalytic amount of Co (II) complex (CoL_2) under solvent- free conditions, using dimedone, aryldehydes, ethyl acetoacetate and ammonium acetate to produce the polyhydroquinoline derivatives in excellent yields [xxx] **(Scheme 25)**.



Ph = 2,4-$Cl_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 4-$NO_2C_6H_4$, 4-BrC_6H_4 , 3-BrC_6H_4 , 4-$MeOC_6H_4$, 4-OHC_6H_4

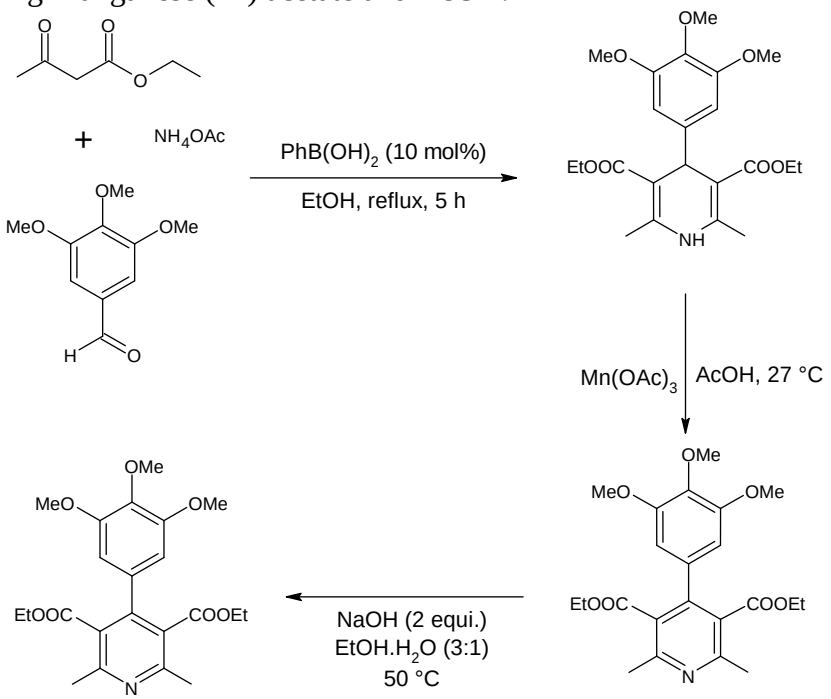
Scheme 25. Synthesis of polyhydroqunolines

A metal-free protocol for the preparation of substituted pyrazoloquinolinones under solvent free environment *via* a MCR of methyl-pyrazolo-amine, 5,5-dimethyl-1,3-cyclohexanedione and substituted aldehydes utilizing L-proline as an organo-catalyst. **(Scheme 26)**. For developed L-proline catalyze stereo-selective MCR protocol, Myrboh and co-workers performed the model reaction of 4-chloro benzaldehyde, dimedone, methyl-pyrazoloamine by using catalytic amount of L-proline. It was found that only trace amount of the product was obtained under prolonged stirring at room temperature. Even at elevated temperature, the desired product was obtained in low yield along with unreacted starting materials. This result prompted us to explore the ideal reaction condition to get maximum product yield [xxxi].



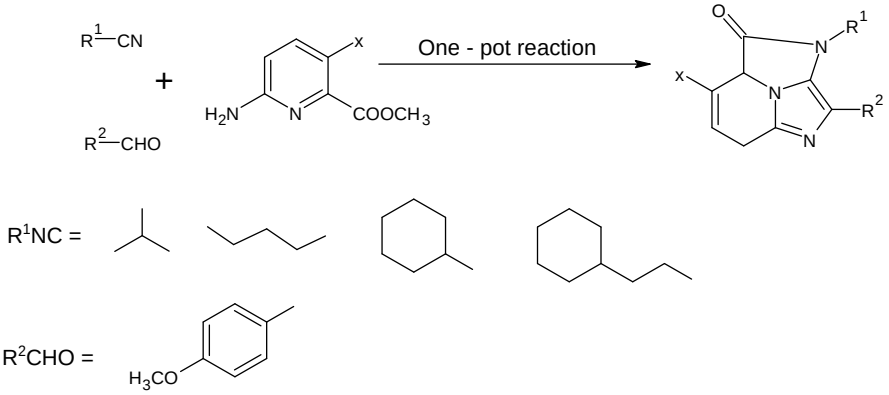
Scheme 26. Synthesis of pyrazoloquinolinone derivatives

Guchhait *et al.* [xxxii] investigated the preparation of nicotinic acid precursor by a Hantzsch multicomponent condensation of aryl aldehyde, ethyl acetoacetate and ammonium acetate to construct dihydropyridine, its dehydrogenative aromatization to product, and mono-hydrolysis of diester **(Scheme 27)**. This protocol was good yielding and established by Hantzsch reaction. Dehydrogenative aromatization reactions utilizing different conditions were performed at room temperature using Manganese (III) acetate and AcOH.



Scheme 27. Synthesis of nicotinic acid derivative

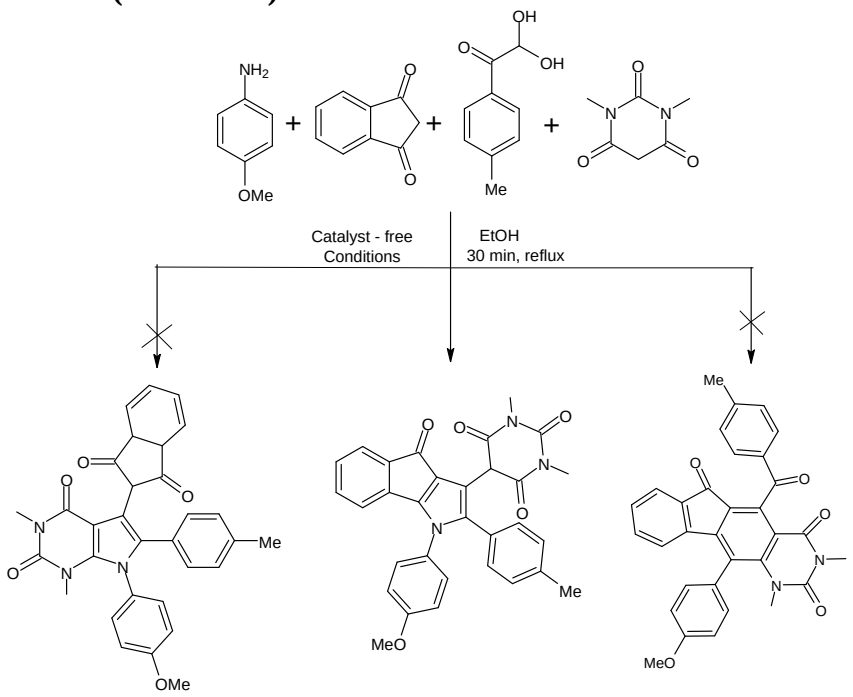
Compounds possessing an imidazopyridine structure show a broad range of bio-activities. Modifications on these scaffolds were well documented in the literature; a frequently applied strategy is fusing the imidazo-heterocycle motif with a heterocyclic moiety in order to design multiple biologically active agents. Meng *et al.* [xxxiii] previously studied the synthesis of functionalized 422yclizine, triazacyclopenta-indene by Groebke-Blackburn-Bienayme (GBB) reaction, followed by *in-situ* Pd (II) acetate-catalyzed intra-molecular cyclization. The functionalized triazacyclopenta-indenones were found platelet-derived growth factor inhibitors I and corticotropin-releasing factor receptor antagonists II **(Scheme 28).**



Scheme 28. Synthesis of triazacyclopenta[c,d]indenes

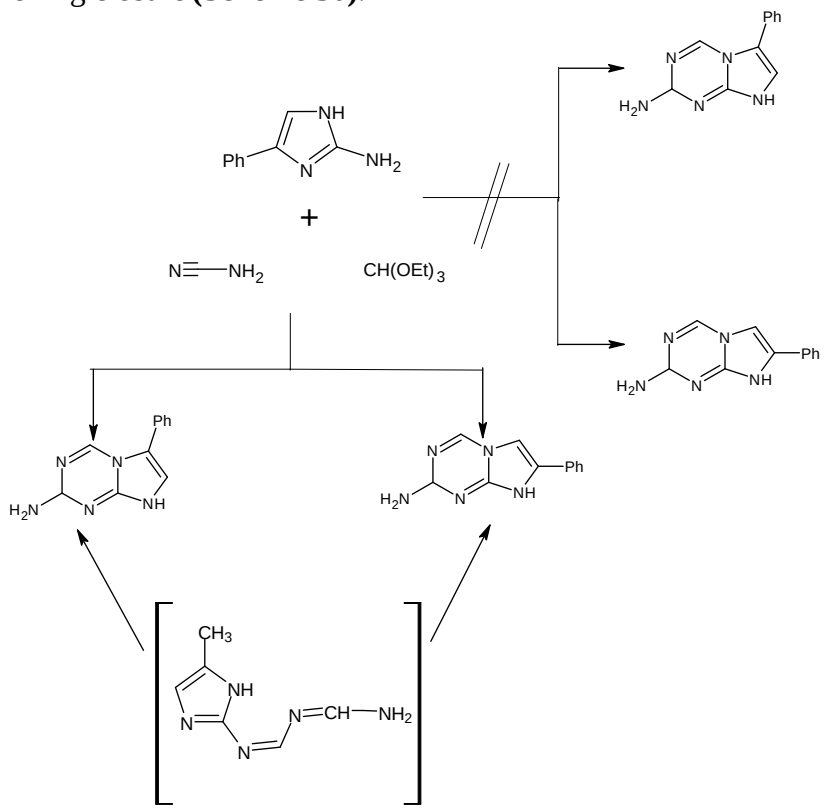
Prajapati and co-workers [xxxiv] designed a facile and efficient one pot eco-friendly MCR protocol for the construction of pyrimidinyl functionalized pyrrole fused heterocyclic framework. Several arylglyoxal hydrates were reported in a clean protocol with barbituric acid and enaminones or *in-situ* formed enaminones from cyclic bi-carbonyls and some aromatic

amines under catalyst free conditions. The protocol provides a rapid access to pyrimidinyl functionalized pyrrolo-annelated moieties with excellent yields with easy work up and purification processes **(Scheme 29)**.



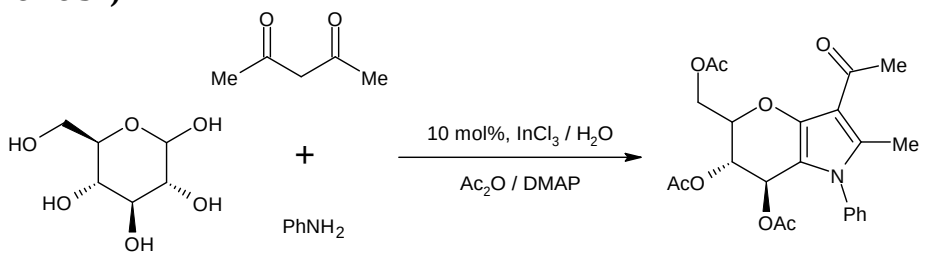
Scheme 29. Synthesis of pyrrolo-annelated derivative

Dolzhenko *et al.* [xxxv] studied microwave assisted, MCR for the preparation of aza-deaza-adenines. The catalyst-free reaction was found to proceed with high selectivity and produced the desired products in good yields and purity. A rearrangement was studied to describe regio-selectivity of the ring closure **(Scheme 30)**.



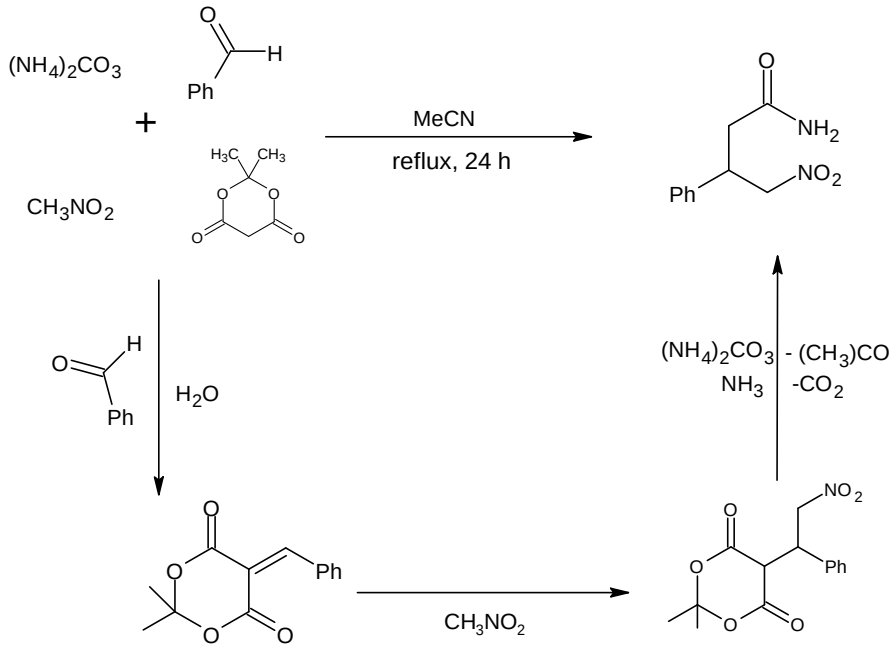
Scheme 30. Annulations of the 1,3,5-triazine ring onto aminoimidazoles.

Yadav *et al*. [xxxvi] made main contribution in this field utilizing a combinatorial coupling reaction of arylamine, diketones and aldose sugars to prepare annulated pyrroles utilizing $InCl_3$ as a catalyst in aq. atmosphere. In this methodology, aldose sugars underwent smooth coupling with enamines that were produced *in-situ* from 1,3 diketones and arylamines by using 10 mol% of Indium chloride in H_2O at 80° C to yield annulated pyrroles in comparatively good to higher yields. **(Scheme 31)**



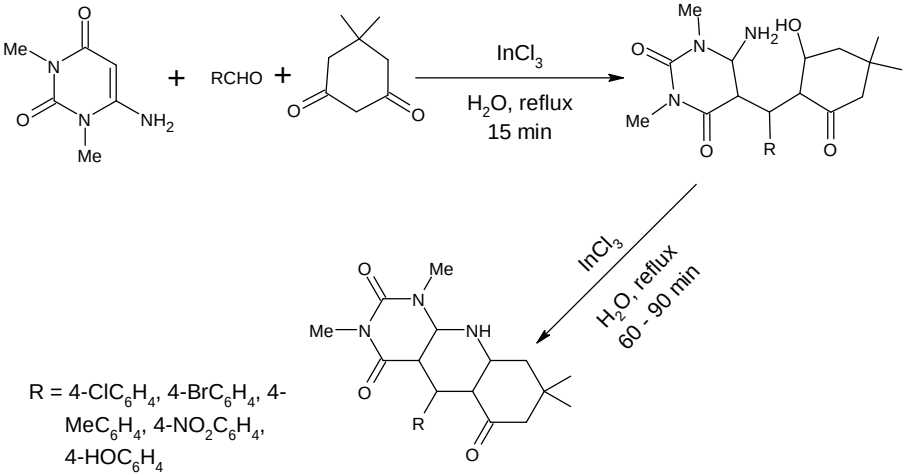
Scheme 31. Synthesis of fused pyrrole derivative

Russowsky and coworkers investigated [xxxvii] a protocol for new γ-nitroamides. By this protocol, β-aryl- or β-alkyl-γ-nitroamides were achieved in a single step reaction. This is based on common and commercially available starting materials, such as: Meldrum's acid, nitromethane and aliphatic or aromatic aldehydes. Ammonium acetate or ammonium carbonate show a vital role as an acid/base catalyst as well as reactant. The methodology was more effective by utilizing aryl aldehydes, affording the desired moieties in reasonable to good yields after purification **(Scheme 32)**.



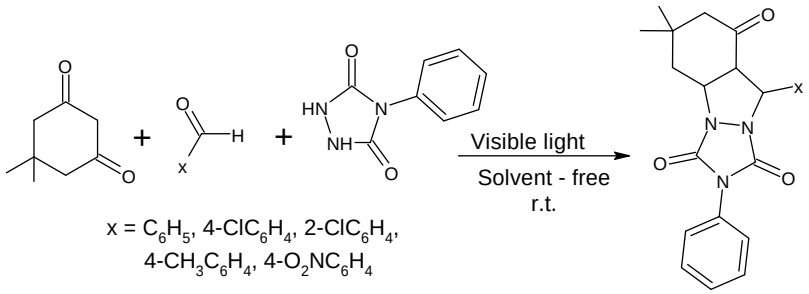
Scheme 32. Combinatorial synthesis of nitroamides

Khurana *et al.* [xxxviii] performed a MCR of 6-amino-1,3-dimethyluracil, aromatic aldehydes, and 5,5-dimethyl-1,3-cyclohexanedione by using $InCl_3$ as a recyclable catalyst and water as the green solvent to generate a variety of bio-active pyrimidines **(Scheme 33)**. Similar procedures were also studied by utilyzing p-TSA, TEBAC (triethylbenzylammonium chloride), a mixture of acetic acid and ethylene glycol, boiling acetic acid, and magnetic nano-particles supported silica sulfuric acid (Fe_3O_4,SiO_2-SO_3H) as catalysts in this protocol. In another study of Shi *et al.* used ionic liquid butyl-methylimidazolium bromide ([bmim]Br) as the reaction media without any catalyst. They found that when an aliphatic aldehyde was treated in [bmim] Br, the desired product was not achieved but the uncyclized product was obtained.



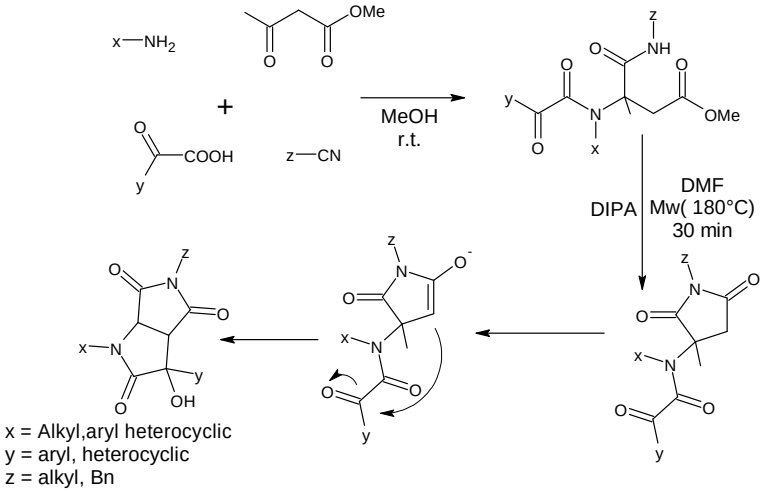
Scheme 33. Synthesis of fused pyrimidines

A multicomponent, solvent-free protocol for the preparation of triazolo-indazolo-triones under the green environment was reported **(Scheme 34).** Seyed developed a clean & highly efficient, visible light activated and 'free' KCC-1, green protocol to provide highly functionalized triazolo-indazolo-triones through a one-pot, MCR. These products of visible light and KCC-1 gives a simple and direct way to access products of the biologically important heterocycles [xxxix].



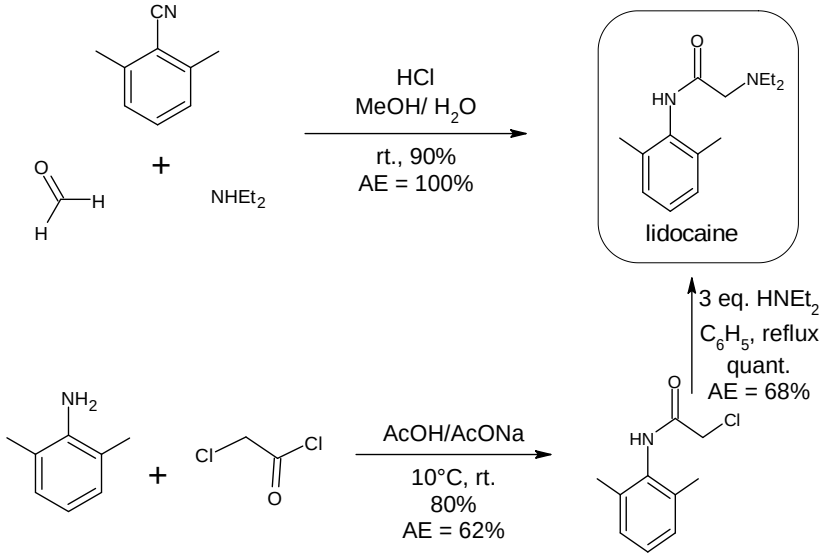
Scheme 34. Synthesis of triazoloindazolotriones

The methodology sequence of fused type bis-pyrrolidinones were prepared as a racemate by some smart modification [xl]. The amines were combined in sequence with the acetoacetic methyl ester oxalyl type carboxylic acids, and the isocyanides in MeOH at room temperature to provide the Ugi adducts, which after a domino aldol sequence allowed the preparation of the products (±)-57 in 47–55% yields **(Scheme 35)**.



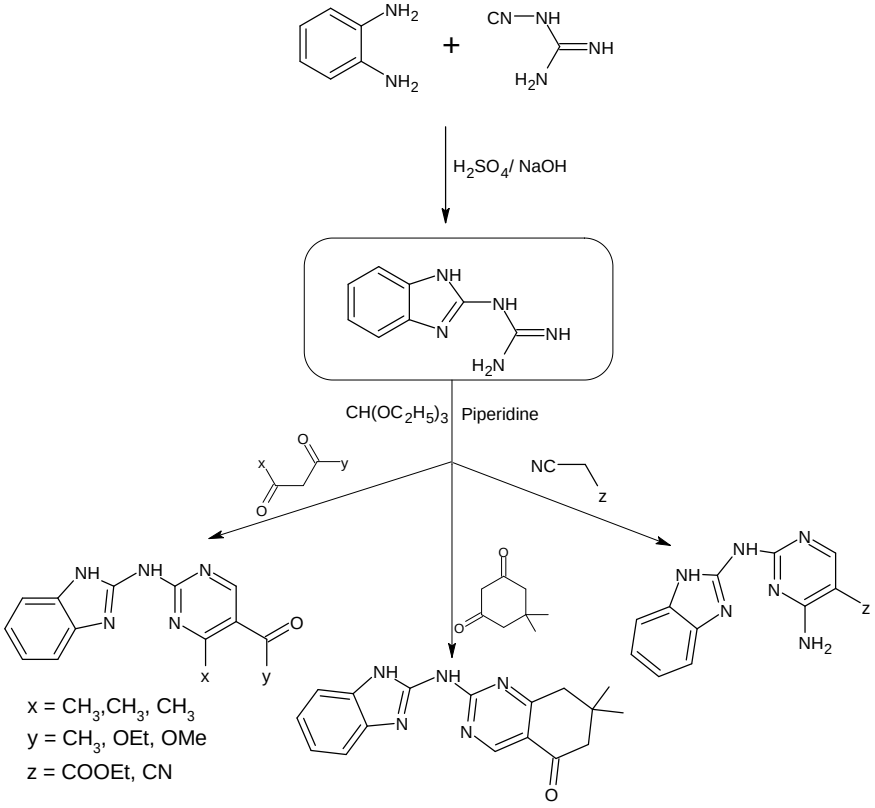
Scheme 35. Synthesis of the polyheterocycles

The Ugi three component reaction alternate with water as acid component also proceeds with perfect particle economy and this advantage was utilized as early as the 1960s in the combinatorial research of lidocaine analogues. The synthesized compounds employs chloroacetyl chloride as a key building block between 2,6-dimethyl aniline and diethylamine *via* standard acylation and alkylation reactions, generating ravage mostly in the form of salts resultant from HCl neutralization [xli] **(Scheme 36)**.



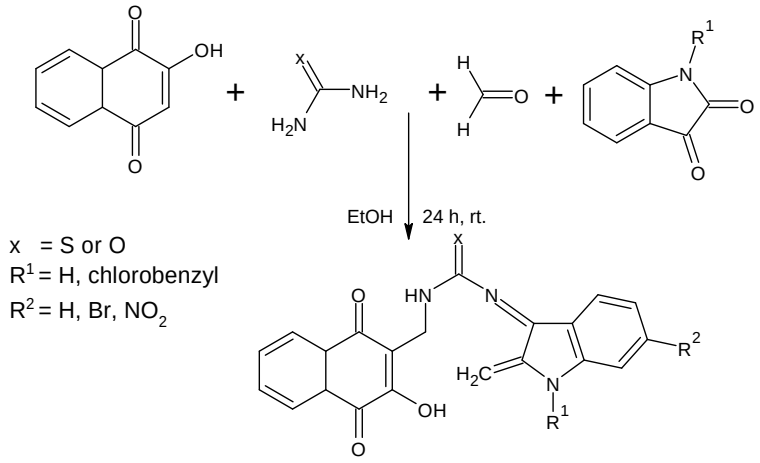
Scheme 36. Multi-component synthesis of lidocaine.

A variety of non-symmetrical benzimidazoloquinazoline and benzimidazolopyrimidines were reported as a multi-component reaction of guanidinobenzimidazole with triethyl orthoformate and different reactive methylene compounds by combinatorial strategies [xlii] **(Scheme 37)**.



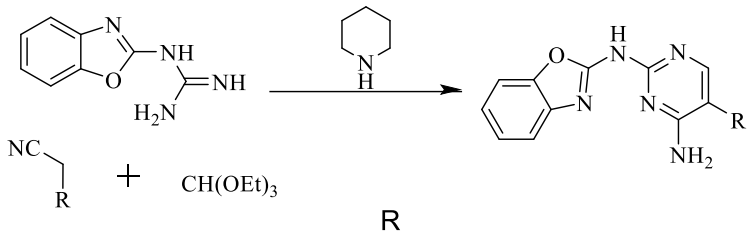
Scheme 37. Synthesis of benzimidazoloquinazoline and benzimidazolopyrimidines

A number of different functional group substituted indoline-based dihydroxycarbamides were prepared and evaluated as selective COX-2 inhibitors (anti-inflammatory agents) by Rajesh *et al* [xliii]. **(Scheme 38)**



Scheme 38. Synthesis of substituted indoline-dihydroxy-carbamides

Prajapat *et al.* [xliv] studied the solvent-free protocol of substituted benzoimidazolyl-amino-pyrimidine derivatives by MCR between guanidino-benzoxazole **(2)**, triethyl orthoformate (TEOF/ortho-ester) and some different active methylene compounds in good yields **(Scheme 39)**.



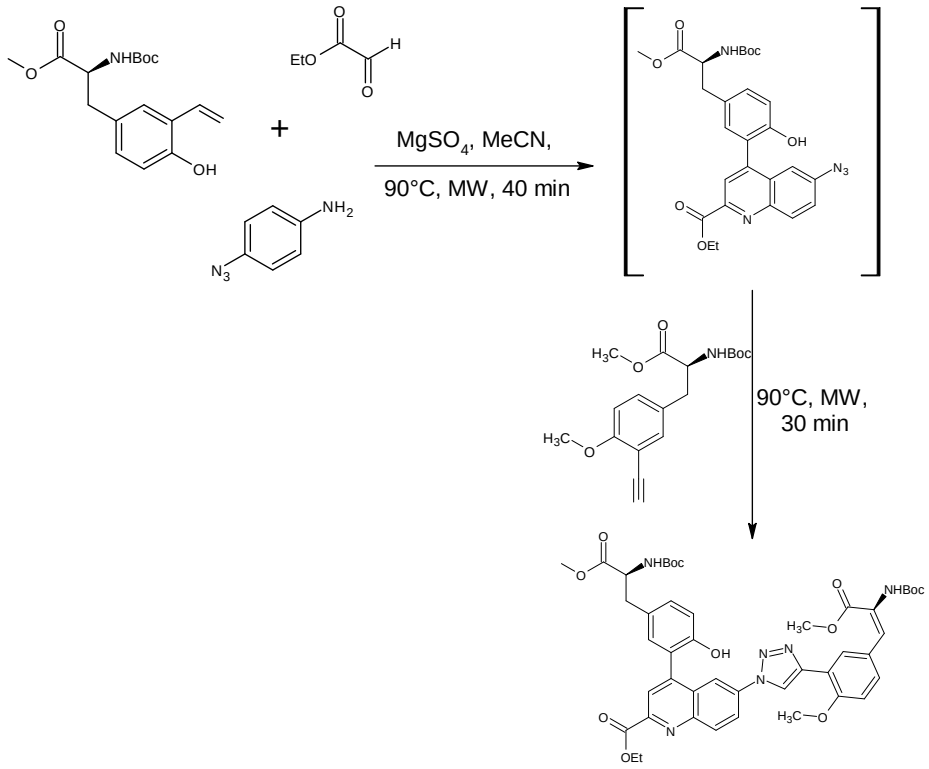
R

a = COOEt,

b = CN

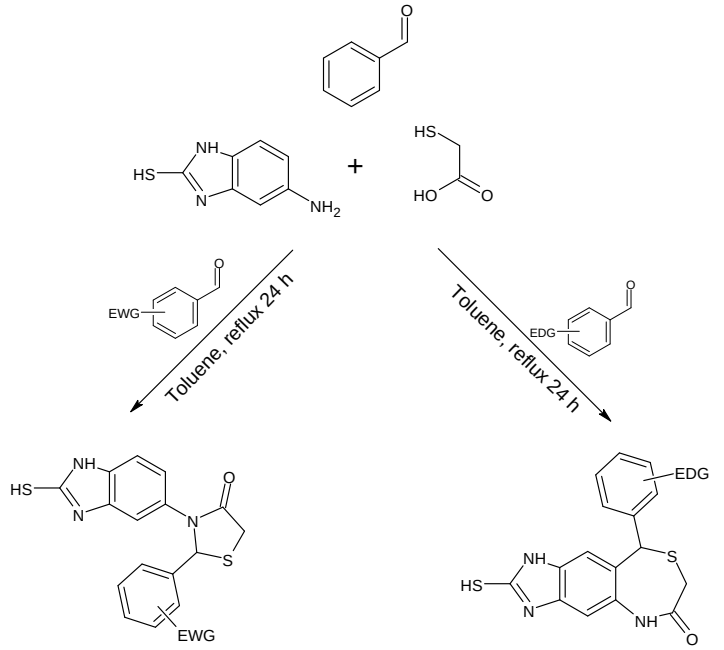
Scheme 39. Synthesis of Benzoxazole based pyrimidines

Suzuki-Miyaura coupling protocols were studied for the synthesis of vinyltyrosine moieties in good yields, which are key intermediates in the synthesis of a combinatorial library of highly functionalized quinoline and tetrahydroquinolines, by an Ag-catalysed, microwave mediated Povarov reaction with minimum reaction time, and yields ranging from 16 to 83%. The synthetic path of 3-vinyltyrosine was also performed with a tandem one pot microwave-mediated Povarov–CuAAC synthesis to give a triazole derivative in acceptable yield [xlv] **(Scheme 40)**.



Scheme 40. Synthesis of quinoline based triazole

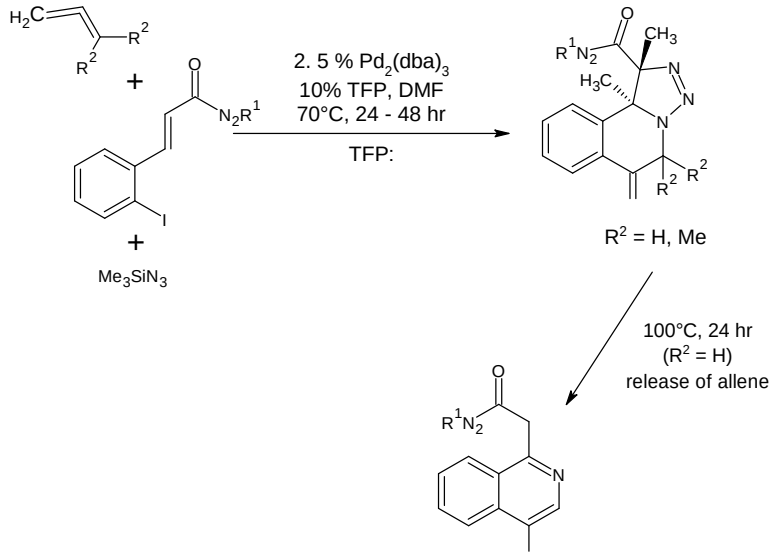
Saini *et al.* were studied the diversity-oriented synthesis of imidazobenzothiazepinones and benzoimidazolyl-thiazolidinones and measured by the nature of substitution effect of the reaction component. The reported one pot protocol of benzimidazole, aromatic aldehyde, and mercaptoacetic acid leads to the generation of imidazobenzothiazepinones with electron releasing group (ERG) as substitution on aromatic aldehyde while electron withdrawing substitutions formed benzoimidazolyl- thiazolidinone. These heterocyclic frameworks were also assayed for their anti-inflammatory and anti-microbial activities [xlvi] **(Scheme 41)**.



EDG = C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4
EWG = 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$CF_3C_6H_4$

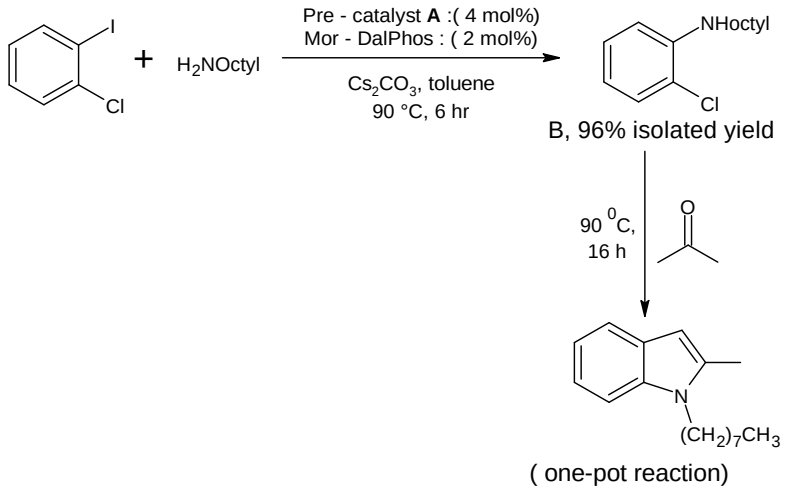
Scheme 41. Synthesis of imidazobenzothiazepinones and benzoimidazolylthiazolidinones

Synthesis of triazolo- and tetrazolo-tetrahydroisoquinolines and isoquinolines *via* temperature-controlled palladium catalysed allene/azide incorporation/intramolecular 1,3-dipolar cycloaddition cascades (**Scheme 42**) were designed and synthesized in very good yields by Gai *et al* [xlvii]. In this reported way, the grouping of addition of allenes, allylic replacement and intramolecular 1,3-dipolar cycloaddition outfits triazolo subsidiaries in a one-pot style Delivering exorbitant allene (R^2 = H) and stretched out warming prompts the expulsion of nitrogen followed by an isomerization-aromatization to give isoquinolines.



Scheme 42. Multicomponent syntheses of isoquinolines

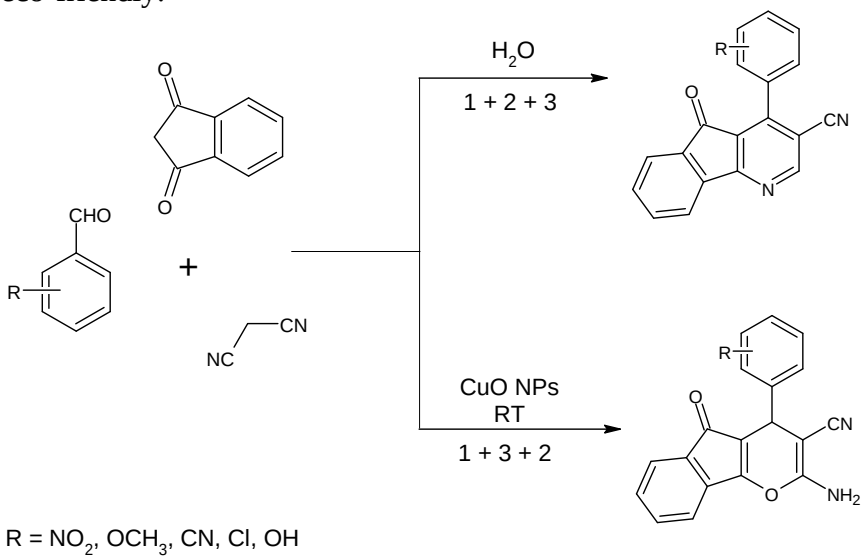
Mor-DalPhos/palladium catalyst system in the one-pot, multicomponent assembly of substituted indoles from ortho-chlorohaloarenes, alkyl ketones (including acetone), and primary amines were studied by Mark Stradiotto and co-workers. The designed protocols offer better-quality substrate scope in all MCR, under more mild conditions and without the need for an added drying agent. In preliminary test reaction (Mor-DalPhos)Pd(h1-cinnamyl)Cl (A[20])/Mor-Dal-Phos mixtures in catalysing the chemo-selective monoarylation of octylamine with 1-chloro-2-iodobenzene, affording N-(2-chlorophenyl)octyl- amine (B) in 96% isolated yield [xlviii]. **(Scheme 43)**



Scheme 43. One pot, two step combinatorial synthesis of indole

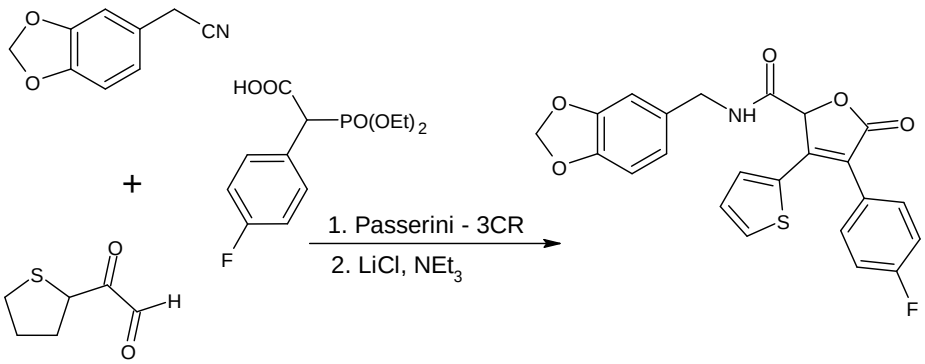
Anbhule *et al.* [xlix] established a Michael addition reaction for the preparation of privileged indeno-pyridine and indeno-pyrans applying an efficient, green, and economically beneficial

step in water **(Scheme 44)**. They found that the preparation of either indeno-pyran & indeno-pyridines based on an accurate variation in the Michael addition of malononitrile or indane-dione on Knoevenagel product during the evolution of reaction. The reaction was achieved up to 30 min. of time using CuO nano-particles in water at an ambient temperature renders the protocol and eco-friendly.



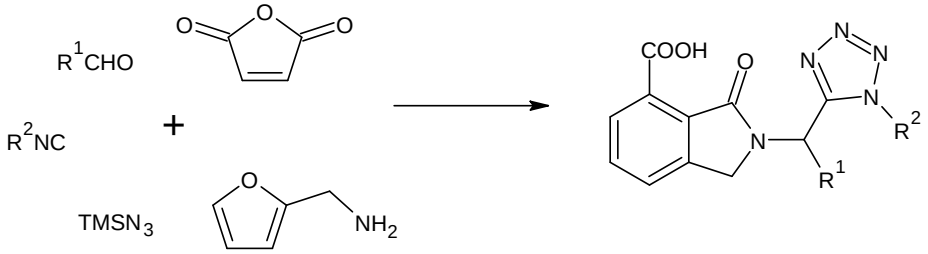
Scheme 44. Synthesis of indenopyridines and indenopyrans

Several intramolecular changes of the adaptable Ugi or Passerini reaction recently were investigated where un-natural; cyclized heterocycles result from by using bi-functional starting reactants with isocyanides. A substitute strategy is to imprison the product *via* a post condensation changes after primary construction of the standard Ugi or Passerini product (**Scheme 45)**. A sequence of facile & efficient, atom economic routes to a number of pharmacologically applicable templates used this synthetic protocol [l].



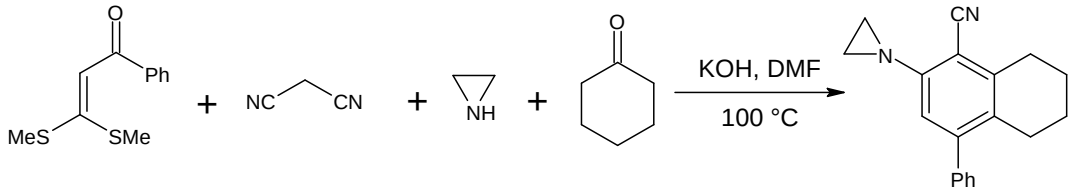
Scheme 45. Passerini three component reaction

Recently, a one pot MCR protocol of tetrazolylmethyl-isoindolinones N-linked with a 1,5-DS-T moiety **(Scheme 46)**, as well as density functional theory (DFT) based computational calculations were carried out by Montano and co-workers [li]. They prepared bis-heterocyclic scaffolds using a combinatorial approach, that is the Ugi-azide reaction, Diels-Alder cycloaddition (from furan moities), and aromatization (from oxa-bridged intermediates).



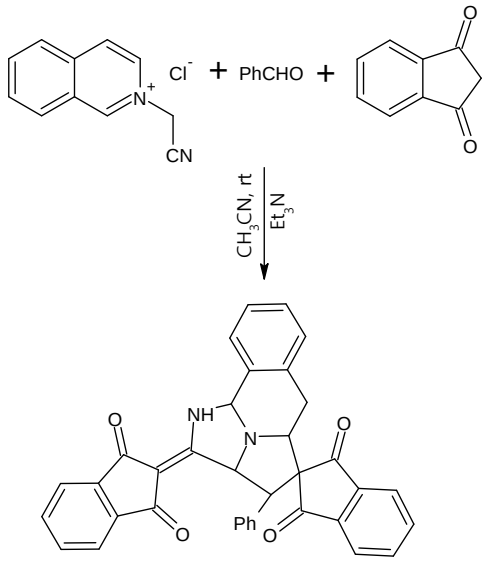
Scheme 46. One pot synthesis of 2-tetrazolylmethyl-isoindolin-1-one

Shanmugam and co-workers [lii] developed four component base-catalyzed domino protocols for the synthesis of tetrahydronaphthalene derivatives by using malononitrile, cyclohexanone and secondary amines as starting materials **(Scheme 47)**. The synthesized tetrahydronaphthalene derivatives were found in excellent yields with AKDTAs by *in-situ* creation of the pyranone between *via* the addition elimination, cyclization, and ring opening and closing approaches without using any organometallic catalyst or reagent.



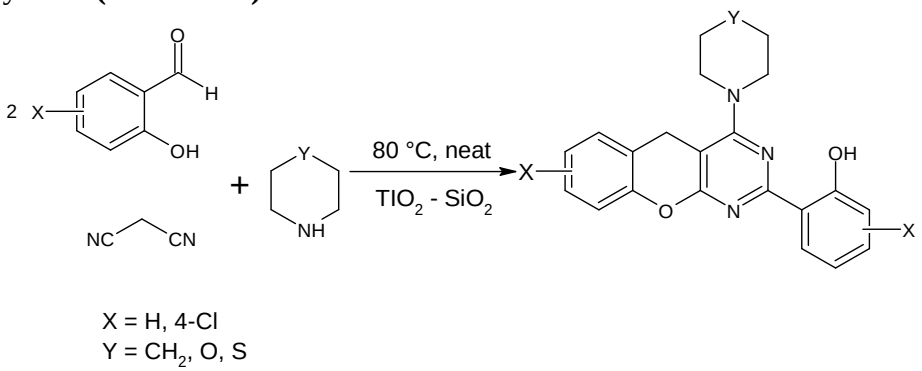
Scheme 47. Synthesis of tetrahydronaphthalene derivative

Yan *et al.* [liii] investigated the base promoted tandem double [3+2] cycloaddition protocol of N-cyanomethylisoquinolinium chloride with 2-arylidene-1,3-indanediones under various reaction conditions. The reaction not only investigated the normal spiro-indenopyrroloisoquinolines through the general 1,3-dipolar cycloaddition reaction but also afforded unique spiro-benzoimidazoindolizinoindene derivatives by the domino cyclization process **(Scheme 48)**. The reaction initiated from the versatile reactivity of the known aromatic hterocyclic N-ylides and successfully discovered a reaction design for isoquinolinium ylides in the protocol.



Scheme 48. Synthesis of Spiro derivative

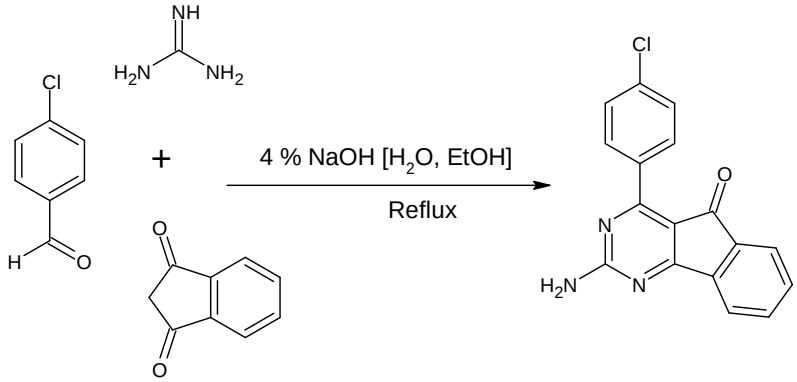
Reddy *et al.* [liv] synthesized an efficient and green synthetic protocol for the preparation of benzopyranopyrimidines utilizing 5% TiO_2–SiO_2 at 80° C temperature as a reusable heterogeneous catalyst, under solvent-free conditions. The major advantages of this approaches are experimental simplicity, simple workup procedure, reusable catalyst, less reaction times, and higher yields. **(Scheme 49)**.



X = H, 4-Cl
Y = CH_2, O, S

Scheme 49. Synthesis of benzopyranopyrimidines

Recently, a combinatorial method was reported [lv] for the preparation of substituted indeno-pyrimidine as active anticancer and CDK inhibitors. They addressed protocols **(Scheme 50)** that were synthesized *via* a one pot, straightforward protocol by utilizing very simple starting reactants like substituted aryldehydes, 1,3 indandione, and guanidinium chloride in aq. EtOH media. The reported combination of convenient and simple reactants renders this green synthetic approach suitable for implementation on large scale.



Scheme 50. Synthesis of indenopyrimidine derivative

Conclusion

MCRs are eco-friendly and effective greener innovation for synthesis of smalls and complex heterocycles. MCRs are only one of the answers for environmental contamination issue because of the less release of organic wastage contrasted and old style two component synthetic protocols. The several modifications and creations of bonds in MCRs guarantee a sustainable synthetic route towards the development of heterocyclic chemistry. In this review, we have discussed the synthetic efficiency of several MCRs under diverse reaction conditions. Some instances covered in this review describe different cyclization's that are being preserved in the final molecules, which provide further opportunities for selective structural modification. The protocols incorporated in this review article will assist with working on the situation with different heterocyclic frameworks in its nearest future synthesis and MCRs applications.

Acknowledgement

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