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Review

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Recent update on synthesis of spiro-heterocycles in alcohol using malononitrile as a building block

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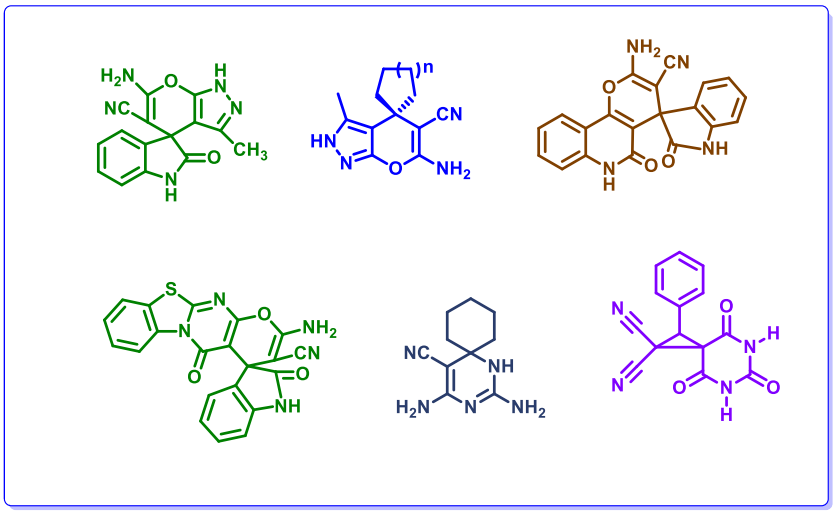
Abstract

Spiro-heterocycles represent an important class of heterocyclic compounds with diverse area of application. These types of heterocycles are found in nature and also available synthetically. Especially, pyran based spiro heterocycles are one such important class of heterocycles among others. Here, in our review we have tried to focus on the recent developments in the synthesis of spiro-heterocycles using malononitrile as a simple and effective building block. We have also focused on alcohol mediated reactions as in most of the cases, the organic compounds are soluble in alcohol. Most of the alcohols are cost effective, easily available and easy to handle.



Keywords: Malononitrile, spiro, heterocycles, alcohol, multicomponent

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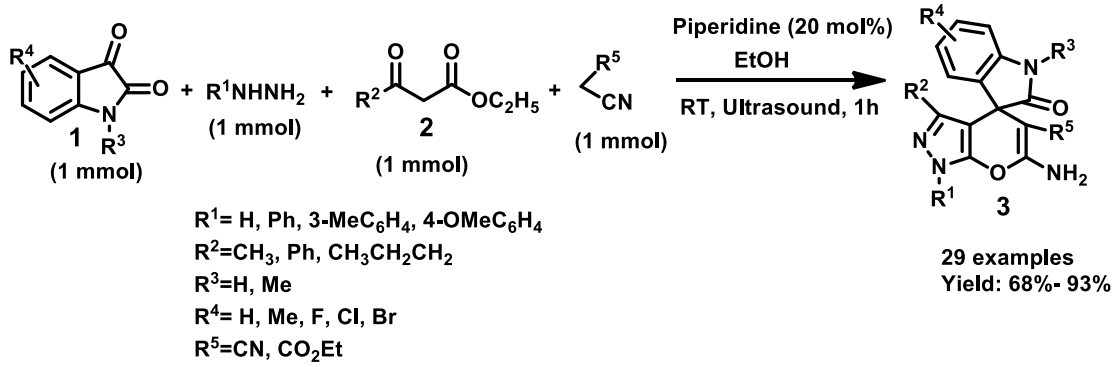
1. Introduction

Malononitrile, over the years, has been serving as a useful building block for various important heterocyclic compounds.[1-3] Heterocycles are sought after by the synthetic chemists due to its overwhelming applications in medicinal and other applied arenas. Various methodologies have been developed to access interesting heterocyclic motifs and to further modify them. One such interesting class of heterocycles is spiro-heterocycles.[4-7] A number of reports can be found on spiro pyran, spiro oxindole, spiro pyrrolidine and other similar moieties and they often depict biological importance such as anti-bacterial and anti-fungal activity[8], anti-tumour activity, anti-tubercular activity or other application.[9-12] Apart from that, some naturally isolated spiro-heterocycles are also used as remedy for food-poisoning and poisonous snake bites.[12] Several spiro-heterocycles show properties like photo-initiated ring closure[13] and also some spiro-bezopyrans have been found to help in the prevention of myocardial ischemia.[14] The two forms of spiro-heterocycles which are generated under photochemical influence can be utilized to develop 3D-optical storage memory device as shown by two eminent researchers Parthenopoulos and Rentzepis.[15] This type of molecules can also act as chemosensors.[16] The ring opening tendency of spiro-heterocycles has also been utilized for other synthetic purpose.[17] Therefore, due to such versatile application of such spiro-heterocycles, it has become important to synthesize new types of spiro-heterocycles as well as the development of new methodologies. Malononitrile often plays an important role in the formation of different types of spiro-heterocycles. [18-19] As a starting material it is comparatively cheaper and easy to handle. Malononitrile itself also incorporates a nitrile group in the product. A number of pharmaceutically active moieties contain nitrile as a substituent.[20] The nitrile group being a good π-acceptor, often helps to design electronic devices.[21] Therefore, synthesis of a diverse range of spiro-heterocycles using malononitrile as a useful tool has attracted chemists far and wide. A number of other strategies have also been employed by different groups using different starting materials, reaction condition and reaction medium. [22-26] Among other solvents, alcohols are comparatively less harmful towards human health as well as environment. The alcohols also dissolve a large number of organic compounds. Therefore, in our review, we have tried to focus on recent developments on the synthesis of spiro-heterocycles in alcohol as solvent using malononitrile as one of the reagents.

2. Synthesis of Spiro-heterocycles with a Pyran Core

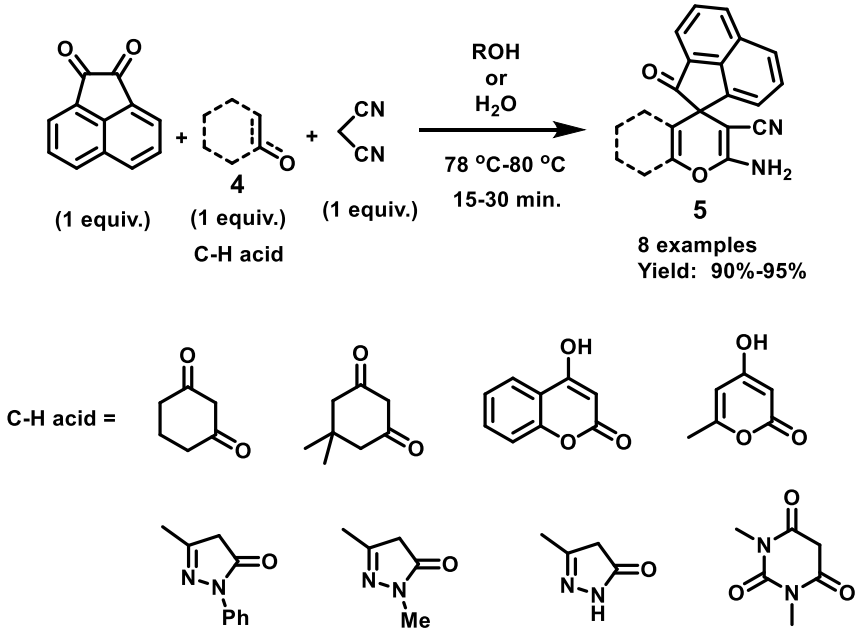
An efficient multi-component reaction protocol for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] system **3** has been developed[27] by Shi *et al.* They involved malononitrie, hydrazine, β-keto ester **2** and isatin **1** in the four component reaction methodology. The reaction was performed in ethanol solvent under the catalytic influence of piperidine and ultrasound irradiation. The reaction completed in one hour at room temperature (Scheme 1). The reactions follow the non-hazardous ultra-sound driven green procedure. No traditional column chromatography was required for purification of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]

derivatives. A triclinic crystal system was found with space group P-1 upon X-ray crystallography of its selected derivative.



Scheme 1. Synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] system under ultra-sound condition.

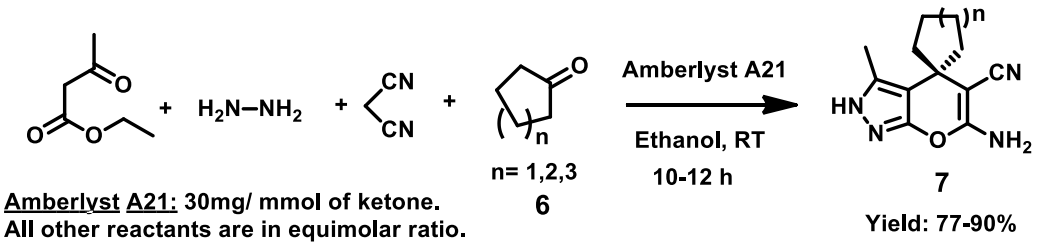
Synthesis of an interesting spiroacenaphthylene heterocycles containing a pyran ring **5** was achieved[28] by Elinson *et al.* in 2012. This multi component reaction methodology involved the heating of a mixture of three components namely malononitrile, acenaphthenequinone and a cyclic active methylene carbon containing compound **4** at 80 °C in alcohol solvent. The reaction is also achievable in water (Scheme 2) as solvent. A broad range of active C-H containing compounds has been studied. Ultimately, this new methodology is a good example of a noncatalytic green procedure.



Scheme 2. Synthesis of spiro acenaphthylene type of heterocycles containing a pyran ring.

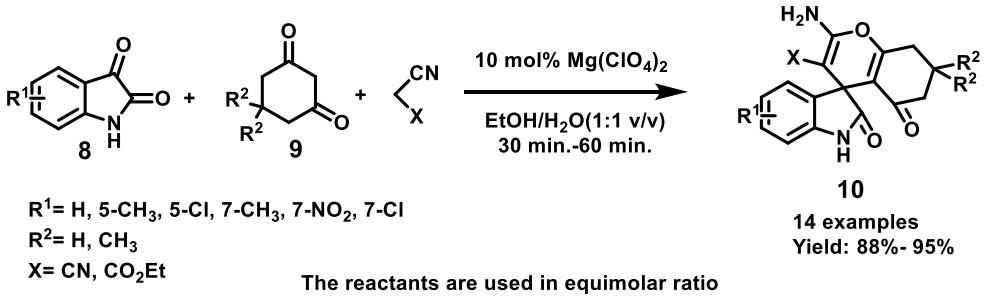
Bez *et al.* developed[29] a methodology to synthesize spirocyclic dihydropyrano[2,3-c]pyrazole derivatives using Amberlyst A21 as the catalyst in ethanol medium (Scheme 3). The methodology involved a four-component reaction involving malononitrile, hydrazine hydrate, ethyl acetoacetate and cyclic ketone **6**. In this methodolgy they have shown a green approach for the synthesis of spiro-substituted dihydropyrano[2,3-

c]pyrazoles **7**. Amberlyst A21 here, acted as an efficient reusable catalyst and the methodology also didn't involve hazardous organic solvent or high temperature.



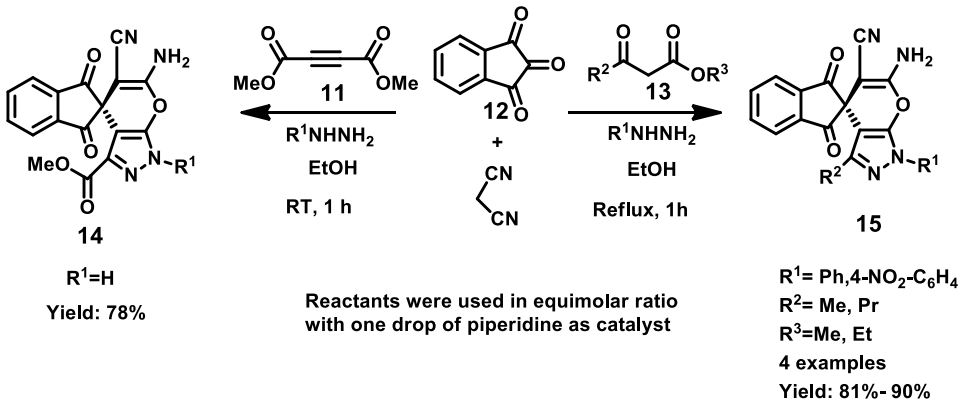
Scheme 3. Synthesis of spiro-substituted dihydropyrano[2,3-c]pyrazoles using Amberlyst A21 as the catalyst.

Spiro[4*H*-pyran-oxindole] derivatives **10** were synthesized[30] by the magnesium perchlorate catalyzed methodology involving malononitrile, isatins **8** and 1, 3-dicarbonyl compounds **9**. Ethyl cyano acetate was also used in place of malononitrile for the synthesis of other derivatives (Scheme 4). The reactions were performed in 50% aqueous ethanol medium and the reaction completed within 30 min. to 60 min. The described protocol is simple, eco-friendly and easy to carry out. The $Mg(ClO_4)_2$ catalyst is non-toxic, inexpensive and readily available also.

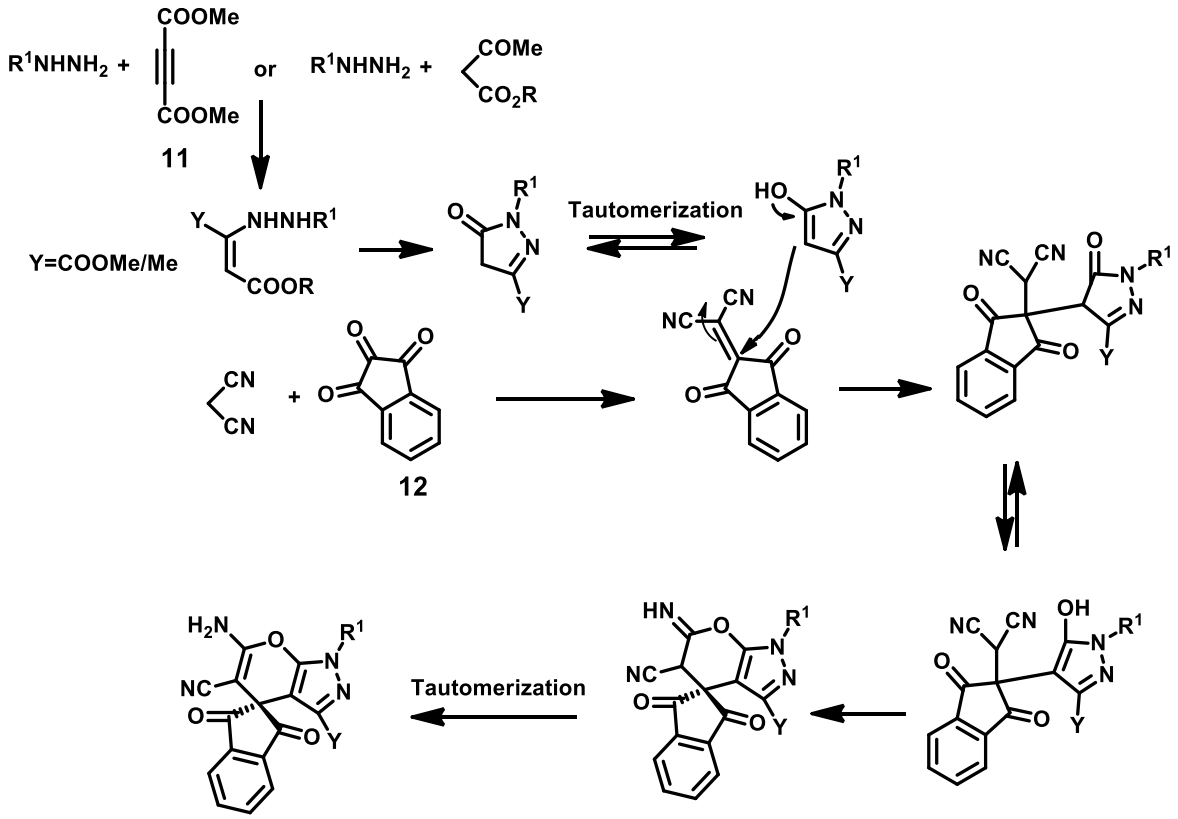


Scheme 4. Synthesis of spiro[4*H*-pyran-oxindole] derivatives using magnesium perchlorate as catalyst.

Synthesis of methyl 6'-amino-5'-cyano-1,3-dihydro-1,3-dioxo-1'*H*-spiro[indene-2,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate **14** has been achieved[31] by Alizadeh and Bayat in 2014. They developed a one-pot methodology involving dimethyl acetylenedicarboxylate (**11**), ninhydrin (**12**), hydrazine derivatives and malononitrile. This reaction occurred at room temperature. This four component methodology was carried out in ethanol medium. On the other hand, derivatives of 6'-amino-1,3-dioxo-1,3-dihydro-1'*H*-spiro[indene-2,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile **15** were obtained when β-keto ester **13** was used instead of the dimethyl acetylenedicarboxylate under refluxing condition. The reactions completed within a short span of time (1 hour) and good yields were obtained and the protocol also had operational simplicity (Scheme 5). The mechanism of the reaction is shown in Scheme 6.

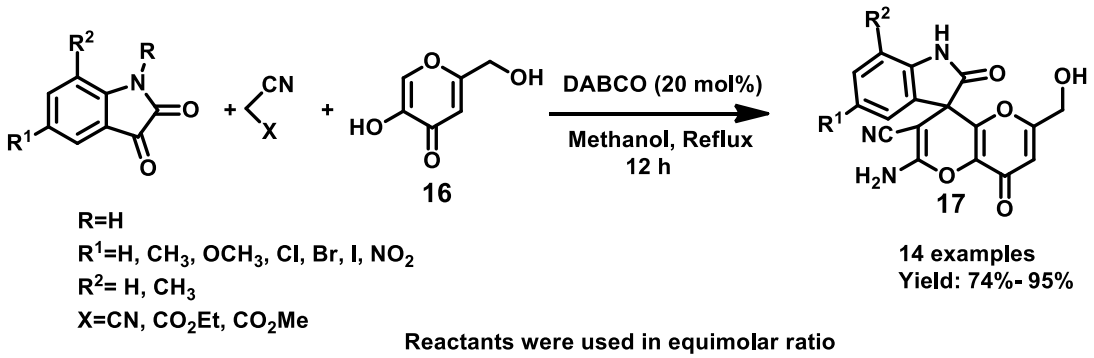


Scheme 5. Regioselective synthesis of spiro-pyranopyrazole derivatives.

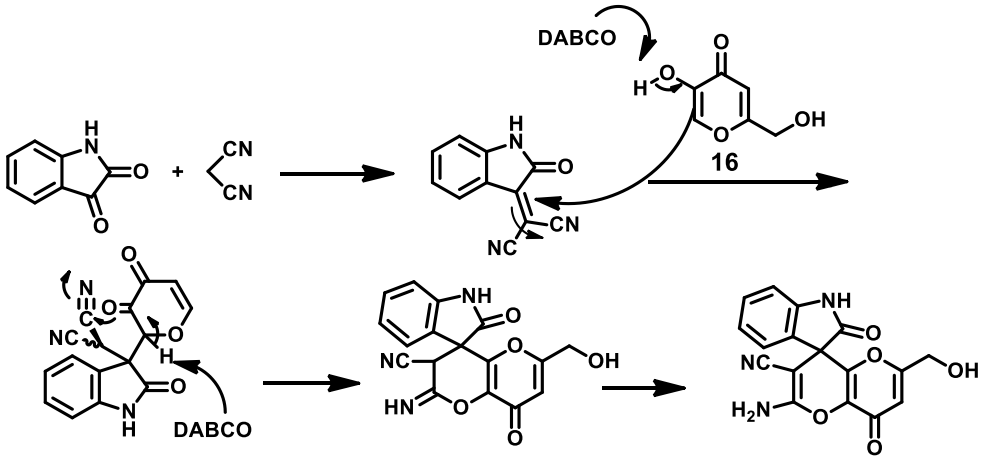


Scheme 6. Mechanism for the regioselective synthesis of spiro-pyranopyrazole derivatives.

Another work by Rahmati *et al.* showed[32] the utility of malononitrile in a one-pot, three component reaction methodology in methanol medium under refluxing condition for the synthesis of spiro[indoline-3,4'-pyrano[3,2-b]pyran]-2,8'-dione derivatives **17**. N-substituted or unsubstituted isatin, kojic acid (**16**) and malononitrile were employed for the synthesis in presence of DABCO. Phenanthrene-9, 10-dione was also used in place of isatin. Some other active methylene groups like methyl cyanoacetate or ethyl cyanoacetate was also used to obtain different derivatives. The reaction completed within 12h under refluxing condition (Scheme 7).The mechanism of the reaction is shown in Scheme 8.

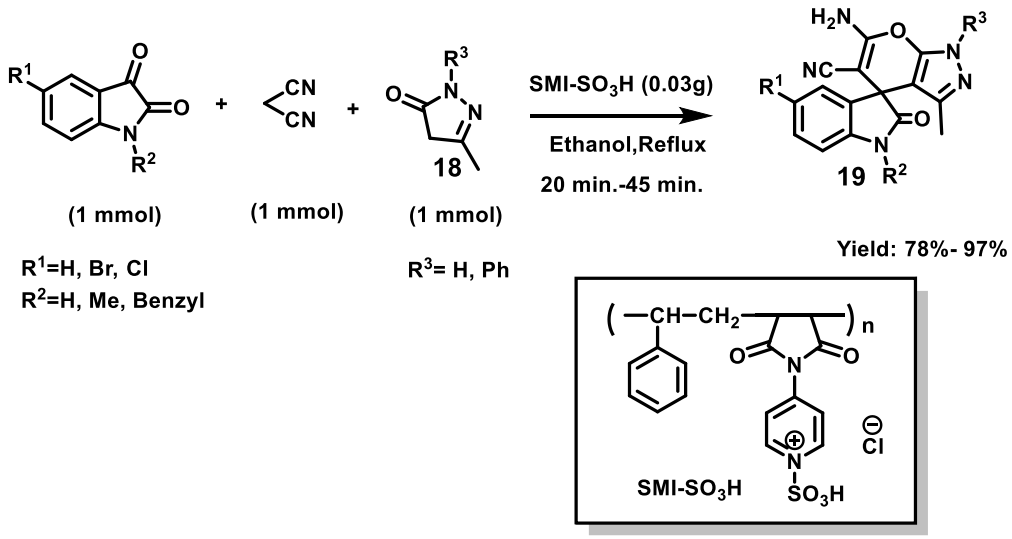


Scheme 7. Synthesis of spiro [indoline-3, 4'-pyrano [3, 2-b]pyran]-2,8'-dione derivatives.



Scheme 8. Mechanistic interpretation of the synthesis of spiro[indoline-3,4'-pyrano[3,2-b]pyran]-2,8'-dione derivatives.

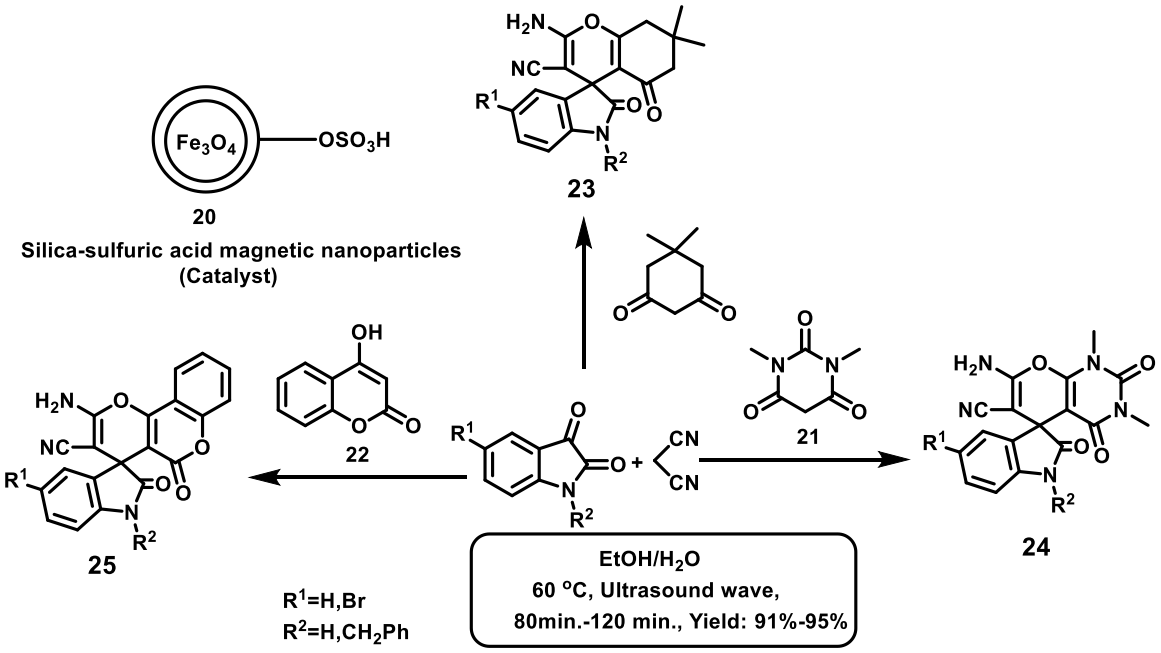
Spiropyrans **19** have been synthesized[33] using poly (styrene-co-maleic anhydride) based N-sulfonic acid containing solid catalyst by Heravi *et al.* in 2014. The methodology was based on multicomponent procedure involving isatin, malononitrile and 3-methyl-1*H*-pyrazol-5-one **18** and the three components were allowed to react together to produce the desired spiro-pyran (Scheme 9). Heravi *et al.* have extended the methodology using acenaphthenequinone or ninhydrin in place of isatin. And, 4-hydroxy coumarin or dimedone was also used in place of pyrazole derivatives for the synthesis of spiro-pyran derivatives. The catalyst was reusable up to six times without any notable loss in activity.



Scheme-9. Synthesis of spiropyrans using poly (styrene-co-maleic anhydride) based N-sulfonic acid containing solid catalyst

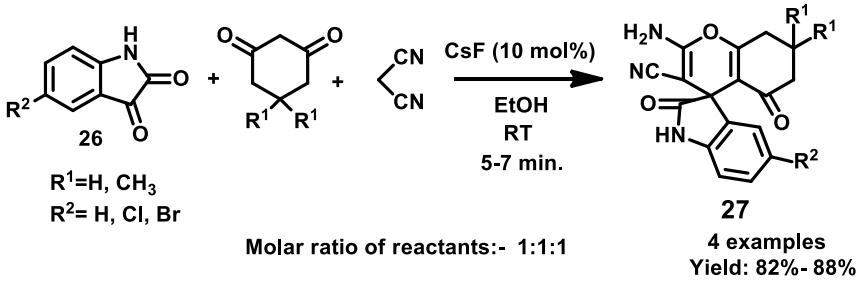
Spiro [2-amino-4*H*-pyran-oxindole]s **23-25** were synthesized[34] by Karimi *et al.* by using magnetic nanoparticles. Silica-sulfuric acid based nanoparticle **20** was used for this purpose. Isatin, malononitrile and dimedone were used under this three-component reaction methodology to produce spiro [2-amino-4*H*-pyran-oxindole] derivatives **23**. 1,3-dimethylbarbituric acid (**21**) or 4-hydroxycoumarin (**22**) was also used in place of dimedone to produce **24** and **25** respectively. The reactions were performed in aqueous ethanol medium at 60 °C with ultrasound (Scheme 10).

Such silica-sulfuric acid based nanoparticle catalyst is reusable and makes the process environmentally benign in comparison with homogeneous acid catalysts.



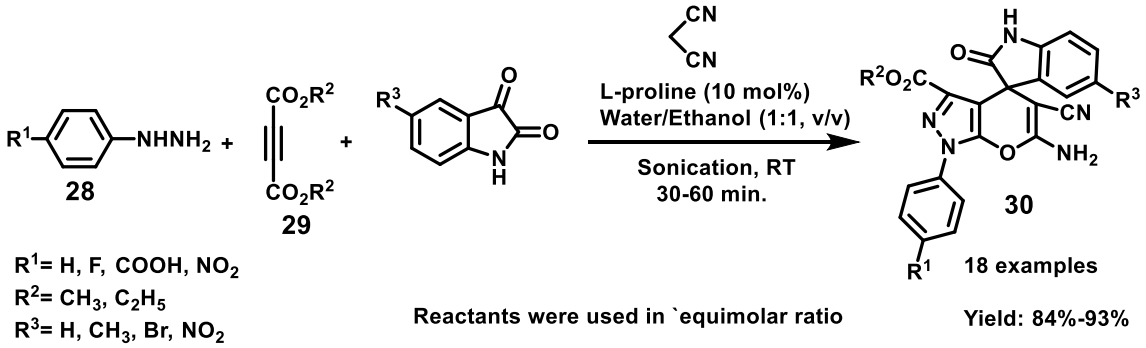
Scheme 10. Synthesis of spiro [2-amino-4*H*-pyran-oxindole]s using magnetic nanoparticles.

Pyran ring containing 2-amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile derivatives **27** were synthesized[35] using CsF as catalyst in ethanol medium by Dalal *et al.* A multicomponent reaction involving malononitrile, indoline-2, 3-dione **26** (isatin) and dimedone or 1, 3-cyclohexadione was performed at room temperature (Scheme 11). Excellent yields of the derivatives were obtained. Dalal *et. al*. have shown that 10 mol% of CsF was sufficient for optimum yield of the reaction.



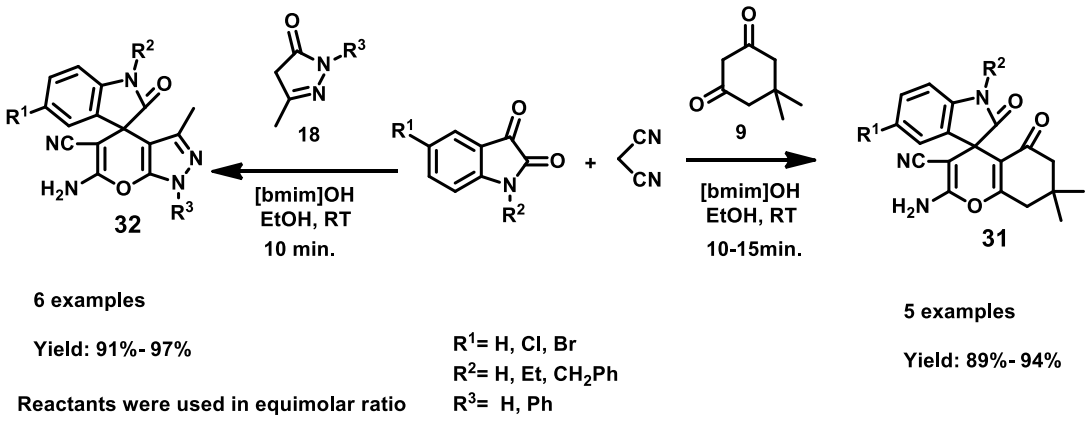
Scheme 11. Synthesis of pyran ring containing spiro oxindole derivatives using CsF as catalyst.

Spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives **30** were synthesized[36] using L-proline as catalyst under the influence of ultrasound wave. The protocol developed by Ablajan *et al*. described a one-pot multicomponent synthetic strategy in aqueous ethanol medium. Excellent yields were obtained at room temperature within an hour. This multicomponent reaction methodology involved malononitrile, an aromatic hydrazine derivative **28**, diethyl acetylenedicarboxylate **29** and isatin (Scheme 12). The methodology has the additional advantage of simple workup and rapid reaction under neutral conditions.



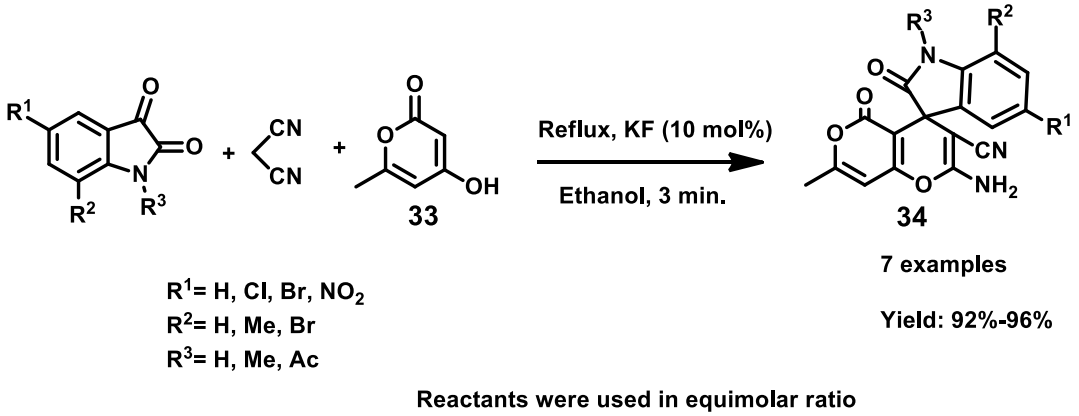
Scheme 12. Synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives using L-proline as catalyst.

An ionic liquid mediated synthesis of 2-amino 7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile derivatives **31** and 6'-amino-2-oxo-1'*H*-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile derivatives **32** has been developed[37] by Dalal *et al.* using [bmim]OH as the effective ionic liquid. The reaction proceeded at room temperature in ethanol medium. This straightforward one-pot synthetic route was effective for both mono and bis-spirooxindole systems. The use of toxic catalyst was avoided in this methodology. Malononitrile, isatins and 3-methyl-1*H*-pyrazole-5(4*H*)-one derivatives **18** or dimedone (**9**) were the ingredients for this one-pot, multicomponent methodology (Scheme 13). Excellent yields were obtained in a short span of time (10-15 min.). The solid product was obtained by filtration and the ionic liquid catalyst was recovered from the ethanol filtrate and it was also recyclable up to five times.



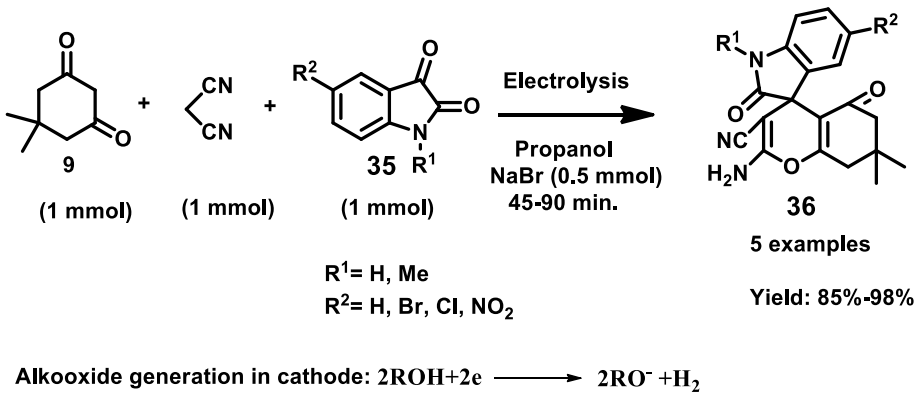
Scheme 13. Ionic liquid mediated synthesis of spiro oxindole derivatives.

Another multicomponent reaction for the synthesis of spiro oxindole-3, 4'-pyrano [4, 3-b]pyran derivatives **34** was developed[38] by Elinson *et al.* in ethanol under reflux. Malononitrile, isatin and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**33**) was used in this protocol (Scheme 14). The reaction could also be performed under solvent-free condition by grinding in mortar. Only 10 mol% of catalyst was required for the reaction.



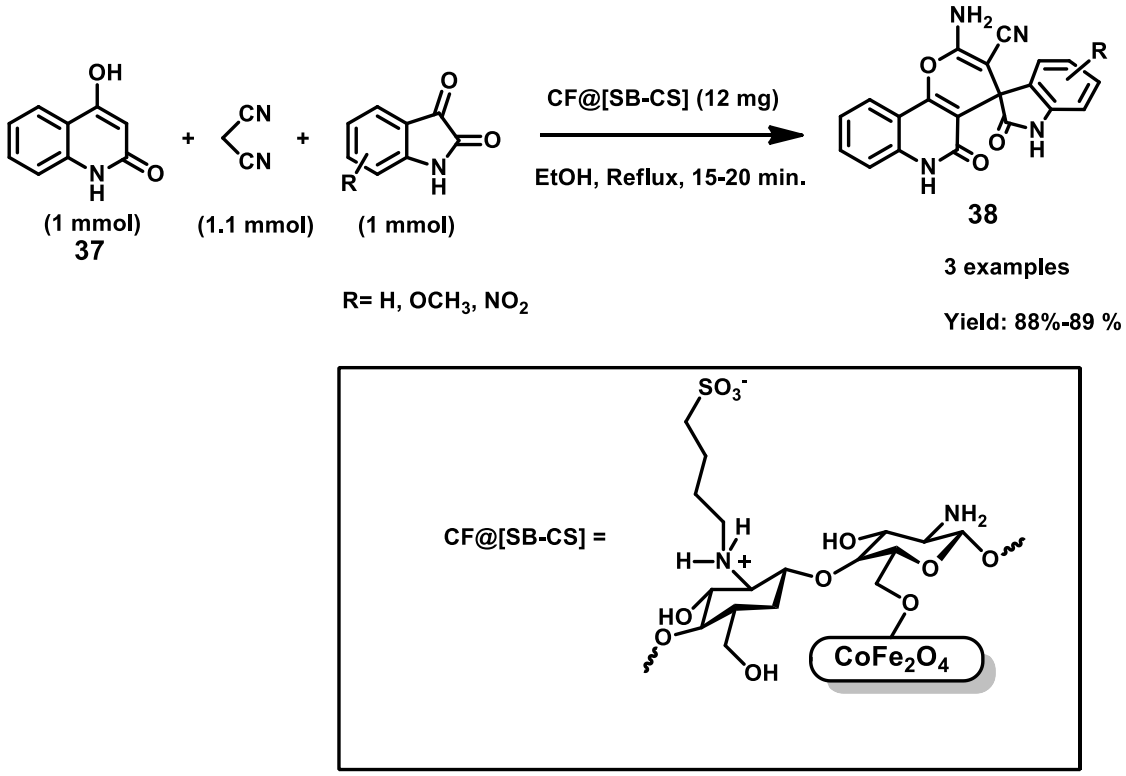
Scheme 14. Multicomponent synthesis of spirooxindole-3, 4'-pyrano [4, 3-b]pyran derivatives using KF as catalyst.

Darvish, Mirza and Makarem established an electrolytic green methodology for the synthesis of pyran containing spiro oxindole **36** derivatives.[39] In this protocol, malononitrile, isatin **35** and dimedone **9** were taken in an undivided cell using NaBr as electrolyte. In this protocol, propanol played the dual role as the solvent and the base as alkoxide anion as well (Scheme 15). The alkoxide anion is generated *via* cathode reduction.The reaction proceeded at 50 ^oC. Nanoparticles of spiro oxindoles were obtained in excellent yields under this protocol.



Scheme 15. Synthesis of pyran containing spirooxindole derivatives under electrolysis.

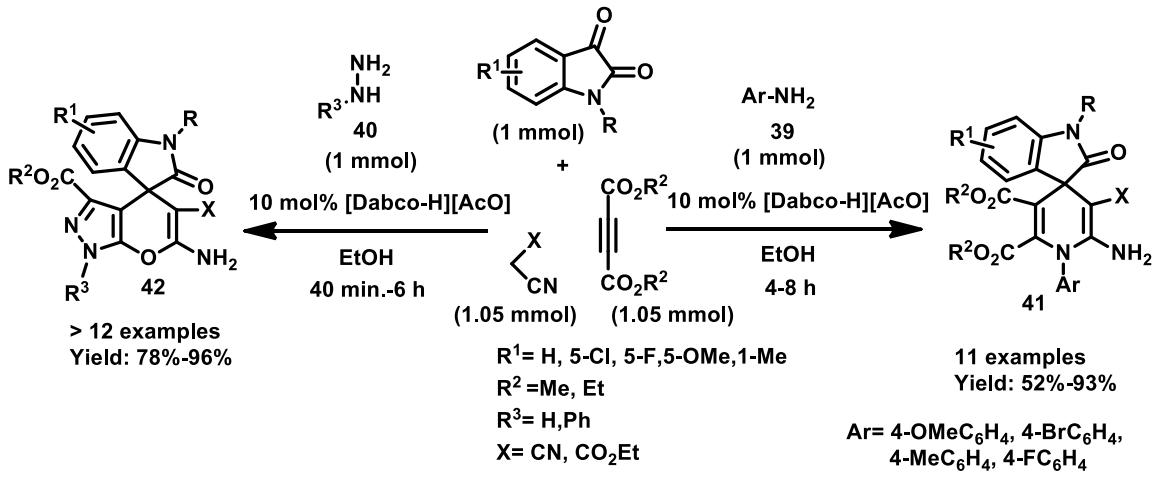
A green methodology was developed[40] for the synthesis of pyran containing 2-amino-2',5- dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3'-indoline]-3-carbonitrile systems **38** by Moghadam *et al.* using chitosan derived heterogeneous catalyst (Scheme 16). The catalyst had a cobalt-ferrite core with amine and hydroxyl groups. Particularly these amine and hydroxyl groups catalyzed the reaction and also the catalyst was recyclable up to 5 times without loss of much reactivity. Malononitrile, isatin and 4-hydroxyquinolin-2-one (**37**) were employed for the synthesis of spiro oxindole systems using multicomponent process.



Scheme 16. Synthesis of pyran containing spiro oxindole systems using chitosan derived heterogeneous catalyst.

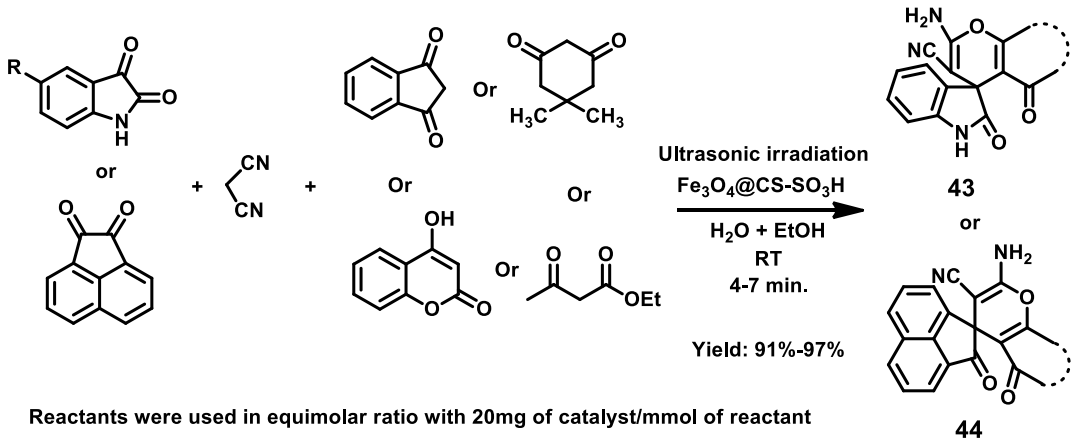
Another one-pot multicomponent reaction methodology was developed[41] by Xu *et al.* by using DABCO-based ionic liquid in ethanol solvent. The reaction involved malononitrile, isatin and dialkyl acetylene

dicarboxylate. These three components when combined with a primary aromatic amine **39**, produced spiro 1,4-dihydro pyridine compounds **41** and when combined with hydrazine derivatives **40** spiro pyrano[2,3-c]pyrazole systems **42** was produced (Scheme 17). This protocol was also extended to carbonyl compounds apart from isatin, like ninhydrin and acenaphthylene-1, 2-dione. A number of DABCO based ionic liquid was screened for optimization and the catalyst could be recycled up to 5 times without loss of much reactivity.



Scheme 17. Synthesis of spiro 1,4-dihydro pyridine and spiro pyrano[2,3-c]pyrazole systems using DABCO-based ionic liquid.

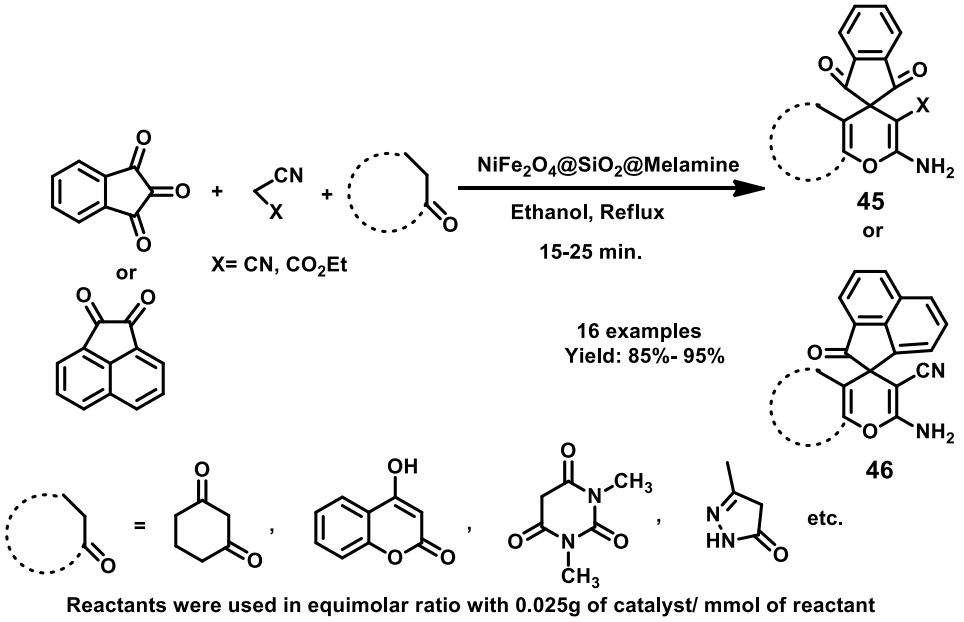
An ultrasound promoted multi-component reaction methodology for the synthesis of spiro-4*H*-pyrans **43-44** was developed[42] by Naeimi and Lahouti (Scheme 18). The reactions were performed in aqueous ethanol medium at room temperature. Malononitrile, 1, 3-dicarbonyl compounds and isatin or acenaphthoquinone were involved in this three-component methodology. The reaction was catalyzed by a recyclable chitosan encapsulated magnetic Fe_3O_4 nanoparticles (Fe_3O_4@CS-SO_3H NPs). A range of 1, 3-dicarbonyl compounds were studied under this methodology.



Scheme 18. Ultrasound promoted multi-component reaction methodology for the synthesis of spiro-4*H*-pyrans.

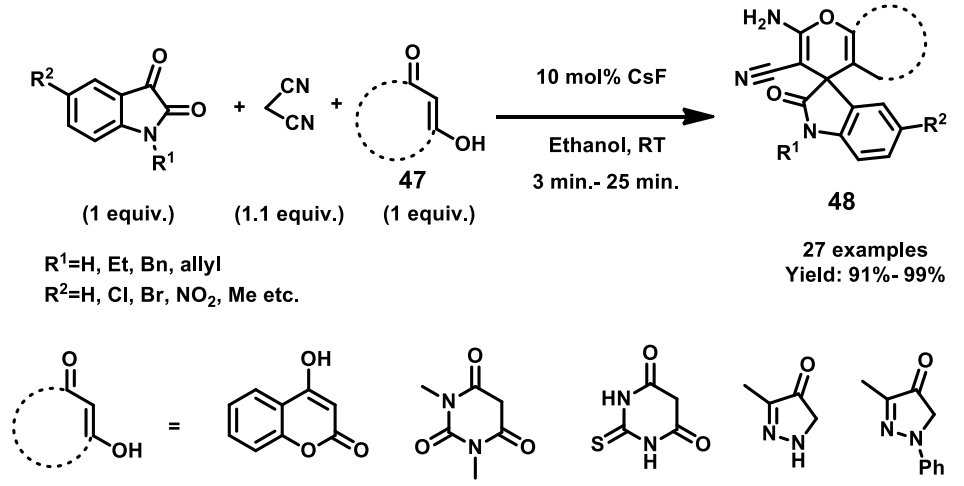
Another multi-component methodology for the synthesis of spiro-pyran derivatives **45-46** as well as spiro-acenaphthylenes was developed[43] by Safari and Nasab using magnetic $NiFe_2O_4$@SiO_2@Melamine

nanoparticles as an effective and reusable catalyst (Scheme 19). Different 1,3-dicarbonyl compounds were allowed to react with ninhydrin/acenaphthoquinone and malononitrile/ethyl cyanoacetate under this one-pot multi-component methodology. The reactions proceeded under reflux in ethanol solvent. The magnetic nanoparticle catalyst was easily separated from the reaction mixture by using an external magnet.



Scheme 19. Synthesis of spiro-pyran derivatives and spiro-acenaphthylenes using magnetic $NiFe_2O_4$@SiO_2@Melamine nanoparticles as an effective and reusable catalyst.

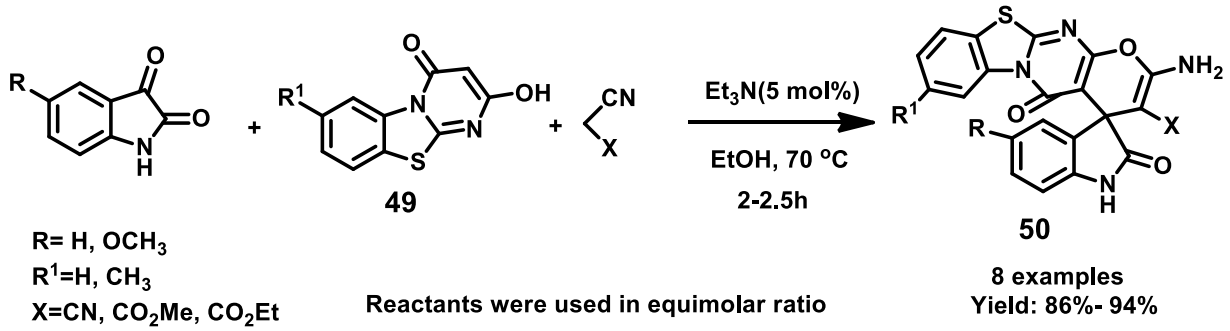
Pawar *et al.* also independently developed[44] a multi-component methodology to synthesize pyran containing spiro-oxindole derivatives using malononitrile, enolizable ketones and isatins in (1:1) aqueous ethanol solvent under the catalytic influence of Cu nanoparticles embeded on carbon microsphere under reflux.



Scheme 20. CsF promoted multi component synthesis of spiro oxindole based heterocycles.

Spirooxindole based heterocycles **48** have been synthesized[45] by the CsF promoted multi component reaction methodology involving isatin and malononitrile along with different 1, 3-dicarbonyl compounds or its equivalent compounds **47** as the third component (Scheme 20). 4-hydroxycoumarin or barbituric acid or pyrazolone was used as the third component in this one-pot three component methodology in ethanol at room temperature. The methodology also worked with *bis*-isatins.

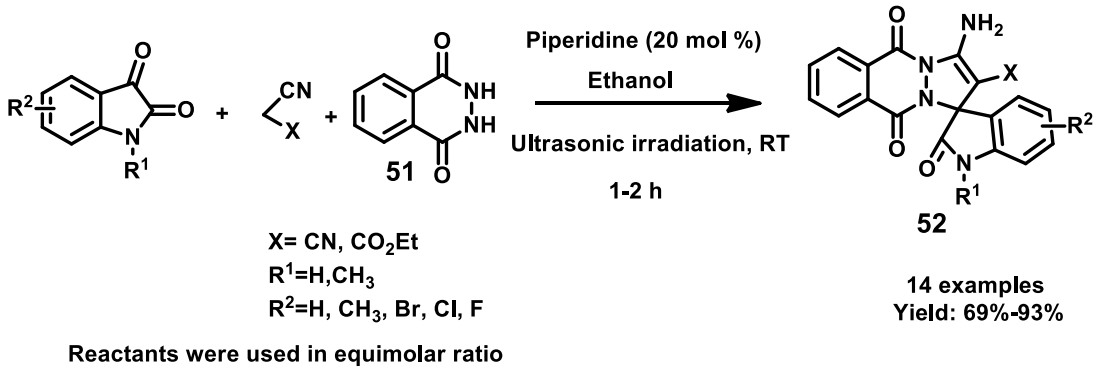
A catalytic amount of triethyl amine was also found effective for the synthesis of 2-amino-2',5-dioxo-5*H*-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3'-indoline]−3-carbonitrile derivatives **50**.[46] Here, Miri *et al*, in this methodology involved malononitrile/active methylene compound, isatins and 2-Hydroxy-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ones **49** in one-pot (Scheme 21). The reaction proceeded in ethanol medium at 70 °C. The merits of this protocol are easy operation, benign towards environment and excellent yields. The methodology avoids purification by column chromatography and follows group assisted purification (GAP)strategy.



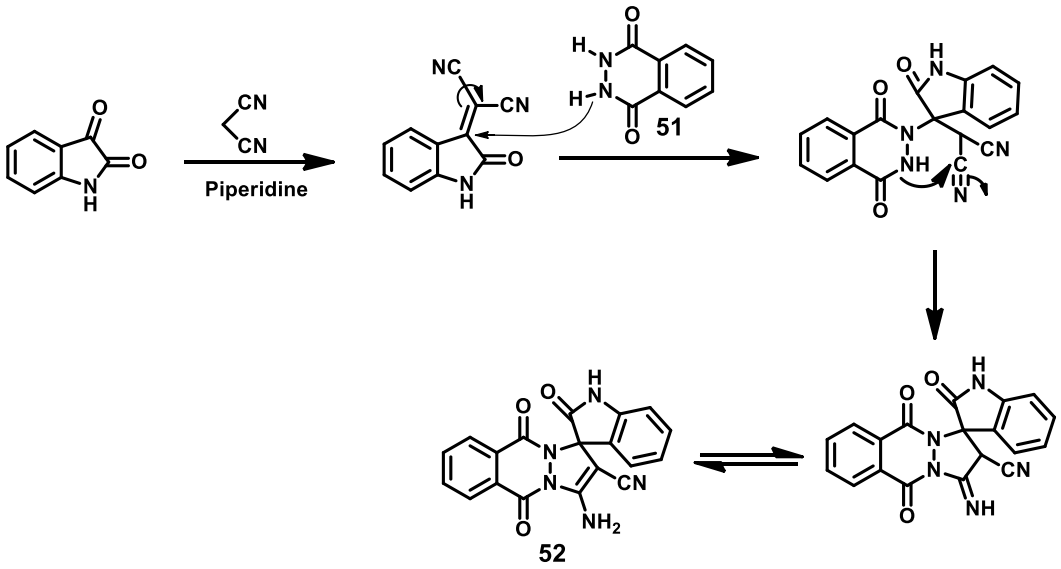
Scheme 21. Synthesis of pyran containing spiro oxindole derivatives using triethyl amine as catalyst.

3. Synthesis of Spiro-heterocycles without a Pyran Core

An ultrasound promoted methodology for the synthesis of spiro [indoline-3,1'-pyrazolo [1,2-b]phthalazine]systems **52** has been developed[47] by Wang *et al.* under a one-pot multi-component reaction protocol in ethanol solvent. Isatin, malononitrile or ethyl cyanoacetate, phthalhydrazide (**51**) and piperidine were involved in this reaction methodology (Scheme 22). The mechanism of the reaction is shown in Scheme 23.

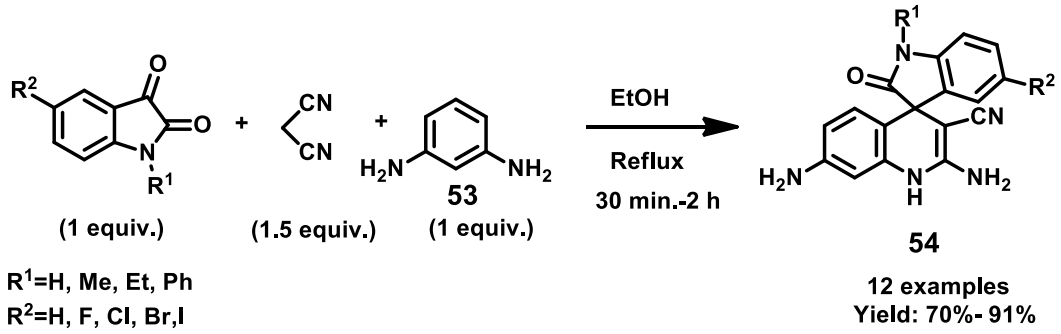


Scheme 22. Ultrasound promoted methodology for the synthesis of spiro [indoline-3, 1'-pyrazolo [1, 2-b]phthalazine]systems



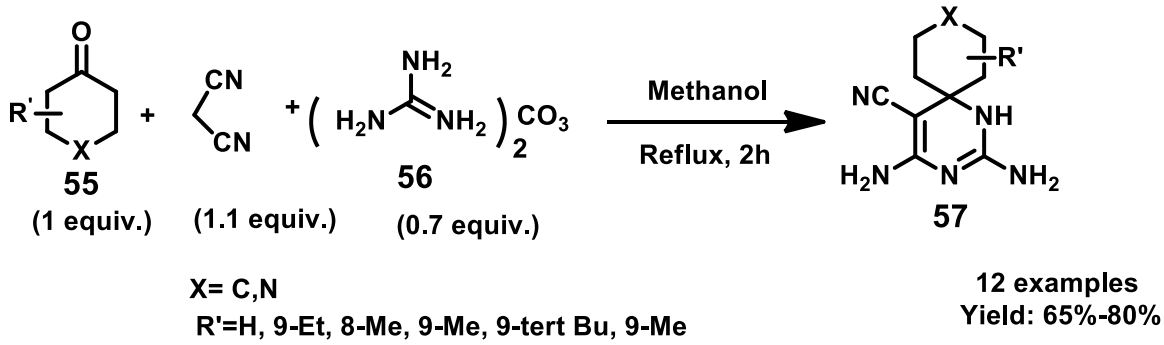
Scheme 23. Mechanism for ultrasound promoted methodology for the synthesis of spiro [indoline-3, 1'-pyrazolo [1, 2-b]phthalazine]systems

2',7'-diamino-2-oxo-1',4'-dihydrospiro[indoline-3,4'-quinoline]-3'-carbonitriles **54** were also synthesized using *meta*-phenylene diamine (**53**), isatin and malononitrile as starting materials.[16] In this methodology Pramanik *et al.* illustrated one-pot multicomponent reaction which was performed in ethanol medium under reflux. The reaction completed within one hour (Scheme 24).

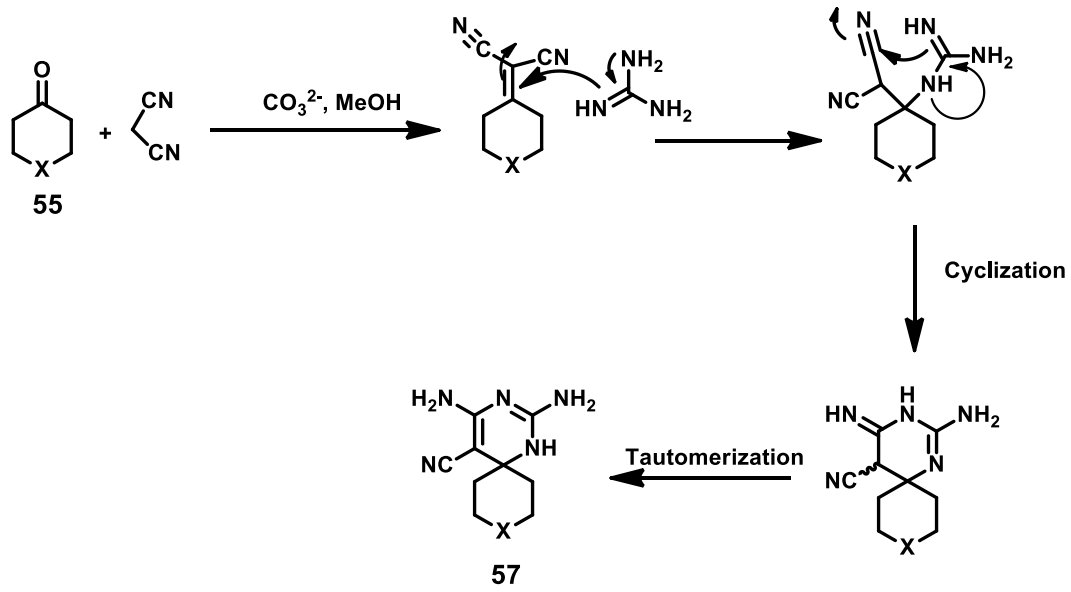


Scheme 24. Synthesis of isatin based spiro heterocycles from *meta*-phenylene diamines.

A one-pot multicomponent reaction methodology was developed[48] for the synthesis of spiro-2,4-diaminopyrimidines **57** by Balalaie *et al.* in 2013. The methodology involved guadinium carbonate (**56**), cyclic ketones **55** and malononitrile/methylcyanoacetate. The reaction proceeded in methanol solvent under reflux (Scheme 25). The reaction progressed *via* Knoevenagel reaction followed by Michael reaction and cyclization. The unique feature of the synthesized compounds is that they are capable of earning extra stability by virtue of having hydrogen bonding property. Moreover, the careful study of antibacterial activity of these spiro aminopyrimidines revealed notable results. The mechanism is shown in Scheme 26.



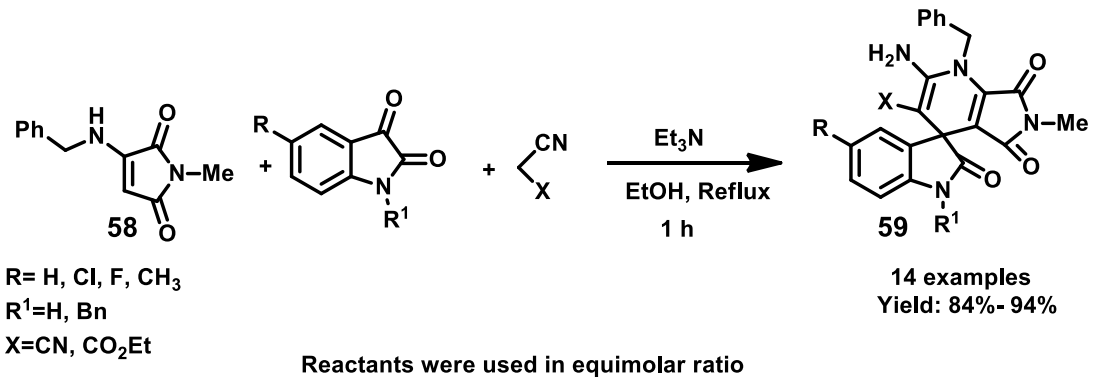
Scheme 25. One-pot multicomponent synthesis of spiro-2,4-diaminopyrimidines.



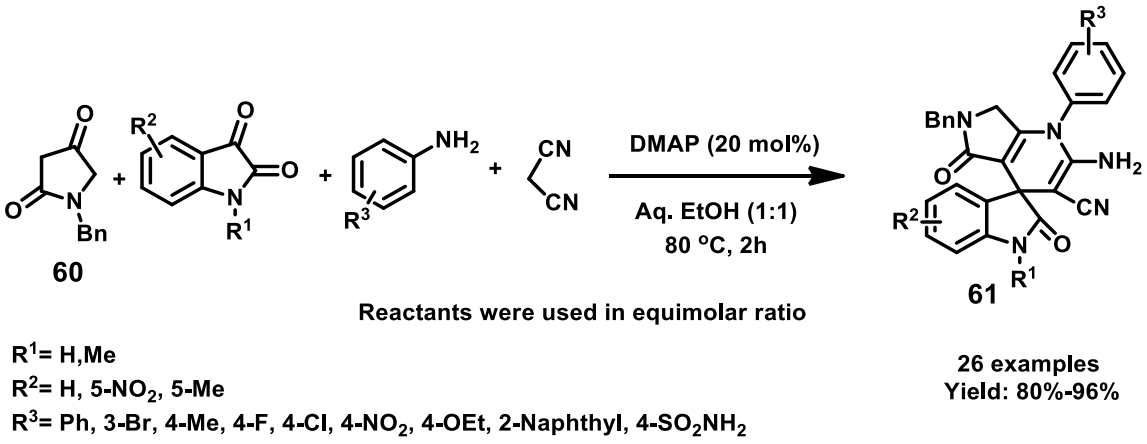
Scheme 26. Mechanism for one-pot multicomponent synthesis of spiro-2-aminopyrimidines.

A multi-component synthetic methodology of spiro[indoline-3,4'-pyrrolo[3,4-b]pyridine] derivatives **59** was achieved[49] using triethylamine as base by Yan *et al.* Malononitrile or ethyl cyanoacetate was chosen as a building block along with isatins and 3-arylamino-1-methyl-1*H*-pyrrole-2,5-dione (**58**). A range of spiro oxindole systems were obtained under this methodology. The reaction proceeded under reflux in ethanol solvent (Scheme 27). This protocol is very simple to handle with respect to easy purification, short span of reaction time (1 hour), easily available starting material.

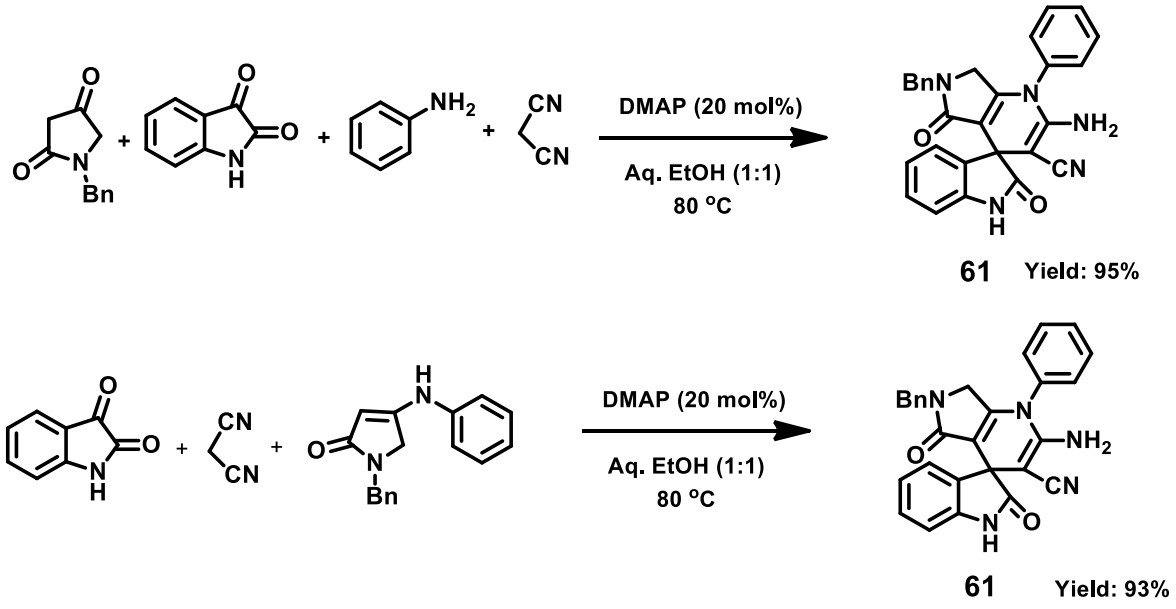
Another one-pot, four component reaction protocol to synthesize spiro oxindole-1,4-dihydropyridine derivatives **61** was developed[50] by Tao *et al.* in aqueous ethanol medium. The components of the reaction methodology include *N*-benzylpyrrolidine-2,4-dione (**60**), aniline, isatin and malononitrile (Scheme 28). The reaction proceeded in presence of 4-DMAP as catalyst and good yields were obtained under this methodology. The aqueous ethanol contained water and ethanol in 1:1 ratio. Comparative study has been done by this group and they also showed a better yield of the product in four component strategy compared to an alternative three-component methodology (Scheme 29).



Scheme 27. Synthesis of spiro [indoline-3, 4'-pyrrolo [3, 4-b] pyridine] derivatives using triethylamine as base.

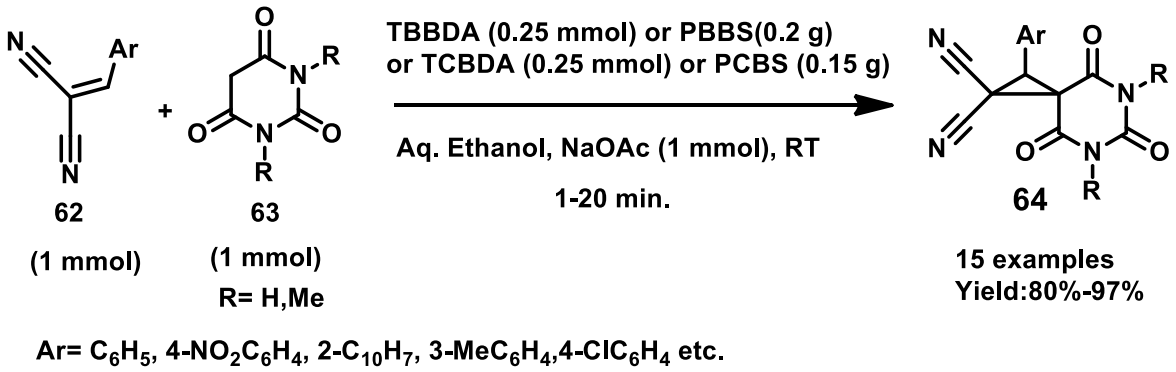


Scheme 28. Synthesis of spiro oxindole-1,4-dihydropyridine derivatives using 4-DMAP as catalyst.

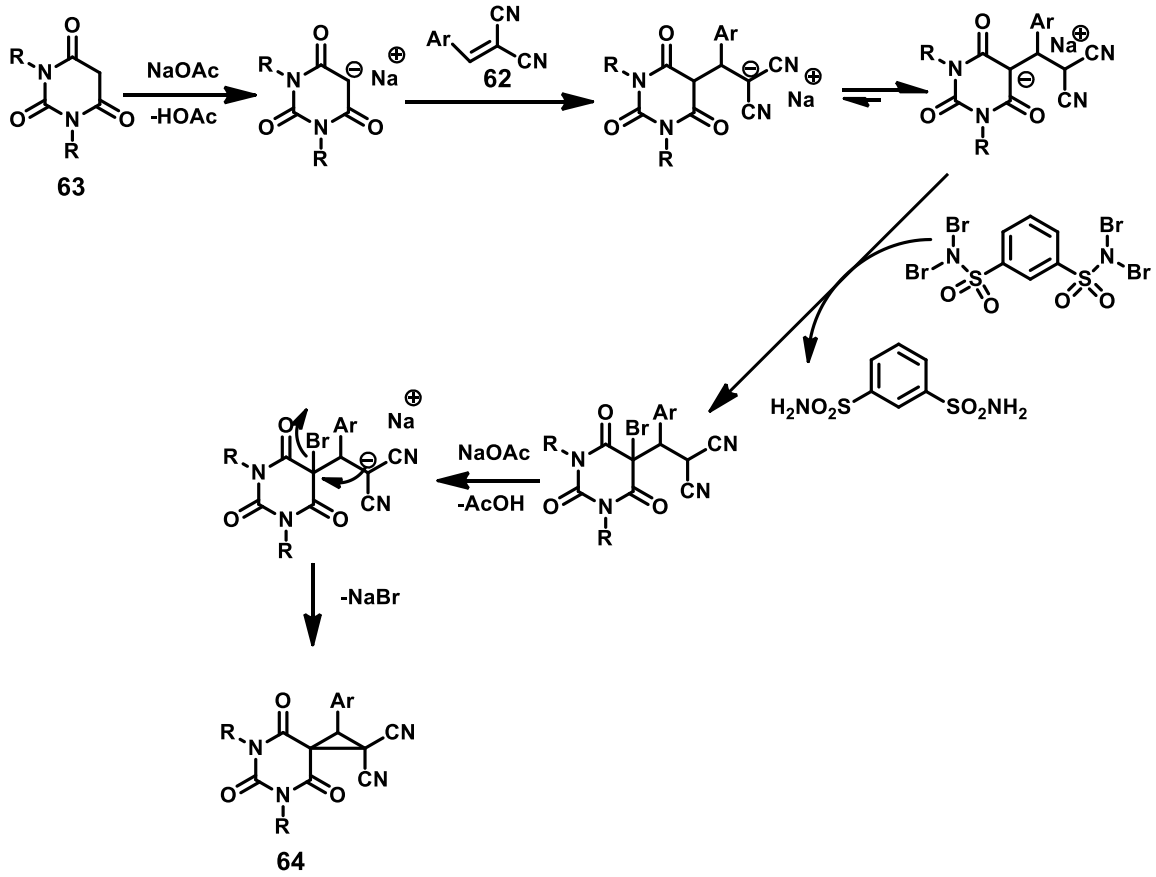


Scheme 29. Comparison between three and four component reaction methodology.

Spirocyclopropylbarbiturates (2-aryl-4,6,8-trioxo-5,7-diazaspiro[2.5]octane-1,1-dicarbonitrile) **64** have been synthesized[51] by Vaghei *et al* by reacting arylidenemalononitriles **62** with barbituric acids **63**. Different catalysts were used for the purpose of this synthesis like *N,N,N,N*-tetrabromobenzene-1,3-disulfonamide (TBBDA), poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide)(PBBS), *N*,*N*,*N*,*N*-tetrachlorobenzene-1,3-disulfonamide (TCBDA), poly(*N*-chloro-*N*-ethylbenzene-1,3-disulfonamide) (PCBS) and more or less comparable yields were obtained for all the catalysts (Scheme 30). The optimum yield were obtained in aqueous ethanol in presence of sodium acetate as base at room temperature. The mechanism of the reaction is shown in Scheme 31.

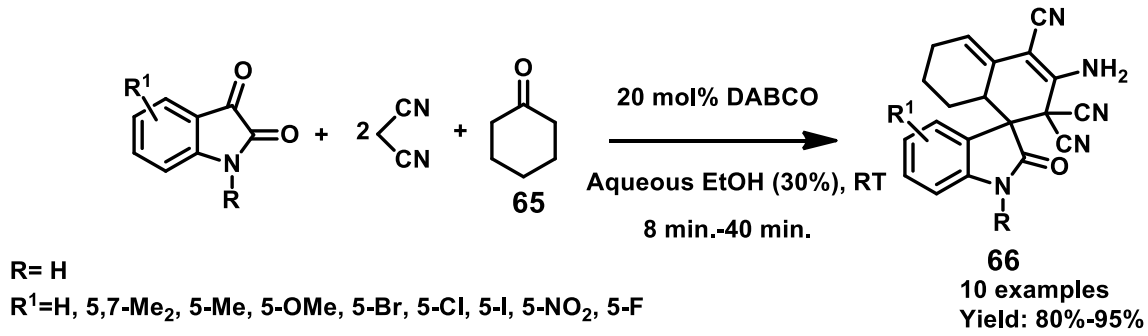


Scheme 30. Synthesis of spirocyclopropylbarbiturates using arylidenemalononitriles.

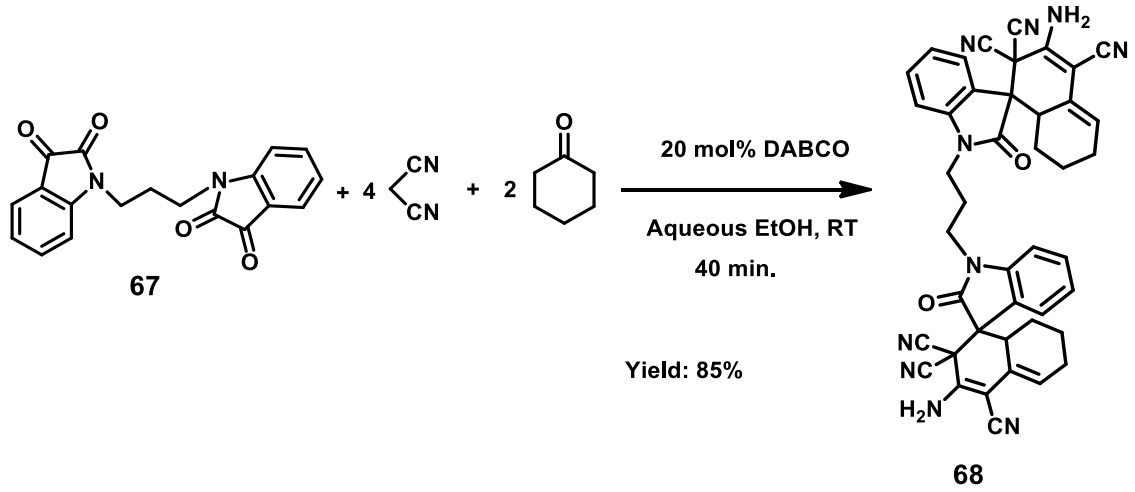


Scheme 31. Mechanism for the synthesis of spirocyclopropylbarbiturates using arylidenemalononitriles.

A DABCO (1,4-diazabicyclo[2.2.2]octane) catalyzed methodology for the synthesis of spiro oxindole derivatives **66** has been developed[52] by Pore *et al.* in aqueous ethanol at room temperature (Scheme 32). This one-pot, three component methodology involved malononitrile, isatin and cyclohexanone **65**. This methodology was further improvised by this group to prepare *bis* spiro compounds **68** (Scheme 33) by using *bis*-isatins **67**.

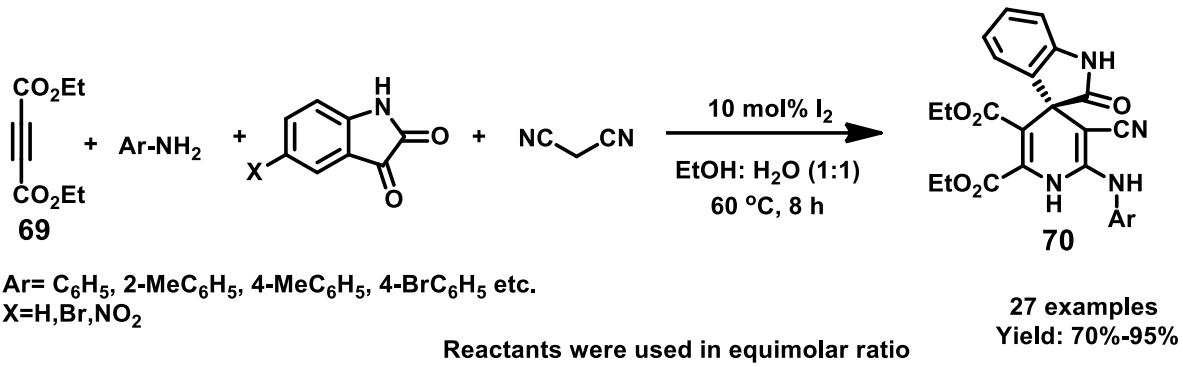


Scheme 32. DABCO catalyzed synthesis of spiro oxindole derivatives.



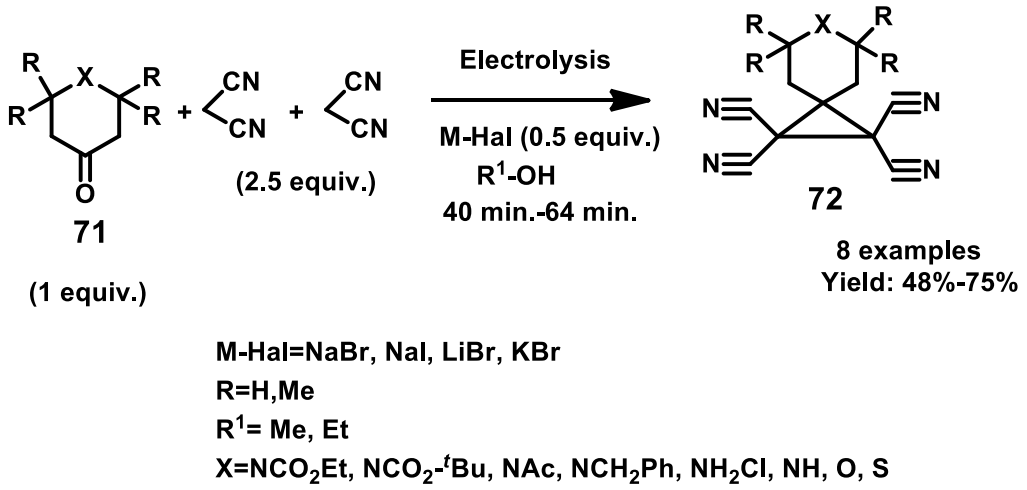
Scheme 33. Synthesis of *bis* spirooxindole derivatives.

Iodine catalyzed multicomponent reaction methodology for the synthesis of spiro[indoline-3,4'-pyridine] derivatives **70** has been developed[53] by Mukhopadhyay *et al.* and they further utilized the compounds as chemosensor devices. The developed product could be utilized selectively for Cu^{2+} detection among other cations. The methodology was based on one-pot, four component strategy involving aniline, diethyl but-2-ynedioate (**69**), isatin and malononitrile. The substrate scope was explored in aqueous ethanol at 60 ^{o}C. Only 10 mol% of the catalyst was required for the reaction (Scheme 34).



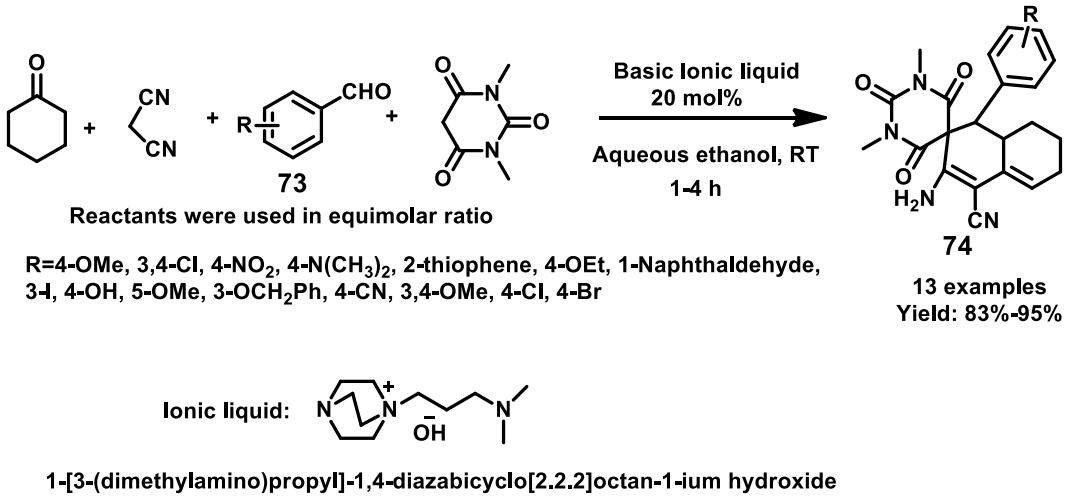
Scheme 34. Iodine catalyzed synthesis of spiro[indoline-3,4'-pyridine] derivatives.

An electrochemical process was developed[54] by Elinson *et al.* to synthesize 6-heterospiro [2.5] octane-1, 1, 2, 2-tetracarbonitrile derivatives **72** in alcohol in presence of bromide salt. One equivalent of heterocyclic ketone **71** and two equivalents of malononitrile were reacted together at 20 °C (Scheme 35).



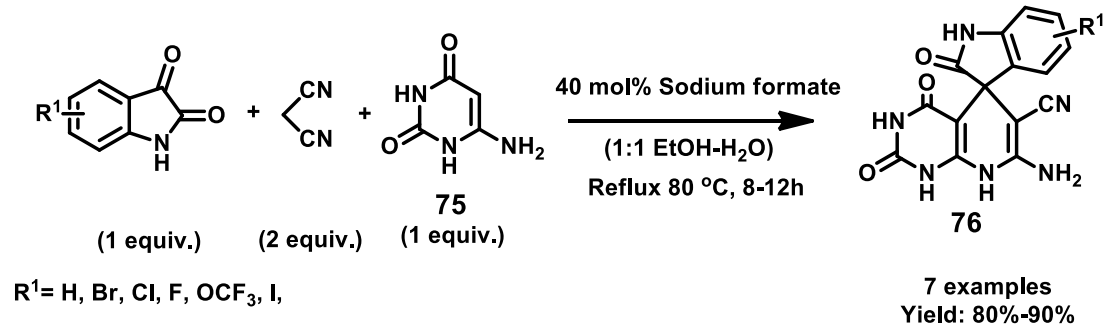
Scheme 35. Electrochemical synthesis of 6-heterospiro [2.5] octane-1, 1, 2, 2-tetracarbonitrile derivatives.

A basic ionic liquid (1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide) promoted methodology for the synthesis of spiro [naphthalene-2, 5'-pyrimidine]-4-carbonitrile derivatives **74** was developed[55] by Gaikwad *et al.* in aqueous ethanol (1:1) at room temperature (Scheme 36). This work also was based on a four component, one-pot methodology involving cyclohexanone, aldehydes **73**, 1, 3-dimethyl barbituric acid and malononitrile.This methodology uses an alternative green catalyst for the synthesis of such type of heterocycles.



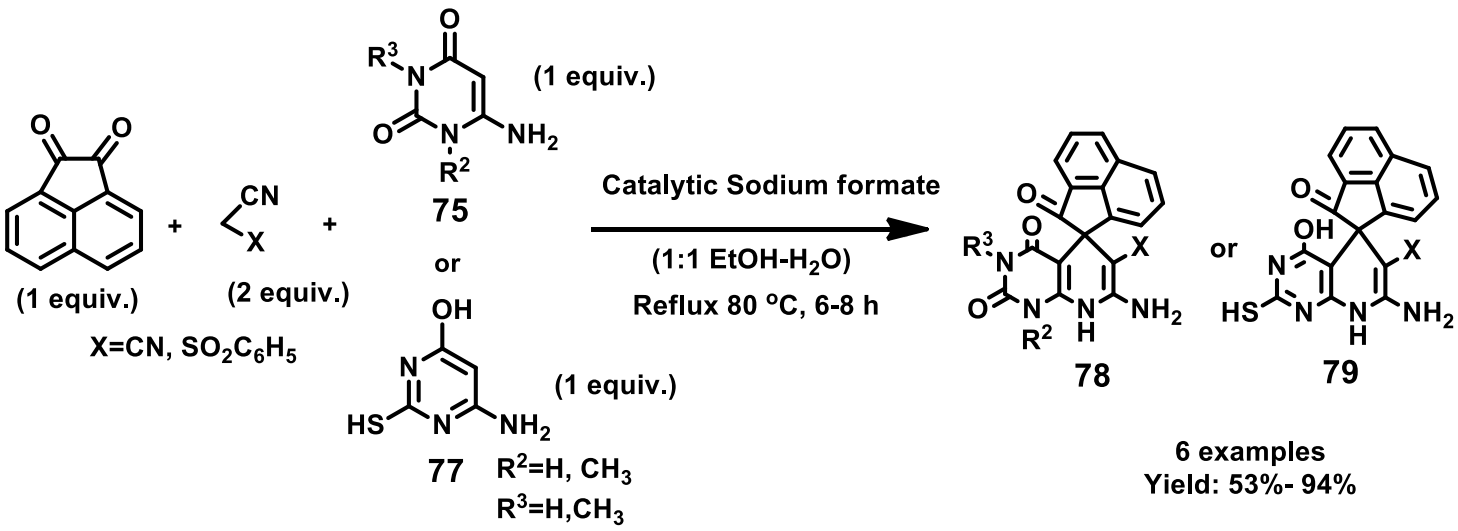
Scheme 36. Ionic liquid promoted synthesis of spiro [naphthalene-2, 5'-pyrimidine]-4-carbonitrile derivatives.

Brahamachari and Nurjamal also developed[56] another straightforward and simple strategy for the synthesis of spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine] derivatives **76** (Scheme 37) and also spiro[acenaphthylene-1,5'-pyrido[2,3-d]-pyrimidine]derivatives **78-79** (Scheme 38) in aqueous ethanol (1:1) in presence of sodium formate as catalyst under reflux. 6-aminouracil **75** or 6-aminothiouracil **77** was used along with C-H acids and isatin or acenaphthylene-1, 2-dione in this multicomponent strategy.

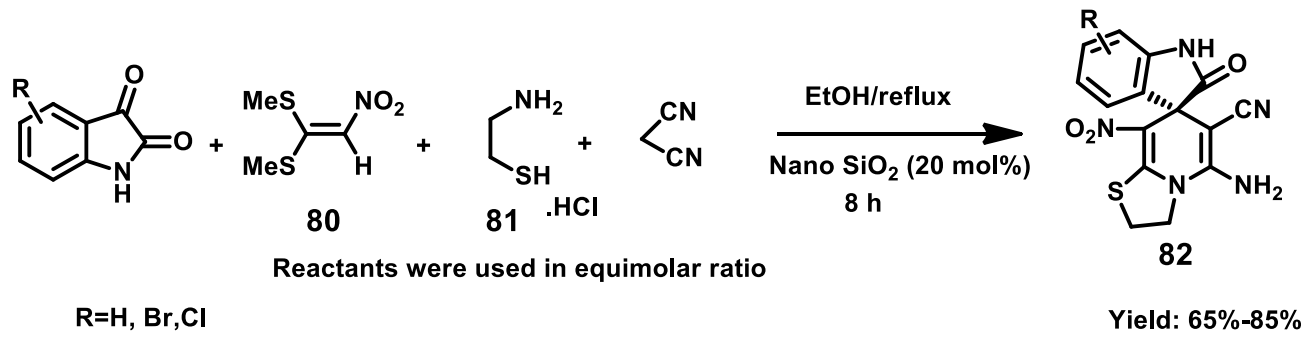


Scheme 37. Synthesis of spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine] derivatives.

5'-Amino-8'-nitro-2-oxo-2',3'-dihydrospiro[indoline-3,7'-thiazolo[3,2-a]pyridine]-6'-carbonitrile derivatives **82** were synthesized[57] under the catalytic influence of SiO_2 nanoparticles in ethanol under reflux (Scheme 39). The methodology is based on one-pot multi component strategy. The components of the protocol include different C-H acid like malononitrile etc. along with nitroketene dithioacetal (**80**), isatin and cysteamine hydrochloride (**81**).



Scheme 38. Synthesis of spiro [acenaphthylene-1, 5'-pyrido[2,3-d]-pyrimidine]derivatives.



Scheme 39. Synthesis of 5'-amino-8'-nitro-2-oxo-2',3'-dihydrospiro[indoline-3,7'-thiazolo[3,2-a]pyridine]-6'-carbonitrile derivatives using SiO_2 nanoparticles in ethanol.

4. Conclusions

Spiroheterocycles are structurally interesting molecules having several useful properties. Hence, development of various synthetic methodologies to synthesize interesting spiroheterocycles has always attracted attention of synthetic chemists as well as medicinal and material chemists. Malononitrile often plays an important role in the synthesis of various important heterocycles and commercially it is also very easily available. Therefore, we have tried to sum up some recent reports on synthesis of spiro-heterocycles using malononitrile as a building block. We have tried to focus on alcohol mediated syntheses which are comparatively operationally simple.

Acknowledgements

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