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Graphical Abstract

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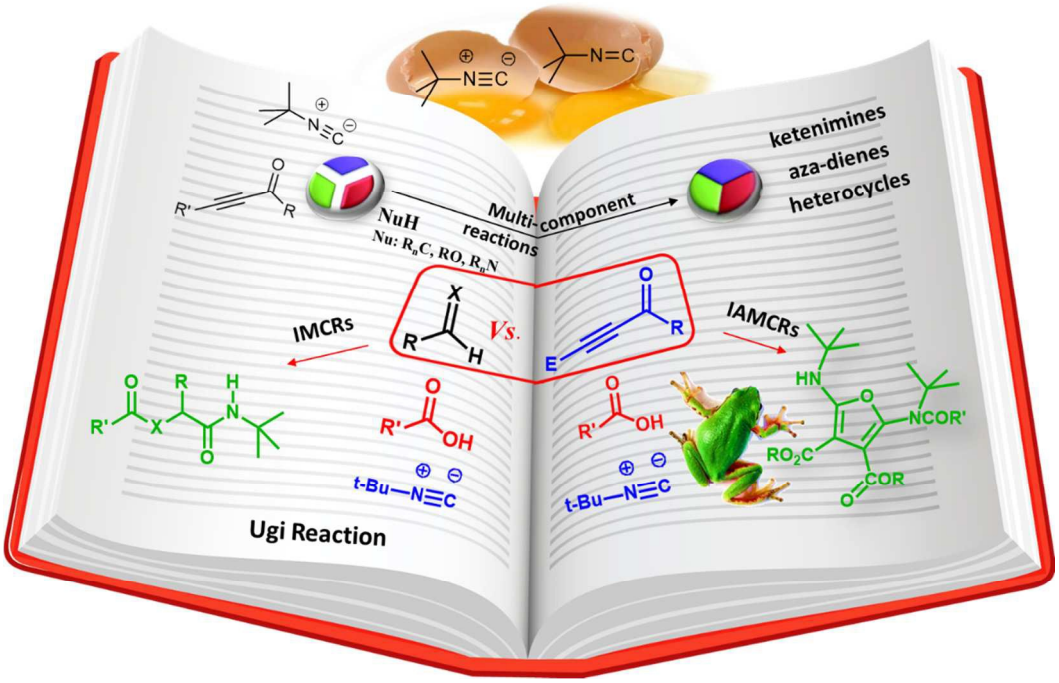

In situ generation and protonation of isocyanide/acetylene adduct: A powerful catalyst-free strategy for multicomponent synthesis of ketenimines, aza-dienes, and heterocycles

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Abstract:

In addition to isocyanide-based Ugi, Passerini, van Leusen and Orru multicomponent reactions (IMCRs), a new class of isocyanide/acetylene-based multicomponent reactions (IAMCRs), through a zwitterionic adduct, have emerged as powerful and elegant methods for the synthesis of biologically interest molecules. Coupling reaction between "in situ" generated Huisgen-type zwitterions of isocyanide/acetylene adduct and *CH*-, *OH*- and *NH*-acids provide a powerful synthetic way to obtain ketenimines, aza-dienes, and heterocycles. This review focuses on the chemistry and applications of isocyanide/acetylene adduct in multicomponent reaction conditions.

Keywords: Isocyanide; acetylene; zwitterion; multicomponent reaction; ketenimine; aza-diene; heterocycle, IAMCRs, Oakes-Yavari-Nair (OYN) betaine.

1 Introduction

Isocyanide-based carbon-carbon and carbon-heteroatom bond-forming reactions have been developed in fascinating way over the past decades.[1] Nowadays, several isocyanide-based multicomponent reactions (IMCRs) have been introduced which allow the preparation of organic molecules.[1,2] After beginning of isocyanide chemistry in 1838, in 1921 Mario Passerini discovered the multicomponent reaction of isocyanides, aldehydes and carboxylic acids. [2b] This reaction became what is now called the "Passerini-3CR". On the other hand, Ugi-MCRs as the modern concept of multicomponent reactions and also one of the most remarkable examples of MCRs are intimately related to the reactions developed with isocyanide reagents.[1-3] In fact, due to unique reactivity of the isocyanides involving the formation of α-adducts with nucleophiles and electrophiles, the multicomponent reactions such as Ugi,[3] Passerini,[4] van Leusen,[5] and Orru [6] are intimately related to the reactions developed with isocyanide reagents as a part of organic synthesis.

Besides Ugi, Passerini, van Leusen, and Orru IMCRs, a new class of isocyanide/acetylene-based multicomponent reactions (IAMCRs) has been started by Oakes [7] and then Yavari, [8] Nair, [9] and others. IAMCRs, as a potent and sophisticated method for organic synthesis, arising from generation of the Huisgen-type zwitterionic adduct **3**. Owing to the simplicity of operation, one-pot IAMCRs are preferred to other multi-step and catalytic reactions when a suitable substrates can be envisioned. The intent of this review is to provide an overview of the generation and application of Huisgen-type Oakes-Yavari-Nair (OYN) betaine **3** in organic synthesis and the review focuses on the recent achievements in the *in situ* generation and protonation of

isocyanide/acetylene adduct in presence of *CH*-, *NH*- and *OH*-acids in multicomponent reaction conditions (Figure 1). In particular, the novel and simple catalyst-free approaches to synthesize of the novel structures of ketenimines, azadienes, and heterocycles (by the reaction of *C*-, *N*- and *O*-nucleophiles (NuH) with protonated OYN betaine) which are known as the crucial part of organic chemistry, are discussed in detail. [1-11] We mainly talk about studies done over the past 16 years, but for a more comprehensive discussion, some earlier works are also included. The reader is referred to the references for more applications of isocyanide in multicomponent reactions [1b,1c,2a,10] and more specifically the engagement of RNC/DMAD in cyclization reactions.[11]

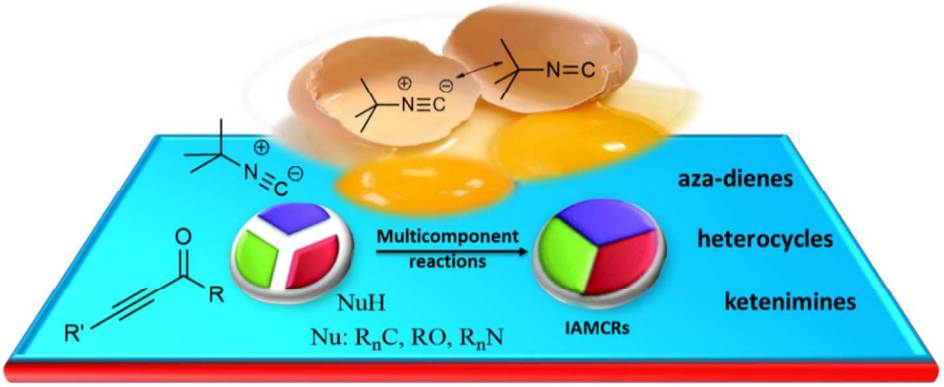


Fig. 1. Isocyanide/acetylene-based multicomponent reactions.

2 Background

In 1932, Diels and Alder reported that pyridine (envisioned as an *N*-heterocyclic diene) condenses with two equivalences of electron-deficient acetylene of dimethyl acetylenedicarboxylate (DMAD).[12] The product was not identified through until Acheson reported that in 1959.[13] Shortly thereafter, Rolf Huisgen recognized this reaction as the 1,4-dipolar variant of the classical Diels-Alder reaction, involving the zwitterionic adduct of pyridine and acetylene.[14]

In fact, Huisgen laid out the classification of 1,n-dipolar reactions (such as 1,3-dipolar cycloaddition) and elaboration of their mechanisms over zwitterions formation by addition of nucleophiles to activated π systems. Since then, impressive developments have been observed in this field, and the mechanism of some organic reactions such as Mitsunobu reaction [15] and Johnson-Tebby adducts [16] were realized in 1969 and 1962, respectively (Figure 2).

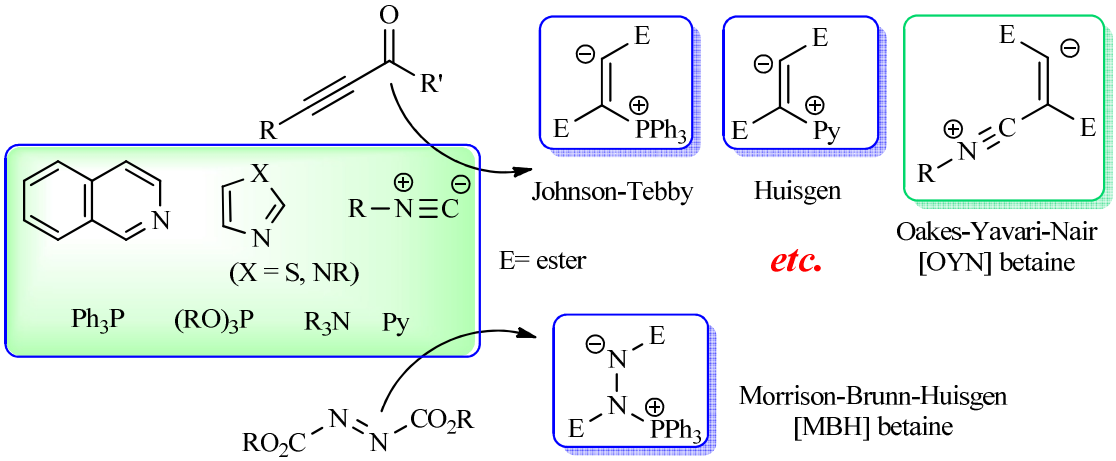
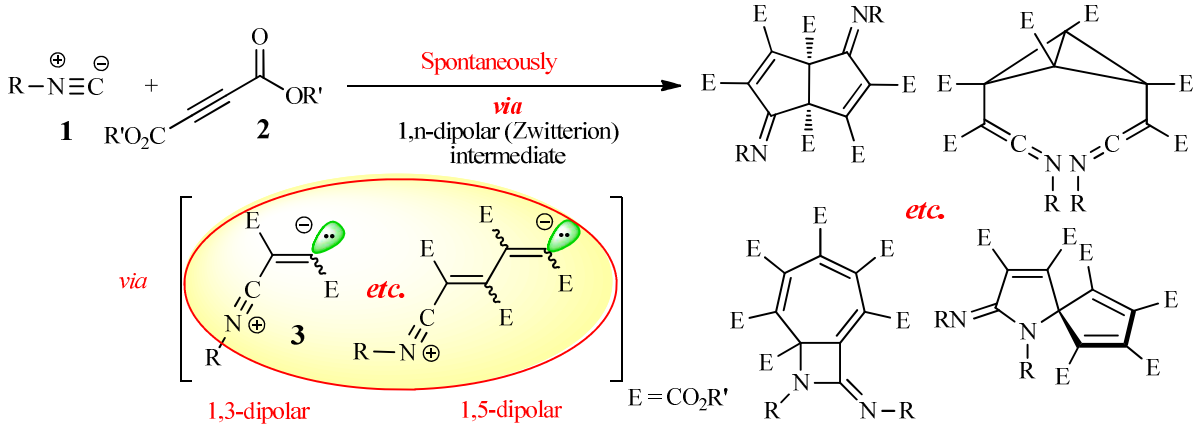


Fig. 2. Well-known zwitterionic adducts.

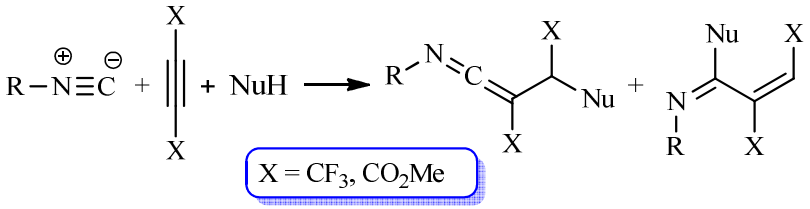
Consequent to the success of the zwitterionic 1,n-dipolar reactions in organic synthesis, the concept of *in situ* generation of a variety of zwitterionic species leading to organic molecules appeared as an attractive topic. After the discovery of Ugi-MCR (isocyanides as the nucleophile) in 1959, nucleophilic property of the isocyanide in presence of the activated acetylene, was studied by Winterfeldt, where he tended to generate zwitterionic species.[17] In 1969, he described the reaction of isocyanide **1** and acetylenes **2**. The chemistry of these reactions are based upon the initial formation of a zwitterion **3** from nucleophilic addition of **1** to acetylene compound **2**. The reactions of aliphatic and aromatic isocyanides with acetylenic compounds have been investigated in detail. However, a mixture of the products have been found with no

chemoselectivity during spontaneous reaction by potential zwitterionic 1,3- and 1,5-dipolar intermediates (Scheme 1).[18]



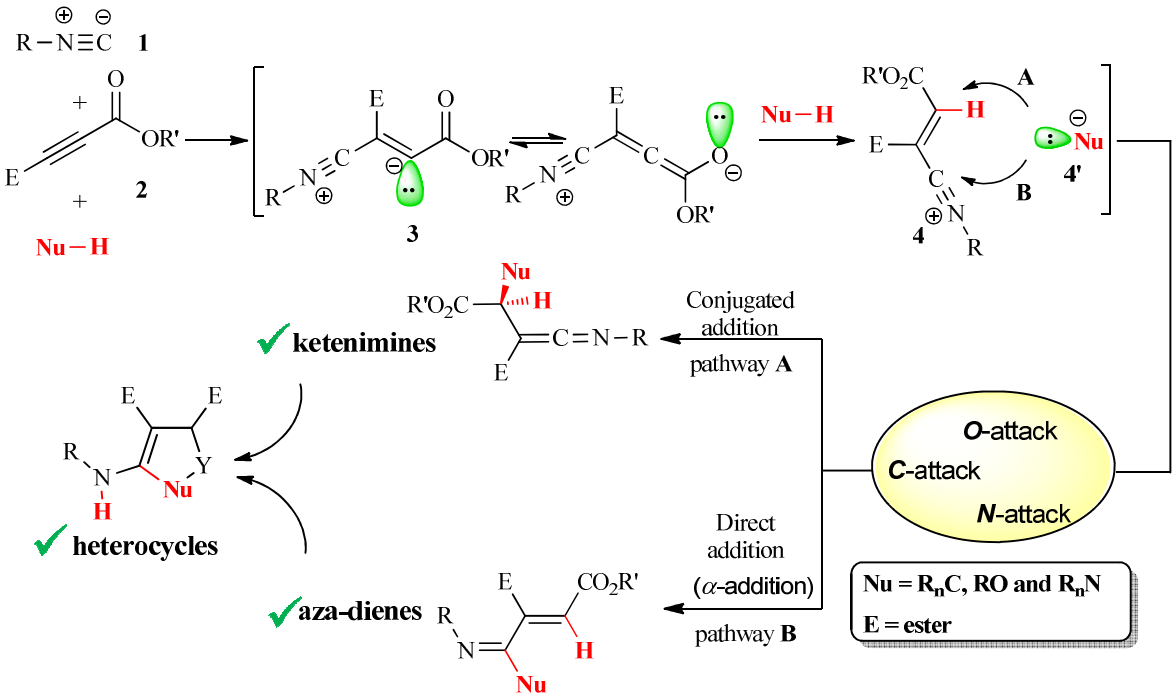
Scheme 1. 1,3- and 1,n-dipolar intermediates by isocyanides/acetylene adduct.

After the discovery of isocyanide and dimethyl acetylenedicarboxylate (DMAD) reaction, trapping of the corresponding zwitterion **3** by *CH*-, *OH*- and *NH*- acids in multicomponent reaction conditions was started a synthetic goal. In fact, reaction between isocyanides, electron-deficient acetylenes, and *C*-, *O*- and *N*-nucleophiles, was first documented by Oakes in 1969. He was applied the dialkyl acetylenedicarboxylates (X = CO_2R) and 1,1,1,4,4,4-hexafluorobut-2-yne (X = CF_3) as an acetylenic component and methanol as the NuH (Scheme 2).[7] Such interesting and promising transformation was nearly disregarded until Yavari in 1996 extended its application to dibenzoylmethane as NuH.[8] Afterward, more publications were published differing mostly in the nature of used NuH.



Scheme 2. Oakes reaction.

It is known that sometimes *CH*- *OH*- and *NH*-based organic acids with nucleophilic behaviour (NuH) can react with zwitterionic adduct of isocyanide **1** and acetylenes **2** in an ABC 3-CR to form ketenimines or aza-dienes, and or heterocycles. A plausible mechanism for these ABC coupling 3-CR reaction is proposed in Scheme 3. First, the zwitterion **3** generates by reacting of acetylene and isocyanide then, the protonation of the intermediate **3** leads the formation of ion pair **4** and **4'**. Finally, the **4'** attack to active site of **4** which produces the procedure A as the conjugated addition or B as the direct addition (α-addition). Although in these reactions intermediate **3** is formed in each case, the chemistry and contribution of NuH building blocks plays a key role in directing of the reaction route.

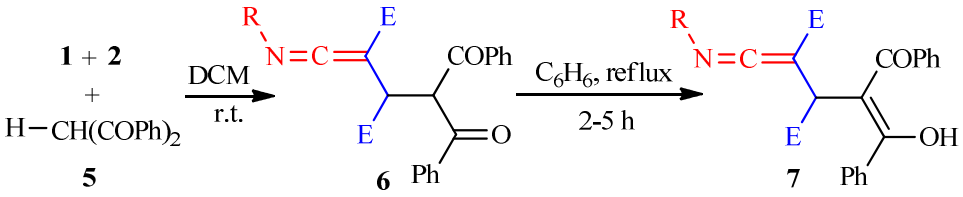


Scheme 3. Proposed mechanism for IAMCRs synthesis of ketenimines, aza-dienes and heterocycles.

3 Isocyanide/acetylene adduct and *CH*-acids

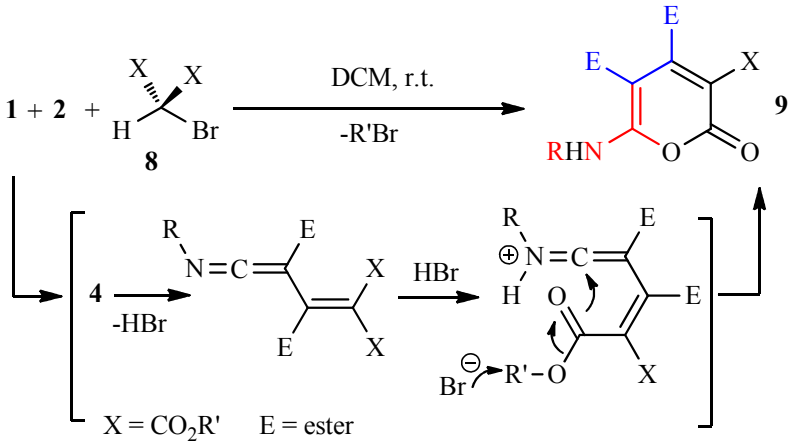
3.1.1 Acyclic *CH*-acids

Yavari *et al.* in 1996 described the first preparation of stable ketenimines **6** and **7** starting from protonation of zwitterion **3** and CH-acid **5** in a multicomponent reaction condition.[8] This method is easy to perform and their synthesized stable ketenimines quantitatively convert to their enol tautomer upon refluxing in benzene (Scheme 4). The formation of these ketenimines can be rationalized by the initial generation of **3** by standard Huisgen reaction of the isocyanide **1** and activated acetylene **2**, followed by an acid-base protonation reaction with **5** to afford a ketenimine **6**, which was then isomerized to enolized ketenimine **7** under reflux conditions in benzene.



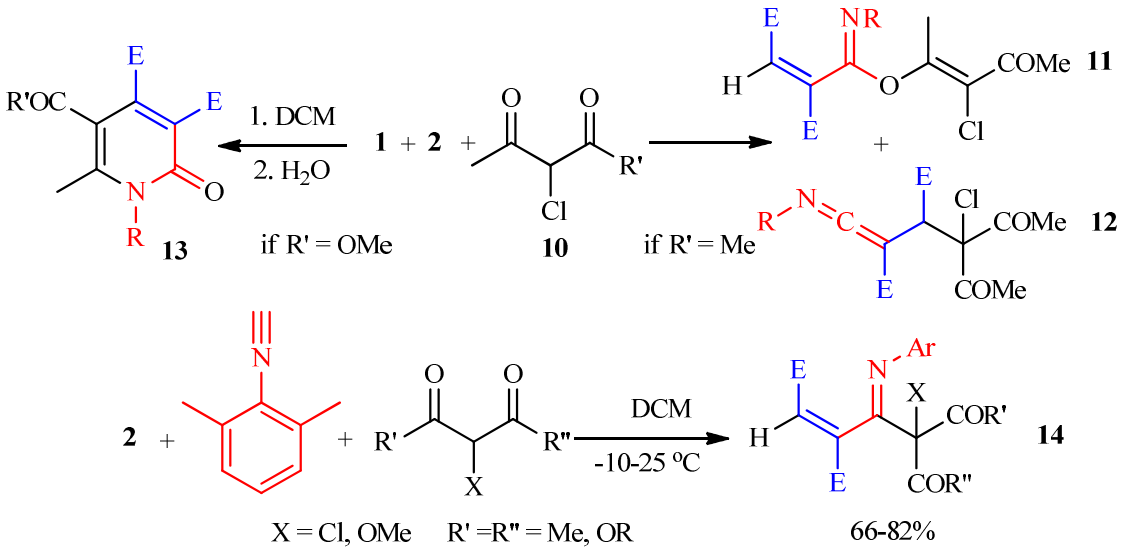
Scheme 4. IMCR synthesis of ketenimines.

Based on the mentioned mechanism, adduct **3** undergoes smooth protonation in exposure to *β*-diesters **8** as *CH*-acid occurred to give 2*H*-pyran-2-one heterocycles **9** at room temperature in CH_2Cl_2 (Scheme 5).[19] The initial event involves the protonation of the zwitterion **3** by **8**. Based on same postulated mechanism for **6**, the bromine content ketenimine species annulated after contribution of removed HBr affording the **9**.



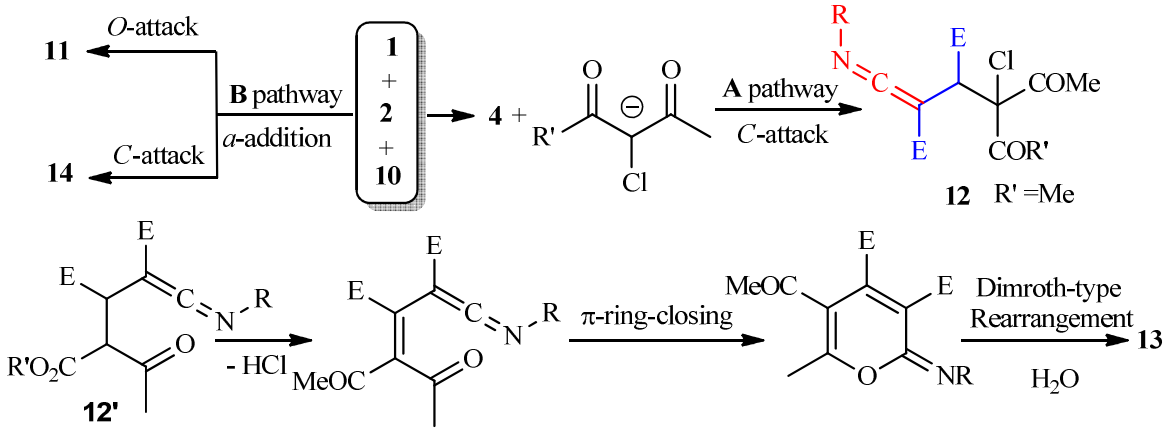
Scheme 5. MCR synthesis of heterocycle **9**.

A novel three-component one-pot synthesis of 1-azadienes **11** and highly functionalized ketenimine **12** was developed by Asghari *et al.,* in which the protonation of **3** and 3-chloropentane-2,4-dione **10** leads to final products.[20] In a typical procedure, equimolar amounts of the all starting materials react together in CH_2Cl_2 at room temperature for 24 h. Based on multicomponent studies, 2-pyridone-3,4,5-tricarboxylate **13** and highly functionalized azadiene **14** are synthesized by an alternative route depending on the nature of *CH*-acid and isocyanide (Scheme 6).[21,22]



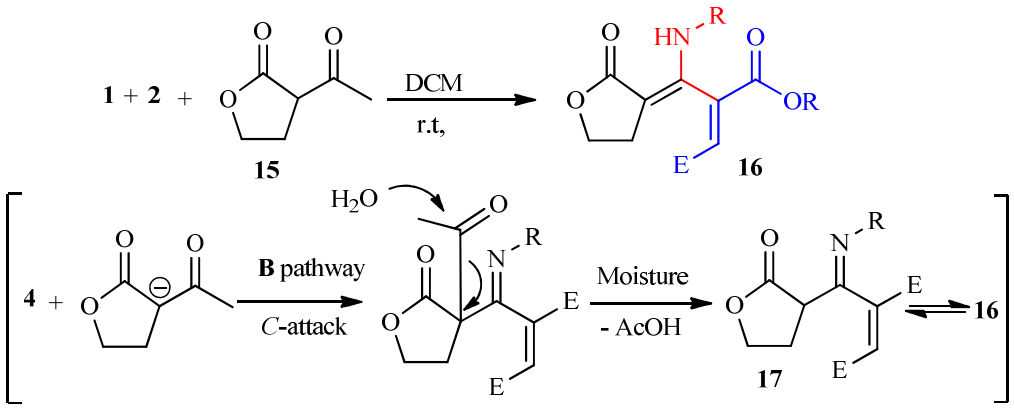
Scheme 6. Synthesis of aza-dienes and pyridone.

The proposed mechanism involves the formation of zwitterion **3** and then protonation by **10**, and the direct *O*- and *C*-attack generate the products **11** and **14** via a *α*-addition, respectively. Stable ketenimine **12** synthesized via conjugated *C*-attack, herein is not stable and converts to **13** during three steps: including removal of HCl from **12'**, subsequent π-ring-closing sigma-bonds, and finally, water promoted Dimroth-type rearrangement (Scheme 7).



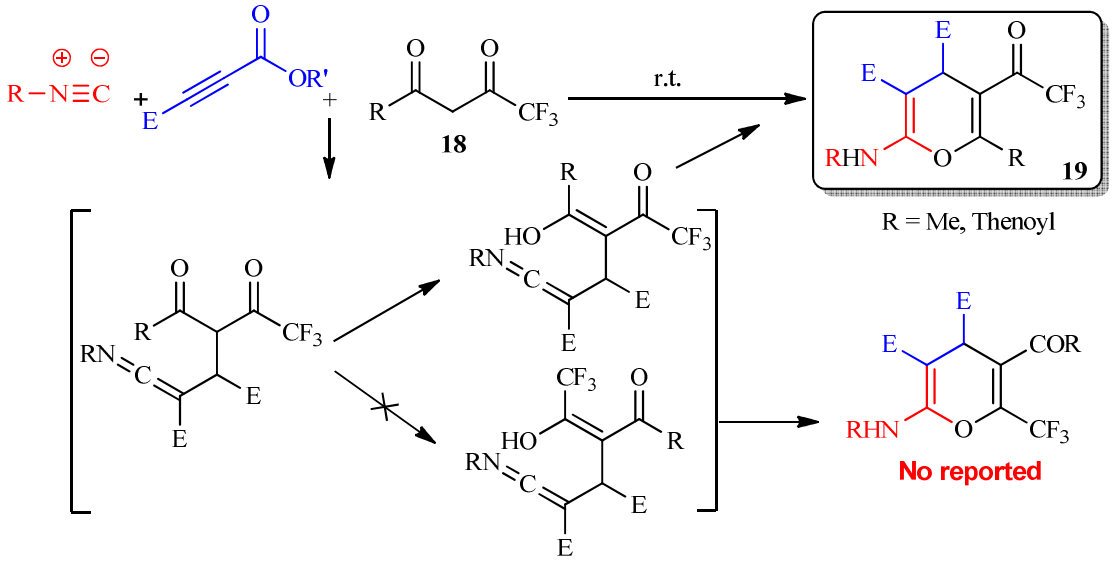
Scheme 7. Proposed mechanism for **11**, **13** and **14**.

Trapping of adduct **3** by 2-acetylbutyrolactone **15** afforded to enaminone- butyrolactone skeleton **16**. As a plausible explanation for synthetic mechanism of **16**, it is reasonable to assume that after generation of **3** and protonation with **15**, the direct *C*-attach procedure and then the moisture accelerated AcOH removal gives the **17** and **16** (Scheme 8).[23]



Scheme 8. MCR synthesis of enaminone **16**.

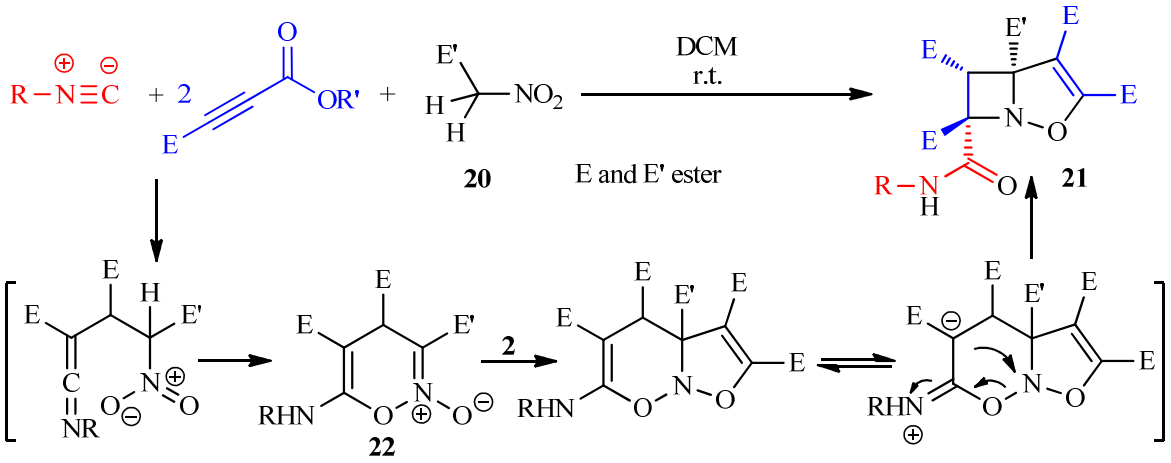
Fluorinated *CH*-acids are used by Baharfar's [24] and Asghari's [25] groups in one-pot three-component method for protonation of 2-amino-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylate **19**. Fluorinated *β*-diketones **18** with aliphatic or aromatic groups produce chemoselective products as indicated in Scheme 9.



Scheme 9. Synthetic pathway for synthesis of **19**.

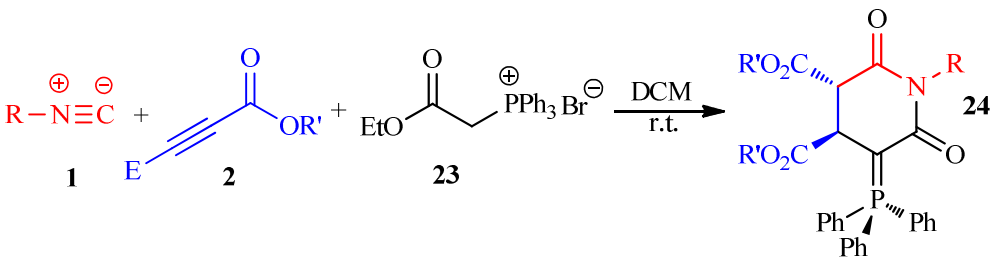
Similarly, zwitterionic protonation of adduct **3** by *CH*- acids, when alkyl 2-nitroethanoates **20** used in one-pot reaction as the third component, the pentaalkyl 7-[(alkylamino)carbonyl]-2-oxa-1-azabicyclo[3.2.0] hept-3-ene-3,4,5,6,7-pentacarboxylate **21** forms via an unusual 1:2:1

(isocyanide: acetylene: *CH*-acid) diastereoselective procedure (Scheme 10).[26] Synthesis process along with the 3D structure of **21** molecules have been well demonstrated by Yavari and Moradi.



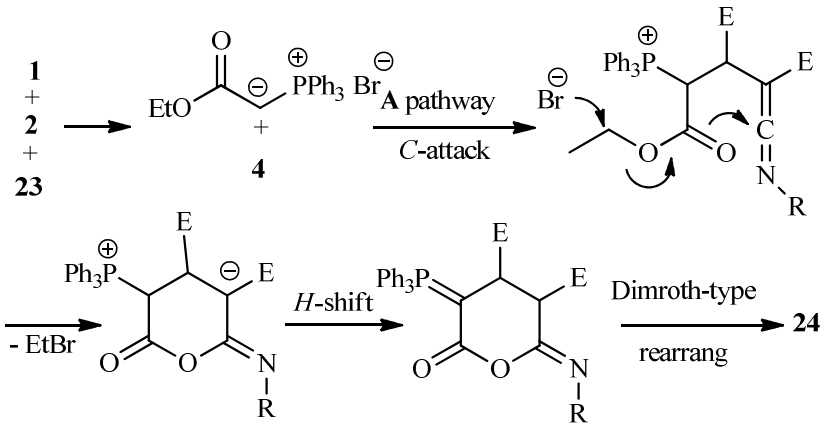
Scheme 10. IAMCRs synthesis of 2-oxa-1-azabicyclo[3.2.0]hept-3-ene **21**.

Shaabani *et al.,* have developed a diastereoselective method for construction of glutarimide skeleton of *N*-alkyl-2-triphenylphosphoranylidene **24** by using *CH*-acid **23**. Ethoxycarbonylmethyl triphenylphosphonium bromide **23** protonates the **3** under one-pot three-component reaction conditions and the reaction undergoes a smooth 1:1:1 addition of substrates in dichloromethane at room temperature. To raise the applicability of this method, the authors extended the procedure to various dialkyl acetylenedicarboxylates **2** in the presence of cyclohexyl or *tert*-butyl isocyanide with ^{1}H and ^{13}C NMR study of the crude reactions, which they found only 4-*trans* diastereoisomer produced by dimethyl- and diethyl acetylenedicarboxylate. However, when di-*tert*-butyl acetylenedicarboxylates was used, 4-*cis* and 4-*trans* (of) diastereoisomers with 37% and 63% yields were obtained, respectively (Scheme 11).[27]



Scheme 11. Heterocyclic phosphoranylidene glutarimides skeleton **24**.

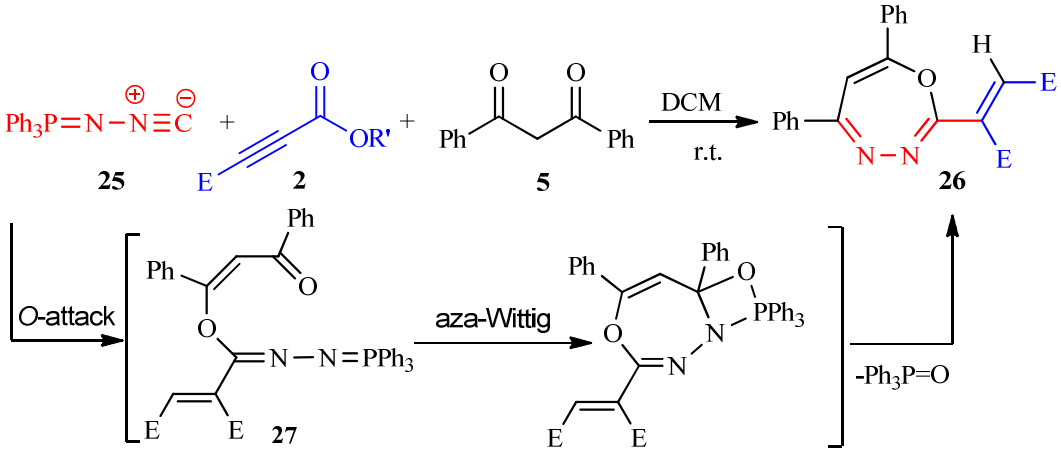
A possible mechanism for synthesis of glutarimides **24** is proposed in Scheme 12. it is reasonable to assume that protonation of the 1:1 zwitterionic intermediate **3** by the ethoxycarbonylmethyl triphenylphosphonium bromide **23** as *CH*- acid is followed by quenching of the cationic centre caused by the conjugate base of the *CH*- acid to generate the ketenimine. Addition of Br^- to ethoxy group of ester may lead to discarding Et- group as EtBr. Then the residue of molecule isomerizes via Dimroth-type rearrangement to produce **24**.



Scheme 12. Proposed mechanism for synthesis of **24**.

Presently, there are a few synthetic methods available for the synthesis of 7-membered oxadiazepine heterocycles backbone. However, Ramazani *et al.,* have used (*N*-isocyanimino)triphenylphosphorane **25** as a novel and interesting isocyanide in presence of DMAD and *CH*-acid **5** for synthesis of 7-membered 1,3,4-oxadiazepin **26**. One-pot three-

component reaction of **5** and **2** with isocyanide **25** in ambient conditions afforded diethyl-(*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioate **26** via a chemo- and stereoselective aza-Wittig annulation (Scheme 13).[28] It is rational to assume that compound **26** could be resulted by protonation of the zwitterion adduct **3** by **5**. Subsequent attack of the enolate anion at positively charged ion pair forms iminophosphorane **27**, which undergoes an intramolecular aza-Wittig reaction under the conditions employed, to produce **26** as non-planar 7-membered oxadiazepin skeleton heterocycle.

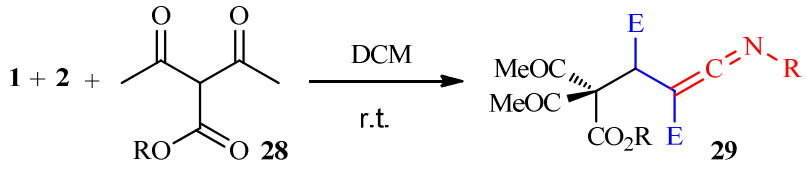


Scheme 13. Isocyanide **25** for synthesis of oxadiazepin **26**.

3.1.2 Acyclic polycarbonyl *CH*-acids

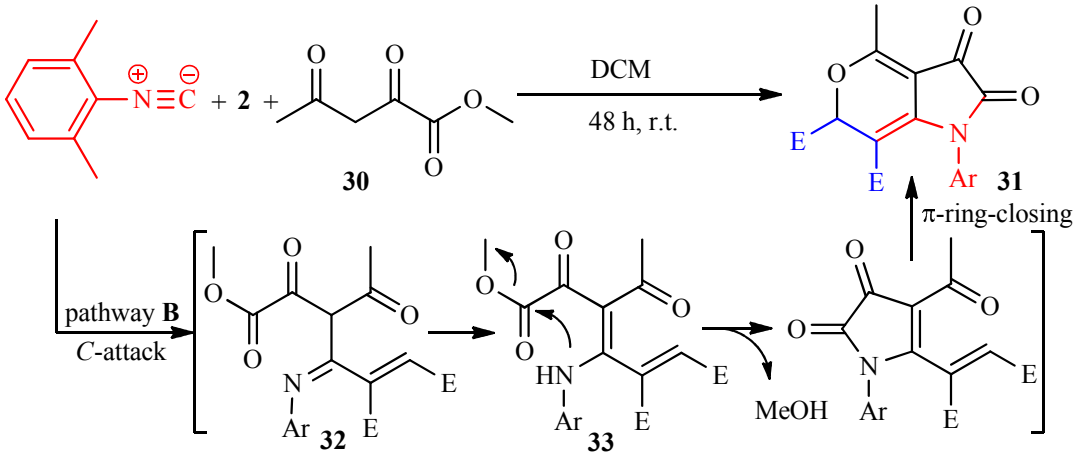
Polycarbonyl compounds have interesting chemistry and generate valuable reagents in organic transformations.[29] The 1:1 zwitterionic intermediate **3** can react with polycarbonyl compounds in three-component reaction conditions to give novel pyran or tetrahydropyranopyrrole annulated heterocyclic systems.

The three-component reaction of tricarbonyl compound **28**, isocyanides and activated acetylenes has been reported by Yavari and Nourmohammadian. The products of the reaction are ketenimines **29** (Scheme 14).[30]



Scheme 14. Three-component synthesis of **29**.

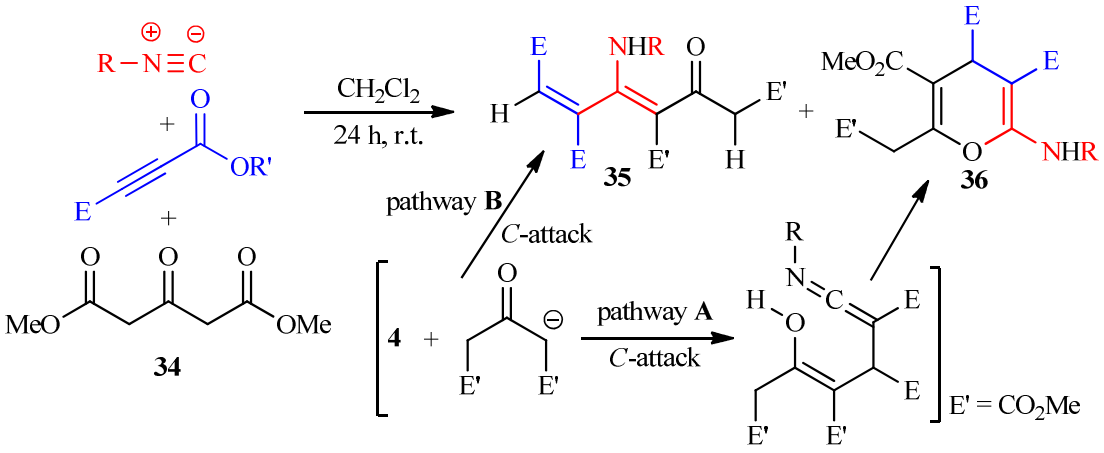
Pyrano[4,3-*b*]pyrrole heterocycles **31** can be prepared by generation and protonation of intermediate **3** with tricarbonyl compound **30**. In this method, the efficient synthesis of 1,2,3,6-tetrahydropyrano[4,3-*b*]pyrrole derivatives **31** was achieved via a one-pot multicomponent reaction of isocyanide **1**, an acetylene **2**, and a tricarbonyl compound **30** in CH_2Cl_2 at room temperature.[31] As shown in Scheme 15, the first step might involve *C*-attack at *α*-carbon of isocyanide to generate **32** as a tautomer of enaminone **33**. Cyclization of the **33** by removal of MeOH followed by π-ring-closing sigma-bonds cyclization gives corresponding pyranopyrrole **31**.



Scheme 15. Fused heterocycle of pyranopyrrole **31**.

Nasiri *et al.,* have used dimethyl 1,3-acetonedicarboxylate **34** as polycarbonyl *CH*-acid for protonation of *in situ* generated of **3**. Three-component reaction of **1** and **2** in presence of the 34 in ambient conditions afforded enaminone **35** and 2-amino-4*H*-pyrans **36**.[32] A possible explanation is proposed in Scheme 16. It is reasonable to assume that **35** and **36** produced by an

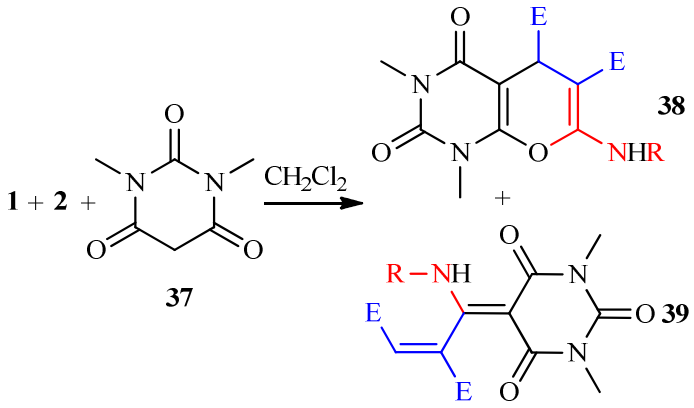
initial protonation of **3**. Then, the positively charged ion **4** might be attacked from two positions by the enolate anion of the *CH*-acid; direct and *C*-attack produces the azadiene, which isomerized to corresponding enaminone **35**. Conjugate addition leads to intermediate ketenimine. Such an addition product may be isomerized under the reaction conditions to produce the aminopyran **36**.



Scheme 16. IAMCRs synthesis of **35** and **36**.

3.2 Cyclic *CH*-acids

Yavari and Maghsoodlou in 1998 used the cyclic *CH*-acids to protonation of the **3**. The reaction of **1** and **2** in the presence of the *N*,*N*'-dimethylbarbituric acid **37** afforded the isomeric products of dimethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-4*H*-pyrano[3,2-d]pyrimidine-5,6-dicarboxylate **38** and dimethyl (*E*)-2-((2,6-dimethylphenylamino)-(1,3-dimethyl-2,4,6-trioxopyrimidine-5-ylidene)-methyl)-but-2-enedioate **39** (Scheme 17).[33]



Scheme 17. One-pot synthesis of **38** and **39**.

As shown in Figure 3, trapping of **3** by cyclic *CH*-acids leads to highly functionalized fused 4*H*-pyrans heterocycles with illustrated mechanism at Scheme 9. Trapping of zwitterions **3**, in three-component reaction condition, with various cyclic *CH*-acids have been reported for the synthesis of 5-oxo-4,5-dihydroindeno[1,2-*b*]pyrans **40**,[34] dialkyl 7-methyl-2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano-[4,3-*b*]pyran-3,4-dicarboxylates **41**,[35] 4*H*-benzo[*g*]chromene-3,4-dicarboxylates **42**,[35] 4*H*-furo[3,4-*b*]pyrans **43**,[37] dimethyl 2-alkylamino-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3,4-dicarboxylates **44**, [38] pyrano[2,3-*c*]pyrazoles **45**,[39] 4*H*-Pyrano[3,2-*d*]isoxazoles **46**,[40] dialkyl 10-(alkylamino)-7-oxo-7*H*,8*H*-naphtho[1,8-*gh*]chromene-8,9-dicarboxylates **47**,[41] pyrano-pyrido-quinoxalines **48**, and benzo[a]pyrano[2,3-c]phenazines **49**.[42,43] For competition of NH- and OH-acid protonation of 3-amido 2-naphthol, in an interesting work by Hassanabadi *et. al*., it was found the **50** is the final product.[44]

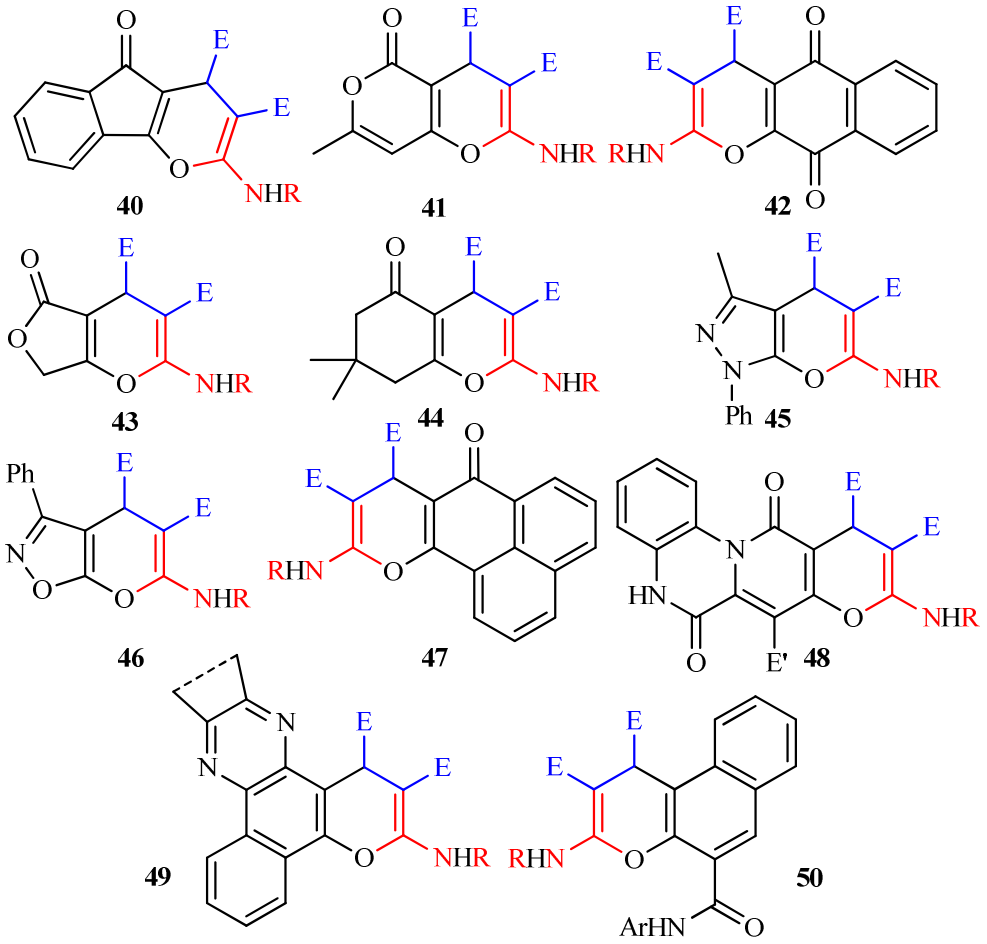
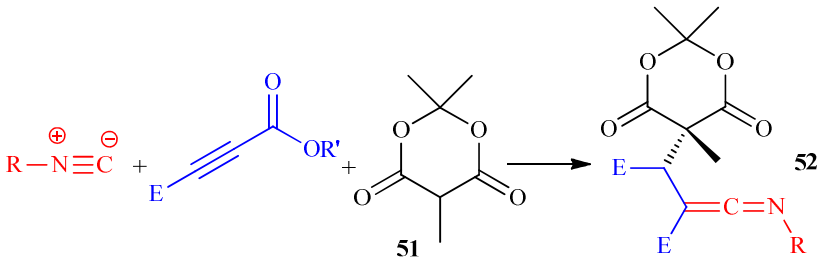


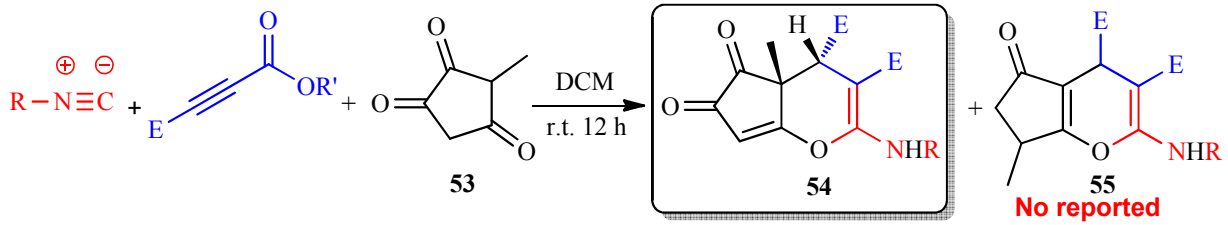
Fig. 3. Products obtained from the cyclic *CH*-acids.

It is reported that the adduct **3** reacts with 5-methyl-Meldrum's acid **51** to afford highly functionalized ketenimines of dialkyl 2-(alkylimino-methylene)-3-(2,2,5-trimethyl-4,6-dioxo-1,3-dioxan-5-yl)-succinates **52** in good yields (Scheme 18).[45]



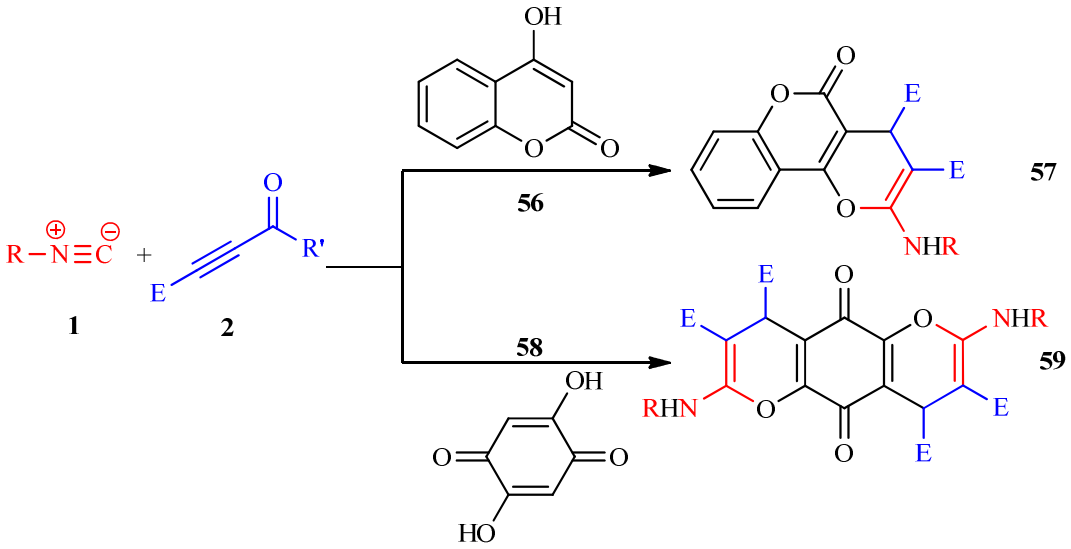
Scheme 18. Synthesis of the ketenimine **52**.

Tetrahydrocyclopenta[*b*]pyran derivatives **54** were synthesized by 3-methylcyclopentane-1,2,4-trione **53** *CH*-acid in the presence of *in situ* generated **3** *via* a chemo- and diastereoselective IAMCRs method during 12 hour at room temperature (Scheme 19). The authors didn't report **55** as neither a main product nor a side product.[46]



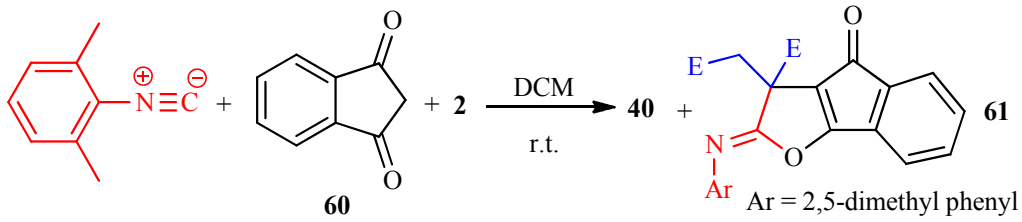
Scheme 19. Tetrahydrocyclopenta[*b*]pyrans **54**.

Nair *et. al.*[47] and then Teimouri *et. al.*[35] have used 4-hydroxycoumarin **56** as a *CH*- acid to yield pyrano[4,3-*b*]pyran **57** as a pyrano-coumarin heterocycle skeleton (Scheme 20). Prajapati *et. al.* have also synthesized pyranocoumarin **57** by a green method in water.[48] Shaabani also reported a novel pseudo-five-component reaction and efficient approach for the synthesis of highly functionalized bis-chromene **59** based on reactivity of **3** with 2,5-dihydroxy-para-benzoquinone **58** (Scheme 20).[36]



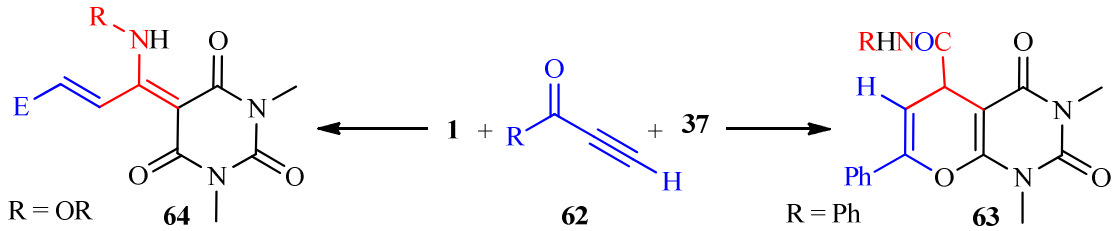
Scheme 20. IAMCRs synthesis of chromene **57** and bis-chromene **59**.

Protonation of the reactive intermediates **3** in a reaction between alkyl(aryl) isocyanides and dialkyl acetylenedicarboxylates **2** in presence of the indan-1,3-dione **60** as a cyclic *CH*- acid leads to produce 5-oxo-4,5-dihydroindeno[1,2-*b*]pyrans **40** and methyl 2-[(aryl)imino]-3-(2-methoxy-2-oxoethyl)-4-oxo-3,4-dihydro-2*H*-indeno[1,2-*b*]furan-3-carboxylates **61** (Scheme 21).[34]



Scheme 21. Protonation of the **3** by indan-1,3-dione.

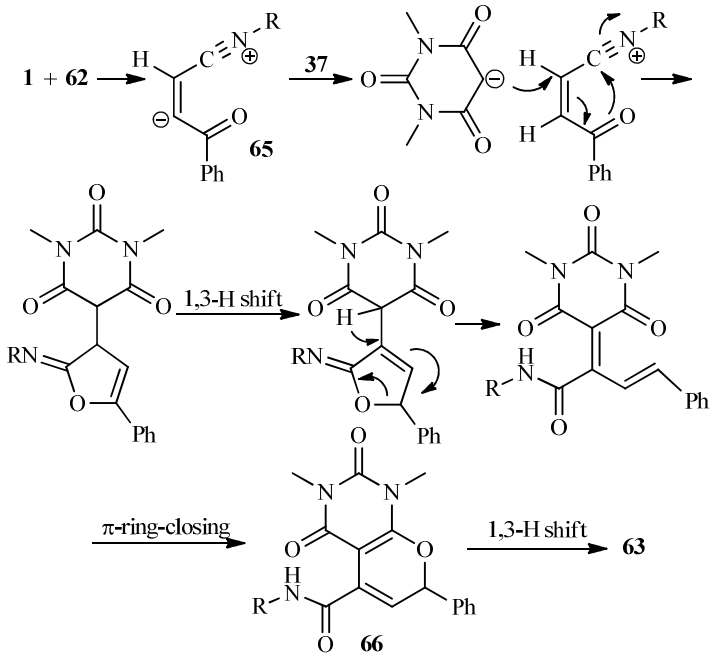
In situ generation of zwitterionic adduct of unsymmetric electron deficient acetylene of ethynylphenylketone **62** and isocyanides **1** and then, protonation of that with *N*,*N*'-dimethylbarbituric acid **37** yields 1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5-carboxamide **63**.[49] Under the same conditions, Maghsoodlou *et al.*, reported cross-conjugated push-pull enaminone systems **64** (Scheme 22).[50]



Scheme 22. Isocyanide/propiolate adduct for synthesis of **63** and **64**.

Plausible mechanism for the synthesis **63** can be started by initial formation of the zwitterionic intermediate **65**, produced from isocyanide **1** and acetylenic ester **62**. Protonation of **62** by **37**

produces intermediates **66** via annulation and ring-closing steps, and finally **66** converted to **63** by a proton transfer (Scheme 23).

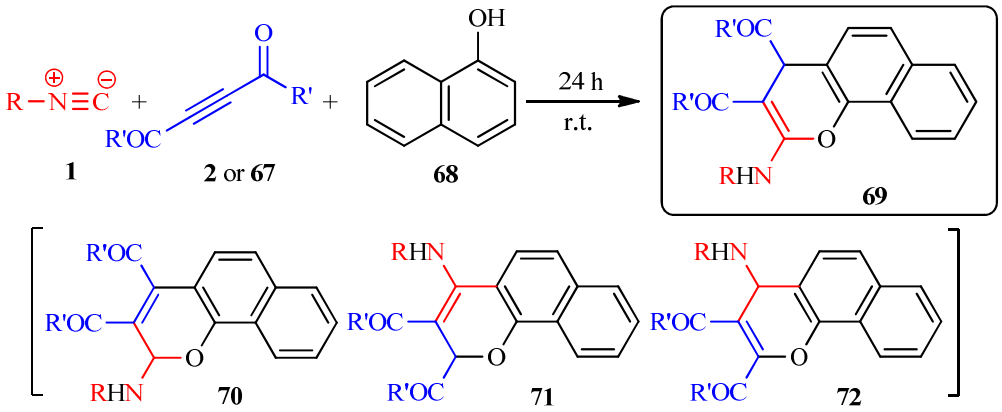


Scheme 23. Proposed mechanism for synthesis of **64**.

4 Isocyanide/acetylene adduct and *OH*-acids

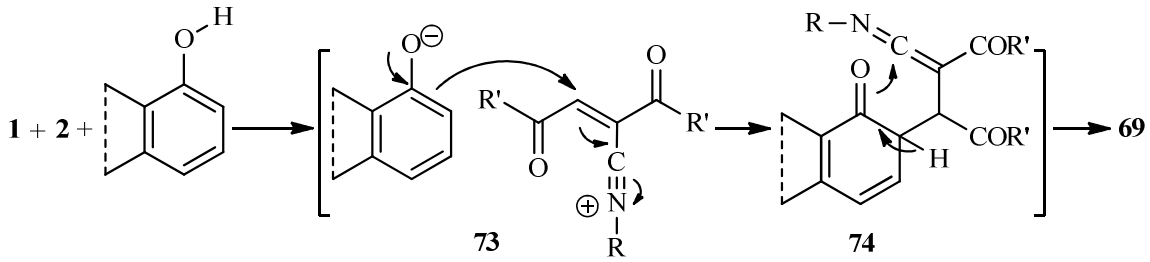
4.1 Aromatic *OH*-acids

Phenol and its derivatives as aromatic *OH*-acids are other alternatives for the synthesis of stable ketenimines and heterocycles based on IAMCRs method. Protonation of the reactive intermediates produced in the reaction between isocyanide **1** and acetylene **2** or dibenzoylacetylene (DBA) **67** with α-naphthol **68** leads to highly functionalized fused-benzochromenes **69** (Scheme 24). The chemical structure of **69** was distinct from the **70**, **71** and **72** by ^{13}C NMR chemical shift of the methine group.[51]



Scheme 24. IAMCRs synthesis of 69.

It is conceivable that the initial ionic pair **73** results by the proton transfer from 1-naphthol **68** to intermediate **3**. Then, the **73** is attacked by the enolate anion of naphthol (*C*-attack) to produce the active ketenimine **74**. Such an addition product may tautomerize and cyclize, under the reaction conditions employed, to produce **69** (Scheme 25).



Scheme 25. Proposed mechanism.

The authors using *in situ* protonation of **3** with aromatic phenolic substrates, such as 2-naphthol, 2,7-dihydroxynaphthalene, 2,3- dihydroxynaphthalene, 4-methyl-8-hydroxycoumarin or phenols, , have synthesized compounds **75**, **76**, **77**, **78**, and **79**, respectively (Figure 4).

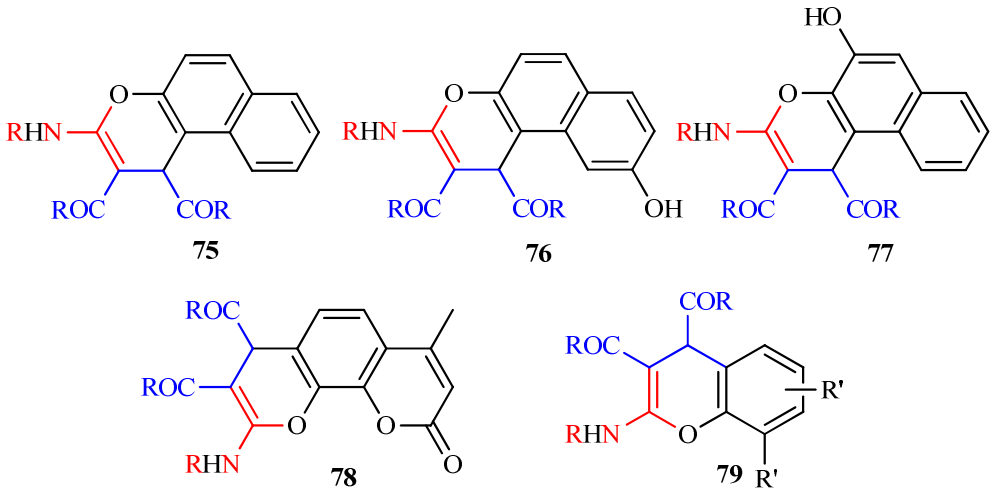
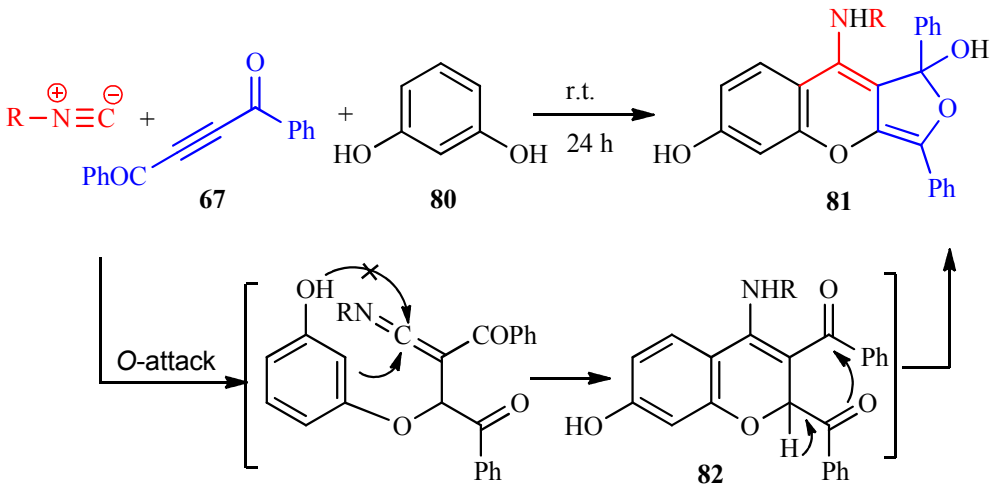


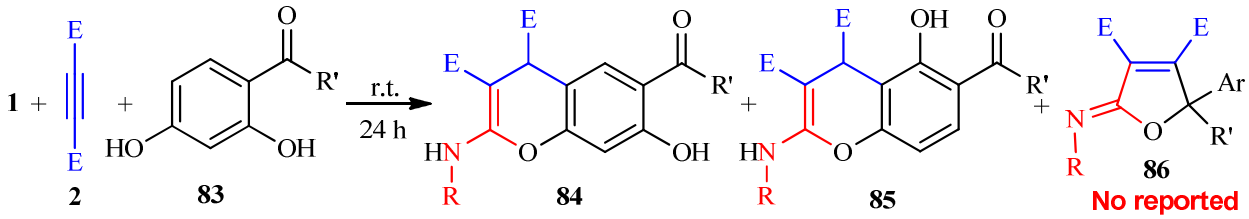
Fig. 4. Examples of IAMCR-based fused-benzochromenes.

The reaction of alkyl isocyanides **1** and dibenzoylacetylene **67** in the presence of resorcinol **80** effectively produce 1*H*-furo[3,4-*b*]chromene-1,6-diols **81**. It is noteworthy that the reaction proceeds by one-pot 3-CR conditions (Scheme 26). A rational mechanism can be speculated to this reaction in which the zwitterion **3,** from isocyanide **1** and dibenzoylacetylene **67**, is protonated by resorcinol to furnish the ketenimine and then aminochromene intermediate **82**. The latter *H*-migration happens and thus, the final product **81** is produced.[52]



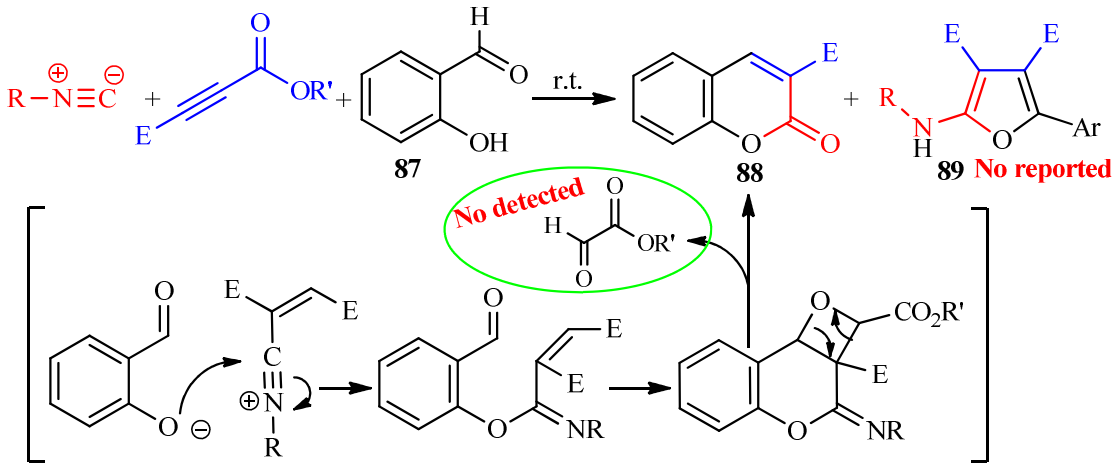
Scheme 26. IAMCR-based synthesis **81**.

Baharfar *et al.* have investigated reactivity of **1** and **2** with 2,4-dihydroxyacetophenones **83**.[53] The addition of **83** to **2** under neutral conditions in the presence of isocyanides **1** leads to 2-amino-4*H*-chromene derivatives **84** and **85** in high yields. The authors didn't report the 1,3-dipolar cyclization of **3** with **83**, in which the protonation of **3** is director of the reaction progress in comparison with cyclization factor to produce Nair's product [9] **86** (Scheme 27).



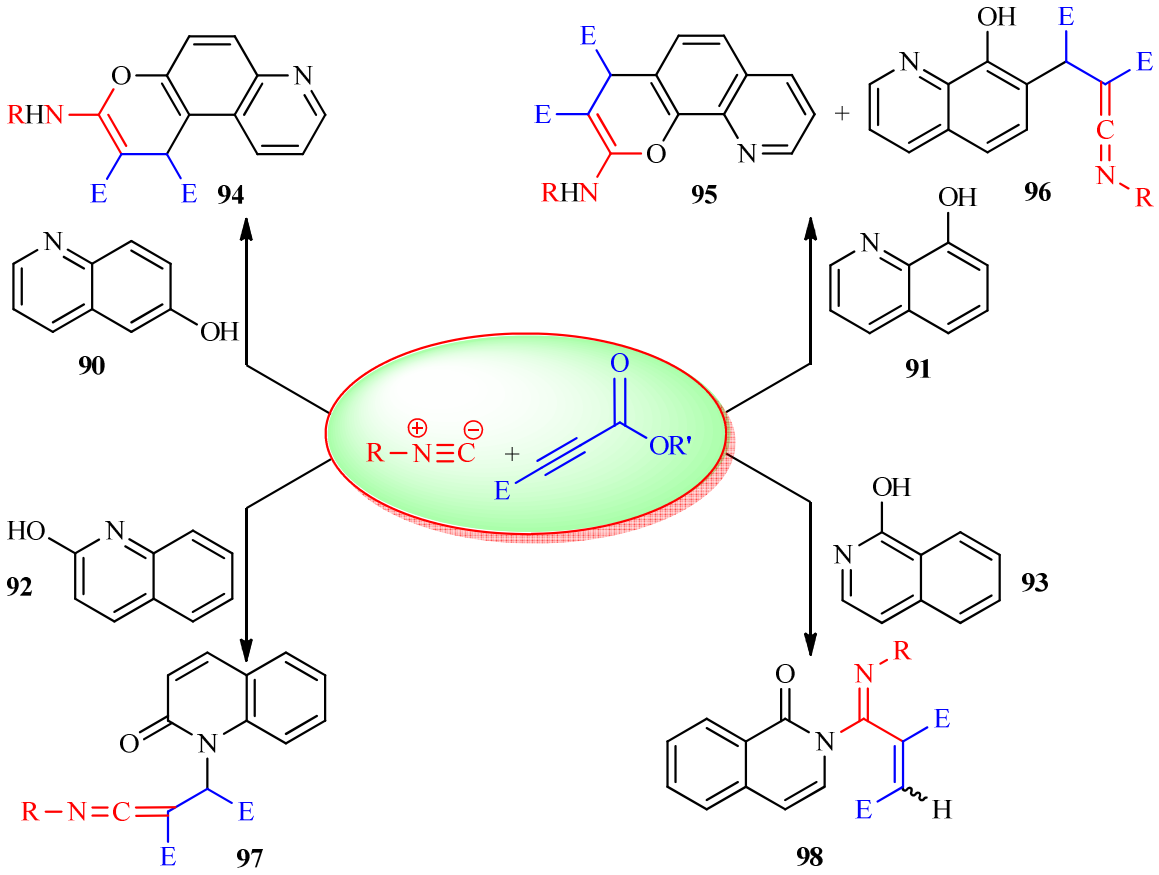
Scheme 27. Synthesis of amino-chromenes **84** and **85**.

In situ generated intermediate **3** can undergo a smooth protonation at room temperature with salicylaldehyde **87** in a IAMCRs condition. In this reaction, an aromatic *OH*-acid occurred to give coumarin (2*H*-chromen-2-one) **88** with interesting heterocycle structure. The proposed mechanism is shown in Scheme 28. Similar to **83**, the aminofuran **89** as Nair's product was not reported.



Scheme 28. IAMCRs strategy for synthesis of 2*H*-chromen-2-one **88**.

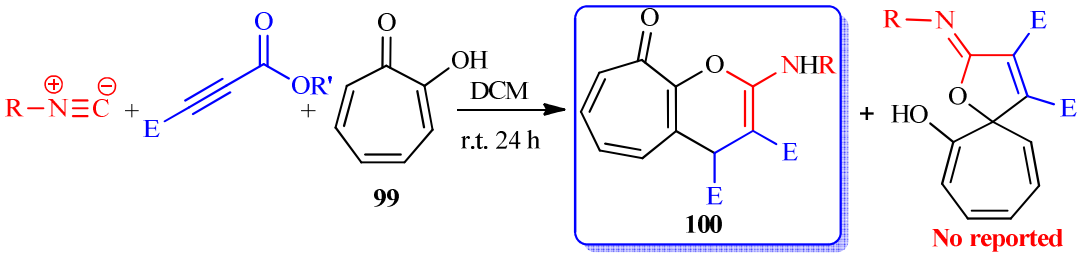
Synthesis of 4*H*-chromene **94** and **95** and ketenimines **96** can be produced through one-pot three-component reaction under the mild conditions by a reaction between alkyl isocyanides **1** and acetylenedicarboxylate **2** in the presence of 6-hydroxyquinoline **90** and 8-hydroxyquinoline **91**. For reaction of isocyanides, acetylenes **2**, and 1-hydroxy isoquinoline **93** (or 2-hydroxy pyridine as *NH* acid), the 1-azadienes **98** are the final products. However in the case of 2-hydroxyquinoline **92**, ketenimine **97** is the final product (Scheme 29).[54-57]



Scheme 29. IAMCRs synthesis of heterocyclic compound **94-98**.

Azizian and Ramazani *et al*. reported a fused pyrano-tropolone heterocycle based on the IAMCRs method (Scheme 30). Dialkyl 2-(alkylamino)-4,9-dihydro-9-oxocyclohepta[b]pyran-3,4-dicarboxylates **100** were prepared in a one-pot three-component reaction of alkyl isocyanide **1**, dialkyl acetylenedicarboxylate **2**, and α-tropolone (2-hydroxycyclohepta-2,4,6-trienone) **99**.

The reaction proceeds smoothly at room temperature and under neutral conditions to afford pyrano -tropolone heterocycle in high yield.[58] Again, the corresponding cyclization Nair's product was not reported.



Scheme 30. Pyrano-tropolone **100**.

4.2 Carboxylic (sulfonic) acids and oximes

In traditional Passerini or Ugi multicomponent reaction, isocyanides react with aldehyde or imine and carboxylic acids. In contrast, it was of interest to investigate the reactivity of the isocyanide/acetylene zwitterion towards carboxylic acids **101**, in comparison with aldehydes or imines of Passerini or Ugi reactions.[1] With this in mind, in 2006 we designed a new class of isocyanide-based Oakes-Yavari-Nair multicomponent reaction, in which activated acetylene was used instead of the carbonyl component of Ugi and Passerini 3-CRs. When we reacted isocyanides and activated acetyls in presence of the aromatic carboxylic acids, the final product was unsaturated linear imides **103**, while the amido-aminofuran **104** synthase for aliphatic and heterocyclic aromatic carboxylic acid (Figure 5).[59,60]

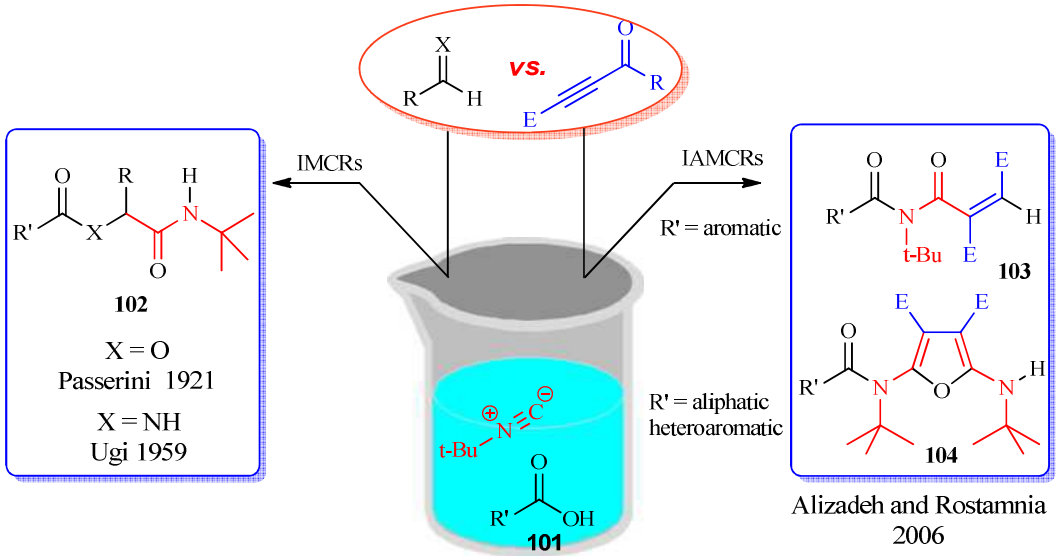
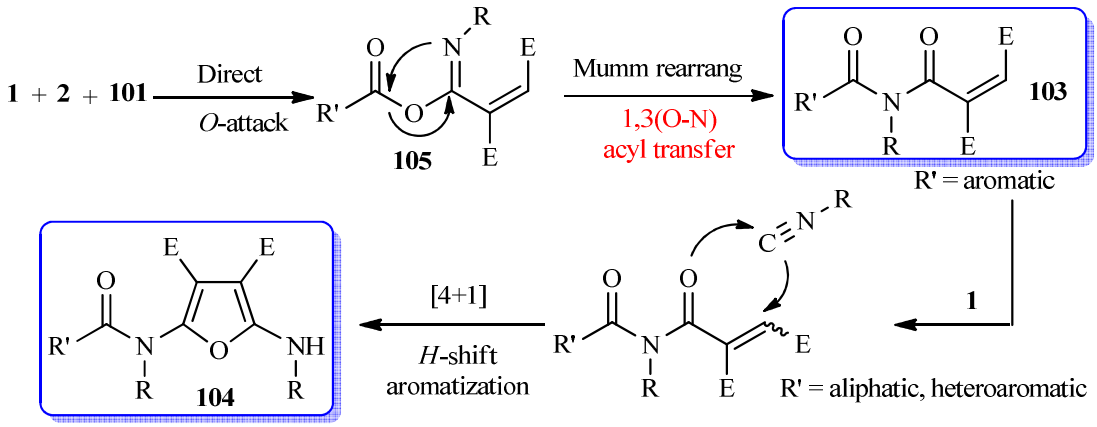


Fig. 5. Component comparison of the Passerini and Ugi reactions with designed reaction of Alizadeh and Rostamnia.

E-diastereomers of unsaturated linear imide **103** was produced with 61-98% yields via protonation of **3** with aromatic carboxylic acid at room temperature. At that time, these results encouraged us to investigate the generality of our method. To our surprise, when we used aliphatic carboxylic acid, the product was amido aminofurans **104** which was coupled by a serendipitous pseudo four-component procedure.

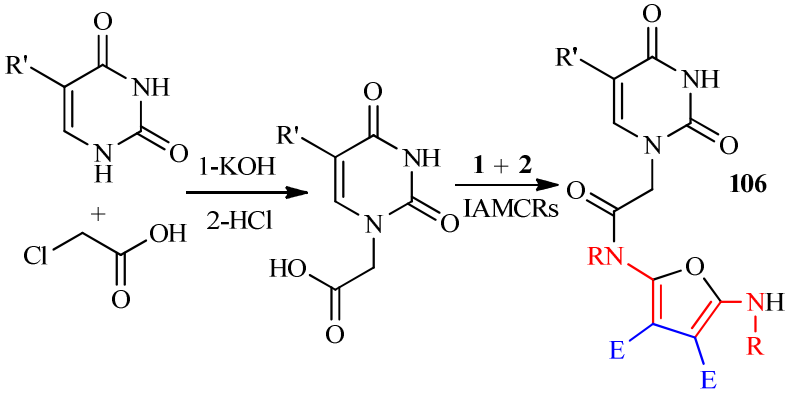
The proposed mechanism included, first the protonation of 1:1 zwitterion adduct of **3** with the carboxylic acids. Then **103** can be formed by a Mumm rearrangement [1,3(O-N) acyl transfer] of imidoylcarboxylate **105**. For aromatic acids, **103** is the final product, which is isolable from the reaction mixture. However, for aliphatic and heteroaromatic acids, the amido aminofuran **104** is formed by attachment of **103** into the second equal isocyanide containing [4+1] and then aromatization of the product through the *H*-shift process (Scheme 31).



Scheme 31. Proposed mechanism for synthesis of **103** and **104**.

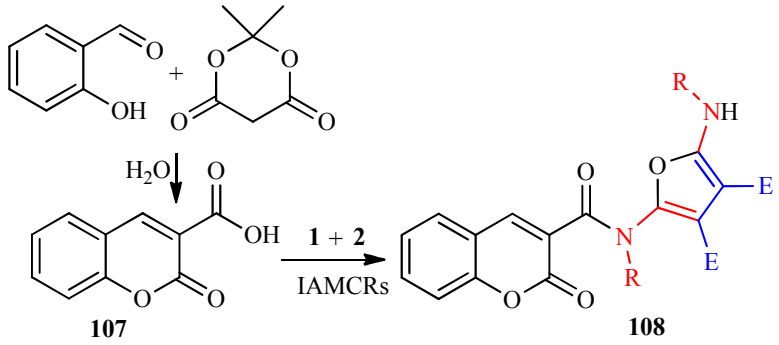
In the following year, reactivity of the zwitterion intermediate **3** was investigated in the presence of hetero-aromatic nicotinic and isonicotinic acids. The final products were aminofurano- nicotinamide and isonicotinamide molecules.[61] The reaction was then explored for the biochemically interesting bicinchoninic acid (BCA), that the bis(aminofuryl)bicinchoninic amide product yielded in 37-52%.[62] In 2009, Huang *et. al*., discovered a new chemistry for this reaction both in regio- and stereo-selectivity during the synthesis of (*Z*)- or (*E*)-*N*-acryl butenedioic monoimides.[63] Bayat and co-workers could also synthesize both **103** and **104** products from the reaction of **1** and **2** with anhydrides.[64]

A simple synthesis of uracil based aminofurans **106** via a IAMCR method was reported by Baharfar and Baghbanian.[65] The reaction was achieved and fairly good yields (Scheme 32).



Scheme 32. IAMCR synthesis uracil based aminofurans **106**.

The synthesis of 2-(alkylamino)-5-{alkyl[(2-oxo-2*H*-chromen-3-yl)carbonyl]amino}-3,4-furandicarboxylates **108**, which was simply accomplished *via* a IAMCR strategy, is reported by Adib *et. al*. *In situ* generated adduct of isocyanides/acetylenedicarboxylates was efficiently reacted with coumarin-3-carboxylic acids **107**, at room temperature (Scheme 33).[66]



Scheme 33. Simple synthesis of chromen-aminofurans **108**.

For the first time in 2007, following to our previous experience in using of trivalent phosphines such as triphenylphosphine as an especial nucleophile in reactivity of activated acetylenes,[67] we began a comparative study on nucleophilicity of isocyanides and phosphines (see Figure 6).[68,69] Our researches led to introduce a novel bi-nucleophilic system in IAMCRs.

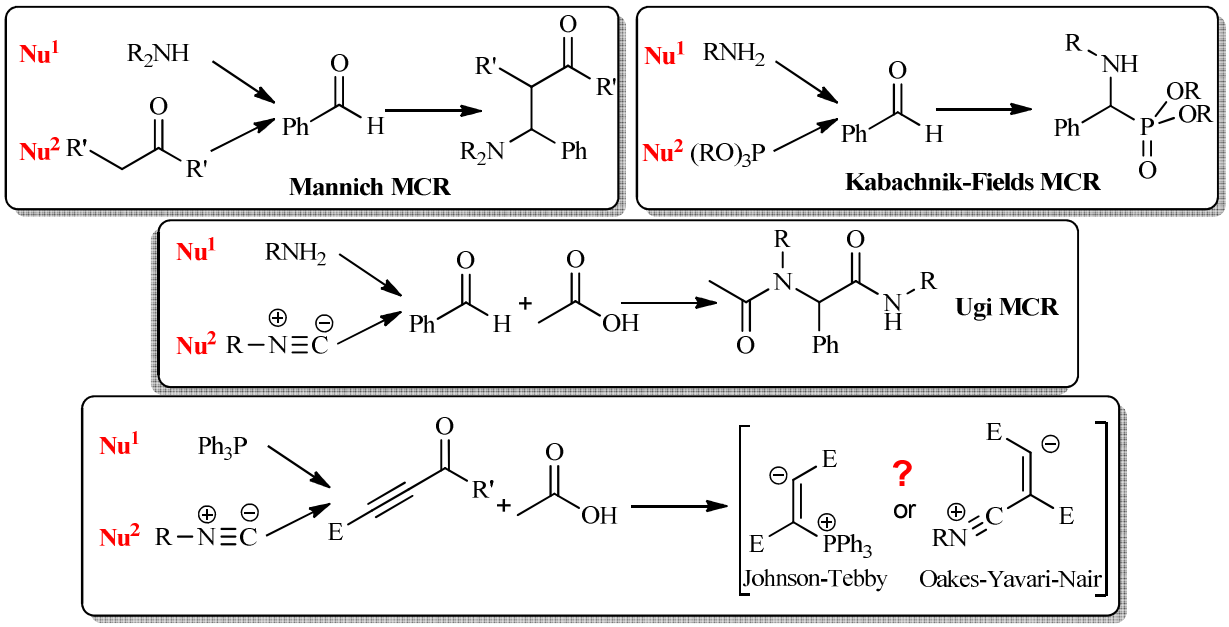
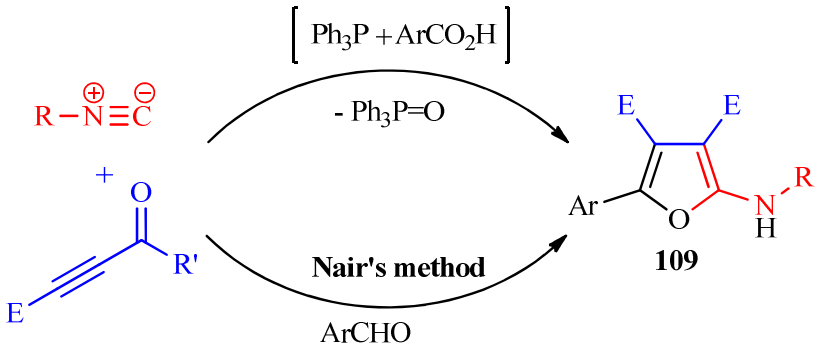


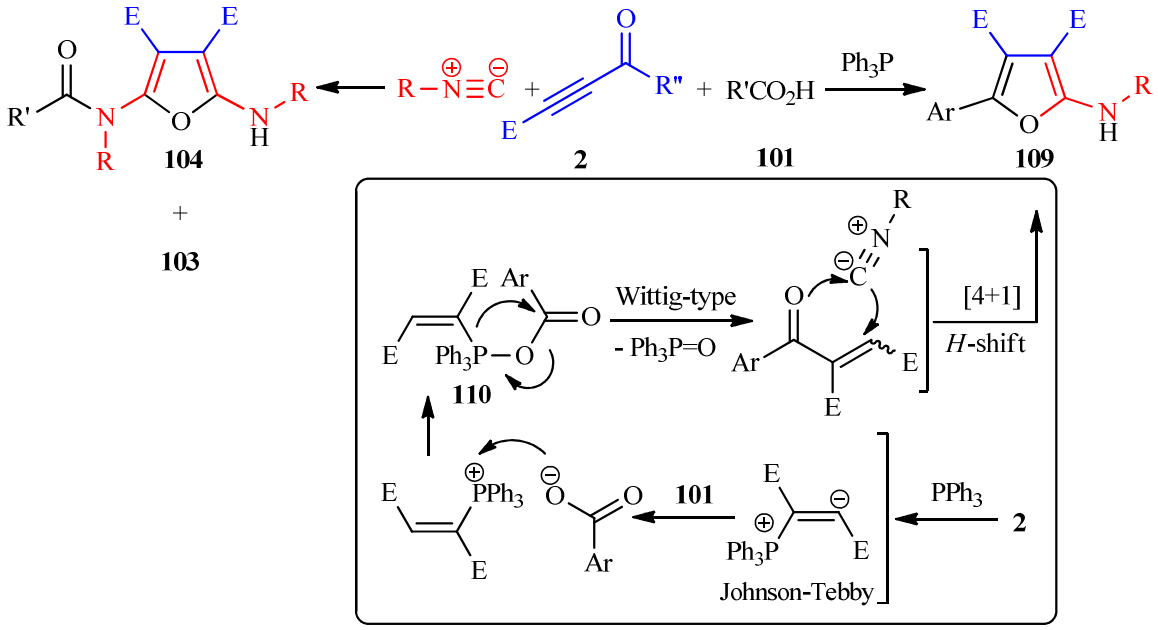
Fig. 6. Examples of binucleophilic multicomponent reaction.[10]

We investigated the reaction of acetylene **2** and carboxylic acid **101** in a binucleophilic system of triphenylphosphine and alkyl isocyanide, which led to highly functionalized aminofuran **109** (Scheme 34). The reaction was also found to be effective with other trivalent organophosphorus compound such as trialkyl phosphites and triaryl phosphites. Formerly, Nair and co-workers had reported the **109** by the cycloaddition reaction of **3** in presence of the aldehydes.[9,11]



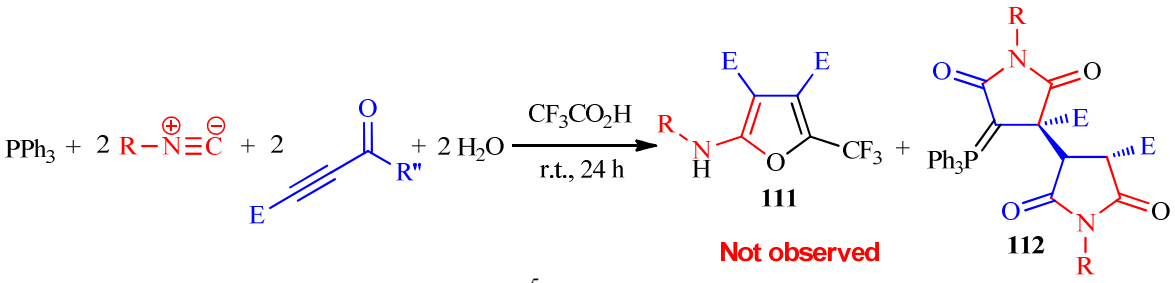
Scheme 34. IAMCRs synthesis of aminofurans **109**.

A possible mechanism can be proposed as follow. First, the formation of zwitterion adducts occurs from the addition of triphenyl phosphine to acetylene **2**. The product is protonated by **101** which is then attacked by carboxylate to produce Ph_3PO. The obtained intermediate **110** loses the Ph_3PO through a Wittig-type reaction and finally, the **109** forms by reaction of the isocyanide through [4+1] reaction and followed by aromatization *H*-shift (Scheme 35).



Scheme 35. Proposed mechanism for synthesis of **109**.

In another binucleophilic system, regarding to chemical importance of fluorinated compounds, we designed a similar reaction (see Scheme 34) for the synthesis of the corresponding fluorinated aminofurans **111,** using trifluoroacetic acid (TFA) as the carboxylic acid.[70] The reaction of phosphine/isocyanide binucleophilic system and activated acetylene in the presence of TFA didn't afford the desired fluorinated aminofurans **111**. Surprisingly, the product λ^5-phosphanylidene bis(dioxotetrahydro-1*H*-pyrrole-3-carboxylates) **112** *via* pseudo-seven-component (7-CR) procedure was produced. We found that the influence of atmospheric moisture was responsible for observed modification, and hence the aforementioned reaction in the presence of H_2O also furnished the main product **112** (Scheme 36).



Scheme 36. 7-CR synthesis of λ^5-phosphanylidene bis-pyrrolidine **112**.

When the structure was clearly demonstrated by X-ray, we were able to perform the reaction based on the component of the **112**. We found that stoichiometric amount of TFA is needed, and also [(1R,2S,3R) or (1S,2R,3S)] stereoisomers of λ^5-phosphanylidene bis-pyrrolidine are the main products, which shows a diastereoselectivity even for three chiral genic centre (Figure 7). We note that, ylide function of the **112** is stable in moisture and room temperature for several month.

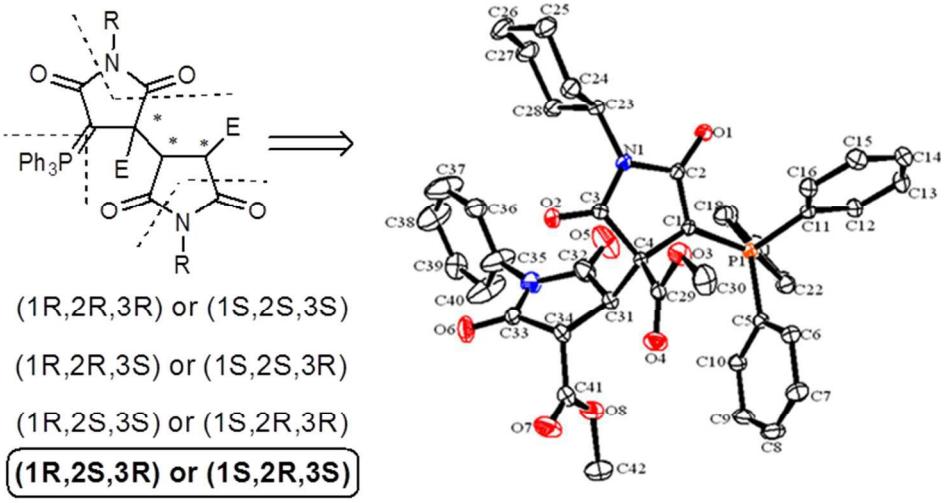
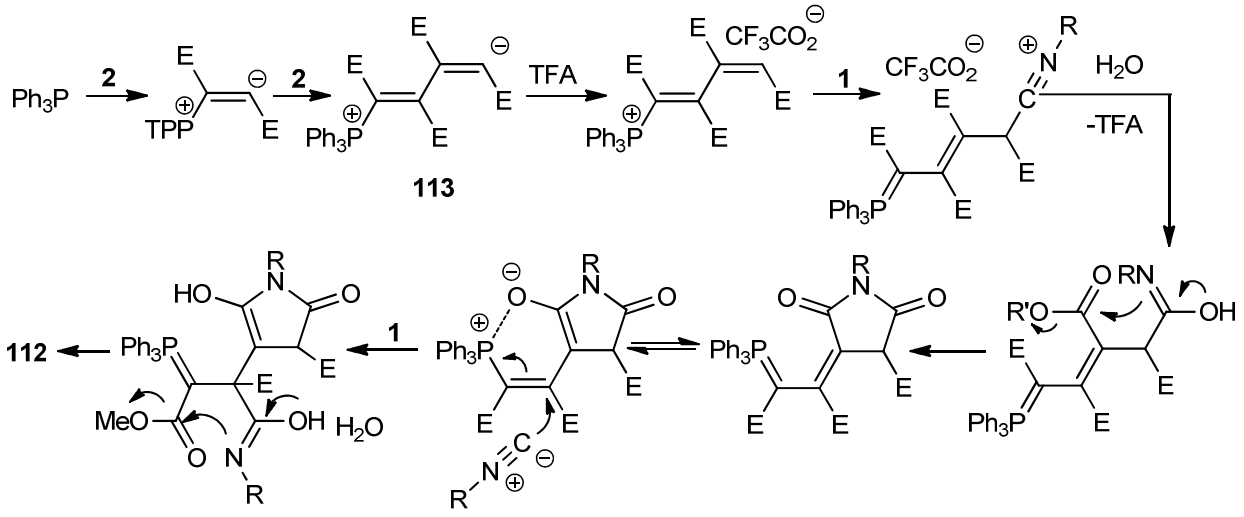


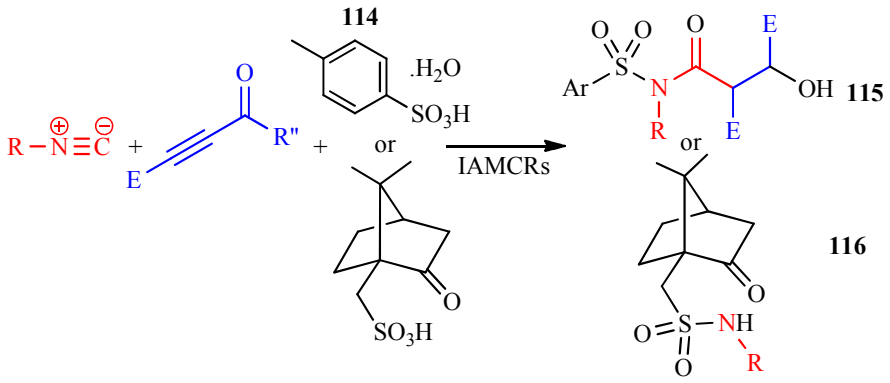
Fig. 7. Main stereoisomers and single crystal X-ray structure of **112**. (Reproduced with permission of Elsevier).

The addition of triphenylphosphine (TPP) to acetylenedicarboxylates **2** and then protonation with TFA yields a 1,5-dipole **113**. 1:2 zwitterionic adduct **113** is protonated by TFA and then by reacting with **1** and water, **112** is produced. In this reaction, stoichiometric amount of TFA is needed. Otherwise, when the reaction was performed using less than the stoichiometric quantity of TFA, fumarate, and maleate were observed as the by-products (Scheme 37).



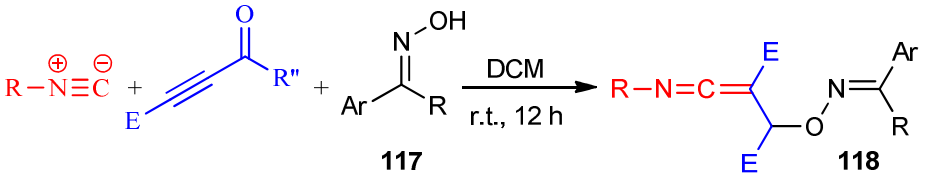
Scheme 37. Proposed mechanism for the synthesis of **112**.

After successful discoveries in new IAMCRs by carboxylic acids, next question was what is the situation of sulfonic acids in the IAMCRs? Synthesis of sulfonamide **115** was recorded when we reacted isocyanide and activated acetyls with monohydrate *p*-toluenesulfonic acid (PTSA) **114** as an aromatic sulfonic acid. The proposed mechanism included, first the protonation of 1:1 zwitterion adduct of **3** with the sulfonic acid. Then sulfonamide **115** can be formed by a Mumm-type rearrangement. By changing PTSA to the camphorsulfonic acid, the product **116** was produced without incorporation of the acetylene (Scheme 38).[71]



Scheme 38. Sulfonic acid mediated IAMCRs for sulfonamide **115**.

2-[(alkylimino)methylene]-3-{(*E*)-[(1-phenylalkylidene)amino]oxy}succinates as thermally stable ketenimines **118** was synthesized by the reaction of alkyl isocyanides **1** and acetylenedicarboxylates **2** in the presence of aryl oximes **117**. The reaction underwent a smooth 1:1:1 conjugated addition (*O*-attack) of substrates in dichloromethane under the ambient conditions (Scheme 39).[72]



Scheme 39. IAMCRs synthesis of stable ketenimine **118**.

The addition of pyridine-2-carboxaldoxime or *α*-furyldioxime to dialkyl acetylenedicarboxylates under neutral conditions in the presence of isocyanides leads to ketenimines **119** and bis-ketenimines **120** in good yields (Figure 8).[73]

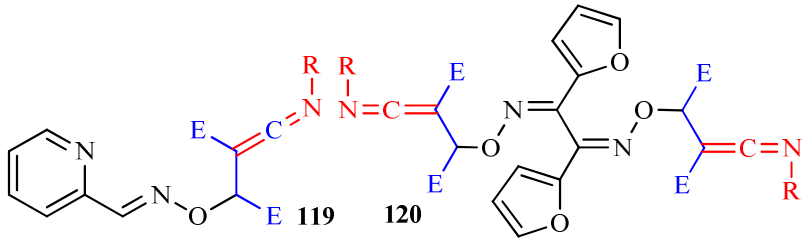
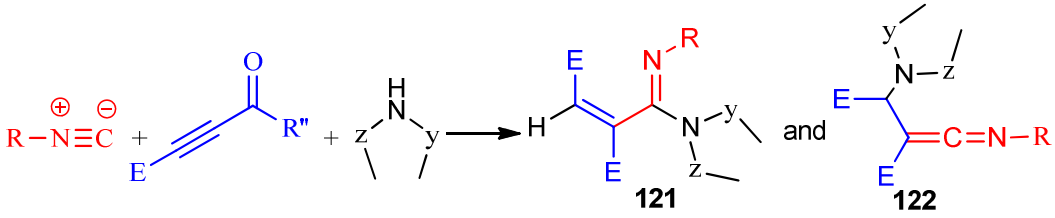


Fig. 8. IAMCR synthesis of ketenimines **119** and **120**.

5 Isocyanide/acetylene adduct and *NH*-acids

Similar to *CH*- and *OH*-acids, it has been known that *NH*-acids can react with zwitterion **3** to form azadienes and ketenimines. The reaction between **1** and acetylenic esters **2** in the presence of different *NH*-acid afforded azadienes and ketenimines. Carbazole or indole afforded the isomeric 1-azadienes **121** based on direct *N*-attack and yielded highly functionalized ketenimines **122,** which is resulted by conjugated addition of *N*-nucleophiles (Scheme 40). Using pyrrole or

2-aminobenzothiazole, direct addition of the nucleophile occurred, leads to the formation of 1-azadiene derivative **121** as the sole product.[74,75]



Scheme 40. IAMCRs of *NH*-acids.

As shown in Figure 9, reaction of *NH*-acids afford interesting ketenimines (**123**,[76] **124**,[77] **125**,[78] **126**,[79] **127**,[80] **128**,[81] **129** and **130** [82], **131**,[83] **132**,[84] and **133**[74]) including sulfonamide, hydantoins, *α*-chlorocarbonyl, and active carbonyl skeletons. All reactions are reported to be done under the ambient conditions without using any acids, bases, or other additives. For some of these *NH*- starting materials, the authors have applied multi-step procedure.[79]

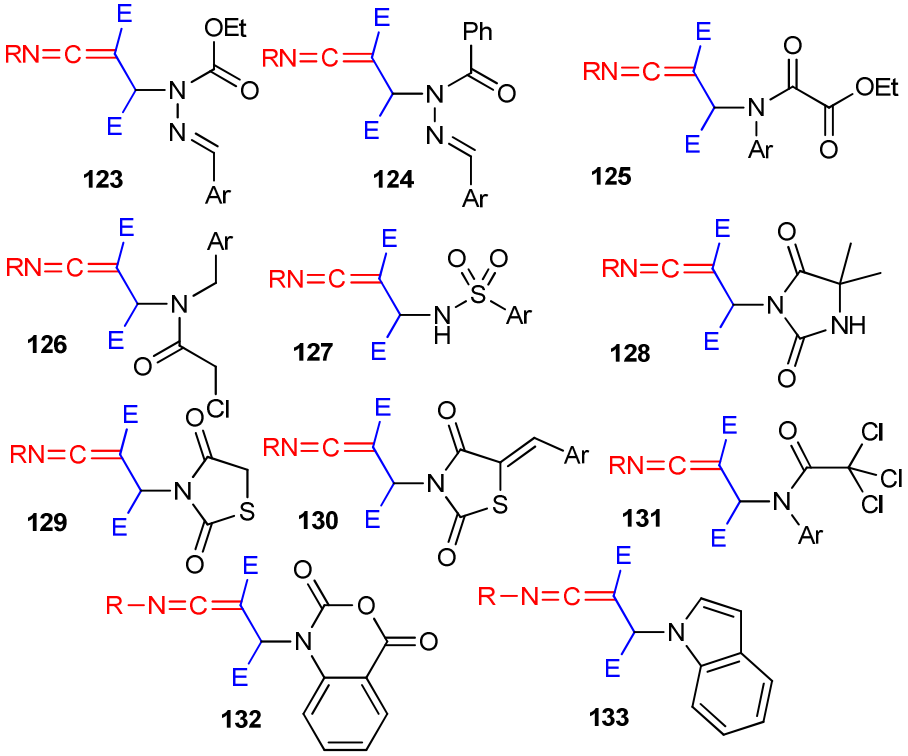
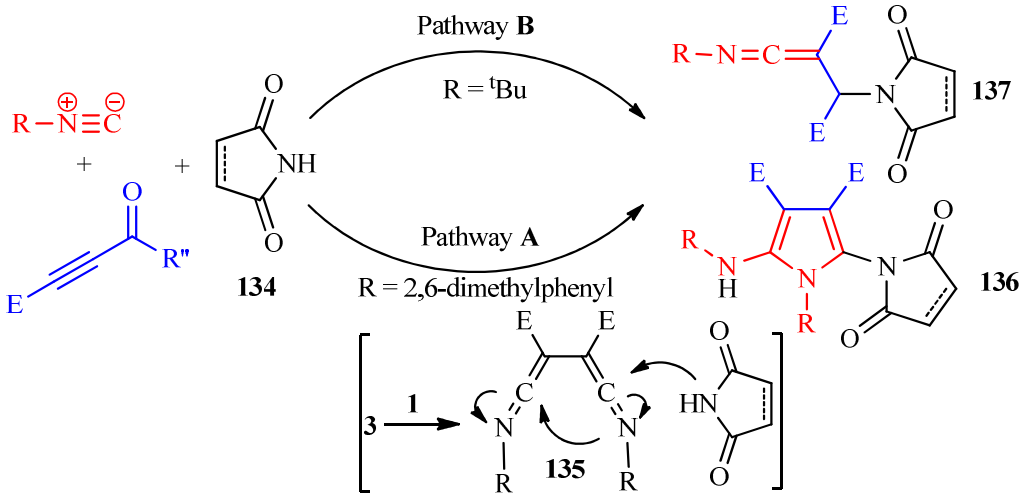


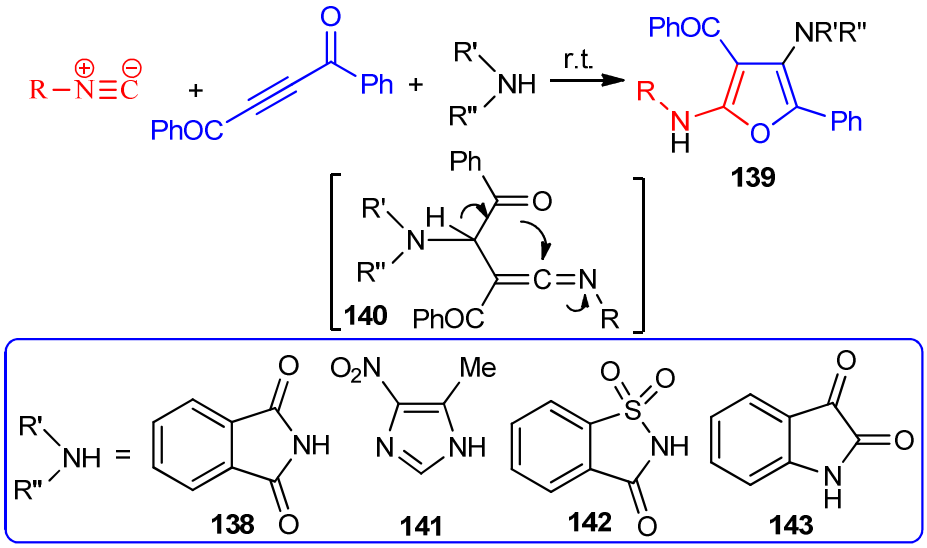
Fig. 9. Products obtained from the IAMCRs of *NH*-acids.

In continuation of isocyanide/acetylene-based MCRs, pseudo four-component reactions of isocyanides and acetylenes were explored in the presence of cyclic *NH*-acid such as succinimide or maleimide **134**. Depending on the isocyanide hindrance, the reaction could proceed through two different pathways. For the unhindered isocyanides, like cyclohexyl isocyanide and 2,6-dimethylphenyl isocyanide, formation of a reactive intermediate **3** followed by further reaction with the isocyanide to form the bis-ketenimine intermediate **135** is predictable. The subsequent reaction of **135** with compound **134** and cyclization under the reaction conditions produced **136** (pathway A). However, the reaction for *tert*-butyl isocyanide (pathway B) as hindered isocyanide produces ketenimine **137** by the conjugated base of the *NH*-acid (Scheme 41).[85]



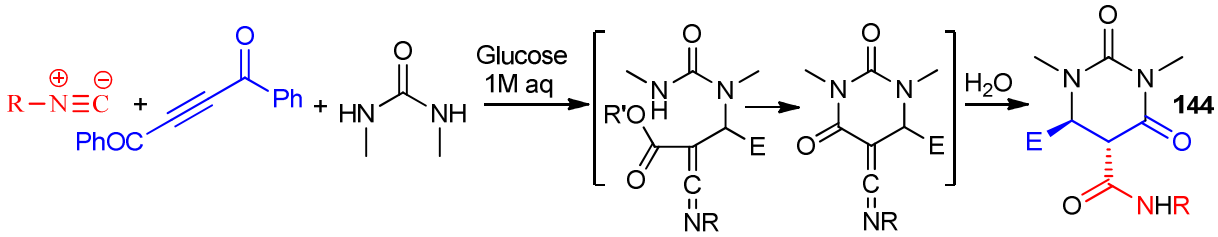
Scheme 41. IAMCR synthesis of **137** and **136**.

In the reaction of dibenzoylacetylene (DBA) with isocyanides **1** in presence of the phthalimide **138**, the corresponding aminofurans **139** is produced. The product **140** is then yielded *via* the crystallization process. The reaction for various *NH*-acids provide excellent yields. The products showed atropisomerism (**141-143**) at room temperature due to restriction in rotation around the new Ar-N bond (Scheme 42).[86,87]



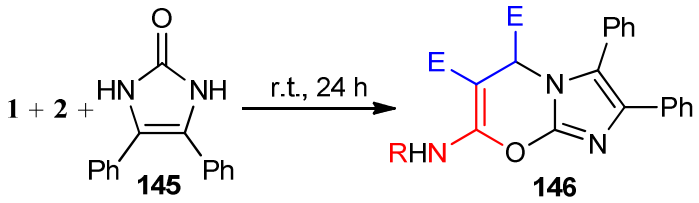
Scheme 42. Isocyanide/DBA protonation.

There are several reactions in which ketenimines are assumed to be as the main products and don't undergo further cyclization or addition. But there are also some examples (e.g. **144**) in which a reaction would occur between dialkyl acetylenedicarboxylates and isocyanide with *NH*-acids. The mechanism of this reaction is consistent with the abovementioned reactions (Scheme 43).[88]



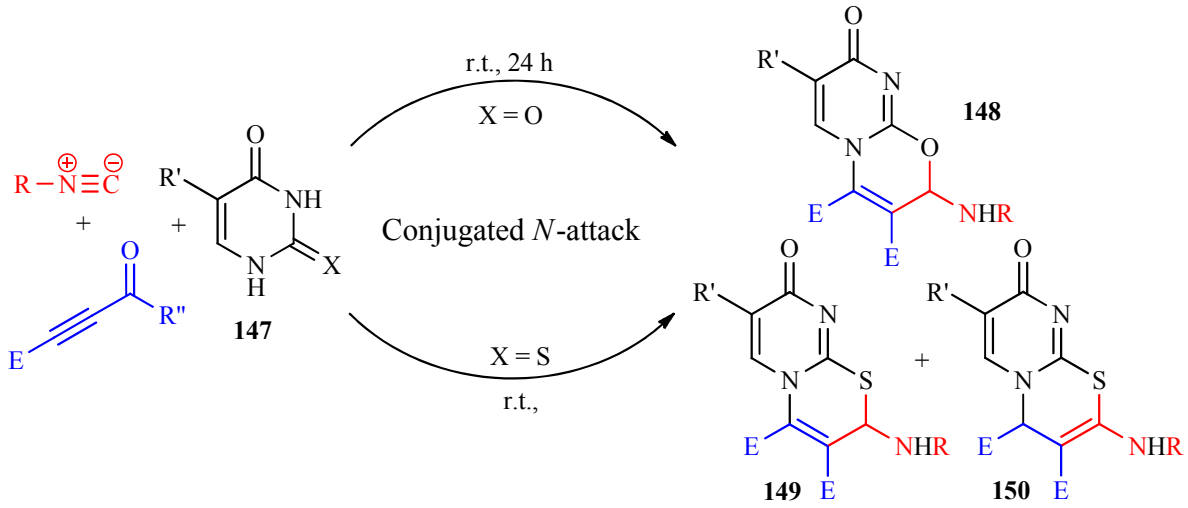
Scheme 43. IAMCRs diastereoselective synthesis of pyrimidine **144**.

In a similar manner, 5*H*-imidazo[2,1-*b*][1,3]oxazine **146** derivatives were synthesized by IAMCR method involving the reaction of isocyanides, dialkyl acetylenedicarboxylates, and 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one **145**. Isomerization of the ketenimine intermediate led to the production of the fused heterocyclic system **146** (Scheme 44).[89]



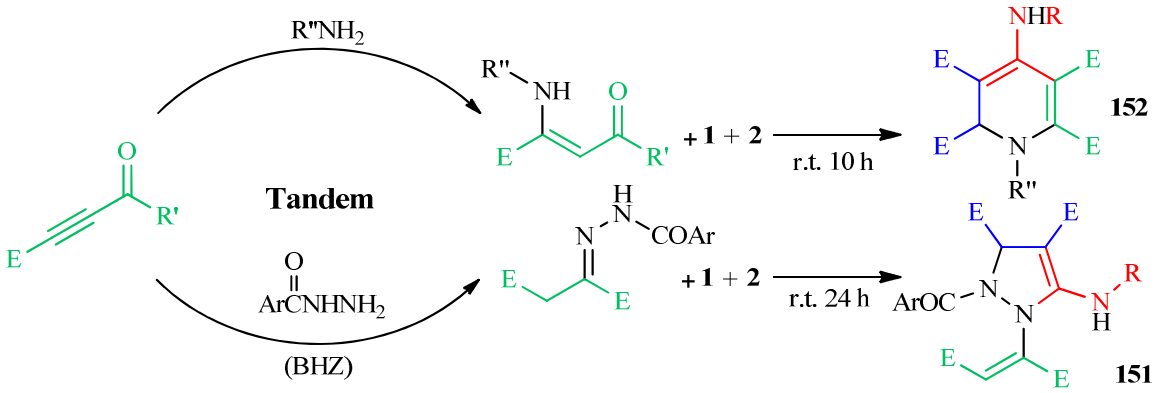
Scheme 44. Fused system of imidazo-oxazine **146**.

Baharfar *et. al*. reported the synthesis of pyrimido[2,1-*b*][1,3]oxazine **148** and pyrimido[2,1-*b*][1,3]thiazine **149** and **150** by the reaction of isocyanides with dialkyl acetylenedicarboxylates in the presence of uracils (or thiouracils) **147** (Scheme 45).[90,91]



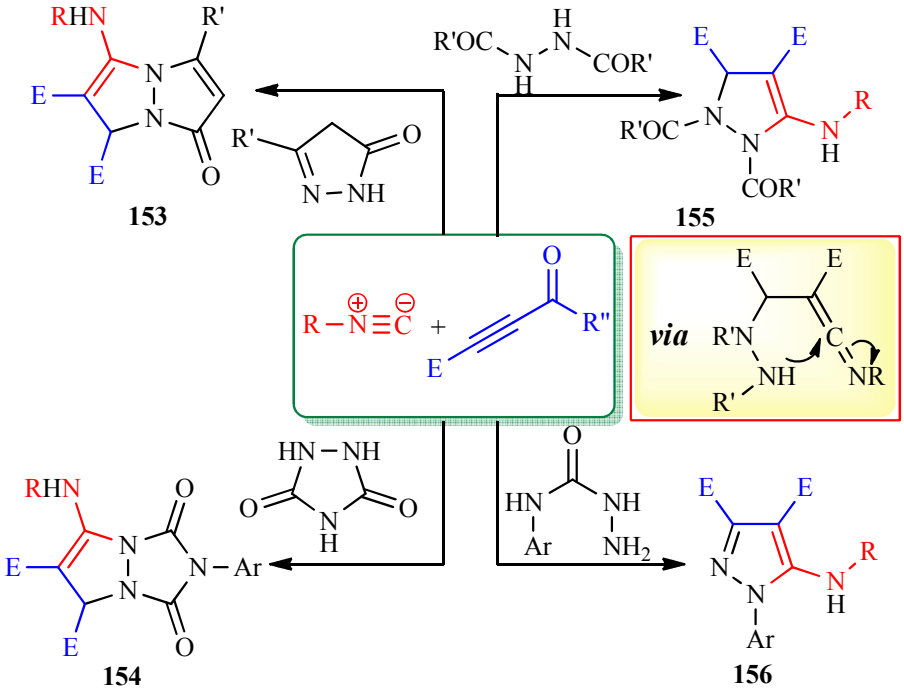
Scheme 45. Fused system of pyrimido-oxazine **148**, pyrimido-thiazine **149** and **150**.

Anary-Abbasinejad *et al*., reported a novel isocyanide-based cascade four-component reaction between benzoyl hydrazine (BHZ), acetylene **2**, and isocyanide **1** which lead to a highly functionalized 1*H*-pyrazoles **151** in excellent yields.[92] Highly functionalized 2-dihydropyridine derives **152** as a result of 1:1:1 addition reaction of isocyanide and dialkyl acetylenedicarboxylates in the presence of *in situ* generated of enaminone (Scheme 46).[93]



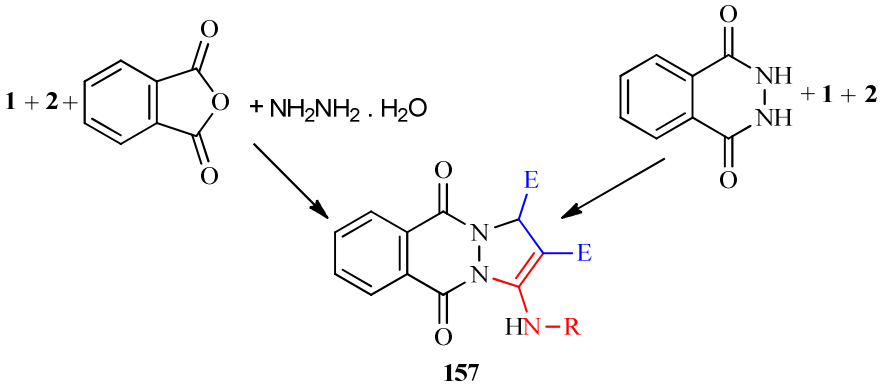
Scheme 46. Tandem synthesis of pyrazoles **151** and dihydropyridine **152**.

Adib *et. al*. reported the synthesis of pyrazole-pyrazoles **153**,[94] pyrazolo-triazoles **154**,[95] highly functionalized pyrazoles **155**,[96] and dialkyl 5-(alkylamino)-1-aryl-1*H*-pyrazole-3,4-dicarboxylates **156**[97] based on *in situ* generation of the 1:1 zwitterion **3** and its subsequent protonation by the substituted hydrazines. These reactions were preceded in acetone at room temperature (Scheme 47).



Scheme 47. IAMCR synthesis of pyrazoles **153**, **154**, **155** and **156**.

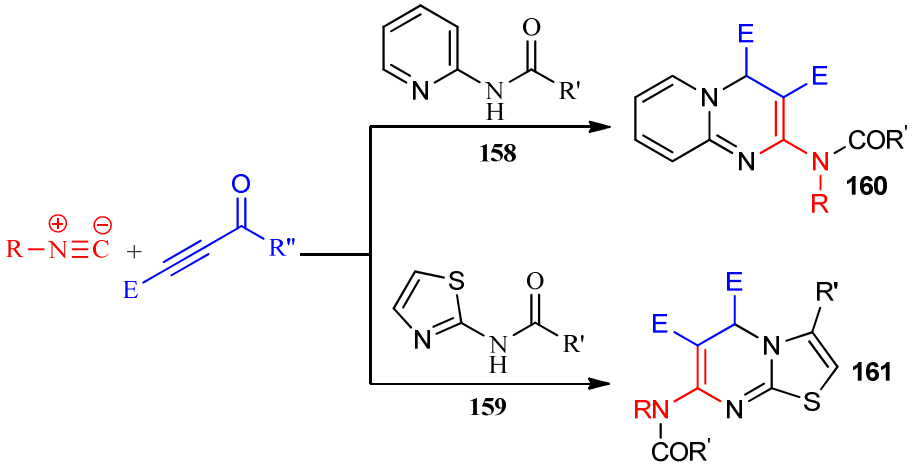
Pyrazolo[1,2-*b*]phthalazines **157** were synthesized by Teimouri in 2006.[98] In an independent work by Shaabani *et al.,* the synthesis of pyrazolo-phthalazine and pyrazolo-pyridazine were done by *in situ* synthesis of *NH*-acids. This protocol has been developed for the synthesis of structurally diverse 1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylates and 1*H*-pyrazolo[1,2-*a*]pyridazine-1,2-dicarboxylates *via* a four-component reaction of hydrazine hydrate, acetylene **2**, isocyanides, and various cyclic anhydrides, such as succinic anhydride, maleic anhydride, and phthalic anhydride in good to moderate yields (Scheme 48).[99]



157

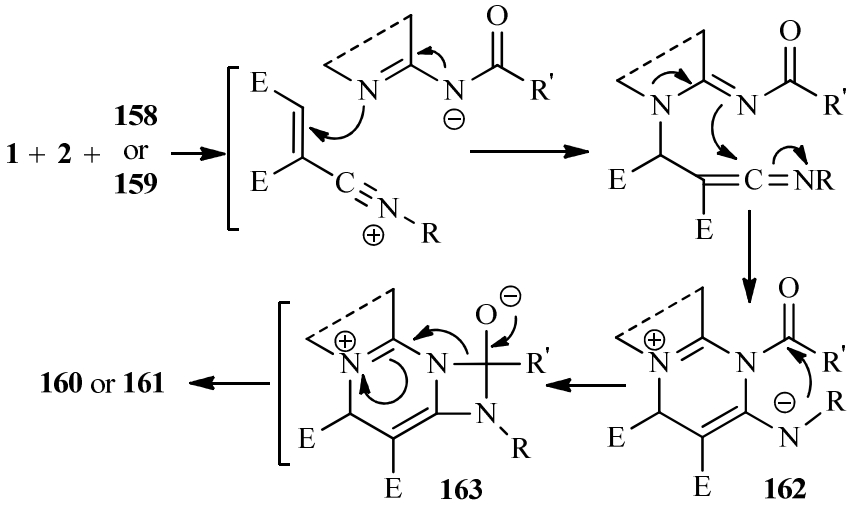
Scheme 48. IAMCR synthesis of pyrazolo-phthalazine **157**.

The reaction of acetylenic esters and isocyanides in the presence of *N*-(2-pyridyl)amides **158** and *N*-(1,3-thiazol-2-yl)amides **159** proceeded spontaneously in dry DCM at ambient temperature. The authors utilized these *NH*-acids for the protonation of the *in situ* generated zwitterions **3**. However, heirein (the ketenimine) wasn't the main product. It could also undergo further intramolecular cyclization to form the bicyclic 4*H*-pyrido[1,2-*a*]pyrimidines **160** and thiazolo[3,2-*a*]pyrimidines **161** (Scheme 49). [100-102]



Scheme 49. IAMCRs synthesis of **160** and **161**.

In this process, formation of the corresponding ketenimines is followed by an intramolecular cyclization to produce bicyclic zwitterion **162**. The last product undergoes facile intramolecular nucleophilic addition of a nitrogen to the neighboring carbonyl group which obtains the tricyclic compound **163**. Finally, the ring opening process cause to yield the fused heterocyclic system **160** or **161** (Scheme 50).



Scheme 50. Proposed mechanism for synthesis of **160** and **161**.

6 Summary

We have tried to summarize in this review the major developments of *in situ* generation isocyanide/acetylene zwitterionic adduct and protonation it by *CH*-, *OH*- and *NH*-acid for syntheses of ketenimines, aza-dienes, and heterocycles, in which the resulting protonated OYN zwitterions will react further with a variety of *C*-, *O*- and *N*-nucleophiles in IAMCRs condition.

In general, in these reactions commercially available starting compound are used in multicomponent reaction strategy without any catalyst and additives. The basis for most of today's known methodologies was laid by I. Yavari already in the mid-1990s and then V. Nair in their work on one-pot protonation of various trivalent phosphine-based zwitterions and other reactive intermediates. This review gives a comprehensive survey regarding the isocyanide/acetylene-based multicomponent (IAMCRs) synthesis of extremely useful organic backbones.

Although developments of more general and efficient protocols are highly warranted, the progress achieved so far in this area holds promise for extensive applications of isocyanide/acetylene adduct towards one-pot multicomponent synthesis.

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