J. Adv. Sci. Edu. Res. **2021: 2: 1-33**, ISSN: 2583-0155 (ONLINE)

https://doi.org/10.56253/JASER.2.1.2021.1-33
Pubished: 25.12.2021(http://jaser.rkmvccrahara.org/)

An overview of Isocyanide

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Abstract:

This tutorial review focuses on isocyanides. It includes the natural abundance of isocyanides and their bio-synthestic routes. Despite of the toxicity and vile ordour of isocyanide, it has been employed in many multicomponent reaction for the synthesis of highly functionalized molecule. A short discussion of the chemistry of isocyanide is also included in this micro review.

Key Words: Isocyanide, Terrestrial isocyanide, Marine isocyanide, Passerini reaction, Ugi reaction

1. Introduction

Discovery of isocyanide is a serendipity. In an attempt to synthesize crotonic acid, W. Lieke treated allyl iodide with AgCN to get allyl cyanide, which on subsequent hydrolysis and isomerization would produce crotonic acid. But Lieke observed a malodorous substance was formed in the first step of the reaction instead of allyl cyanide. Latter Hofmann (1867) and Gautier (1868) proposed this vile order substance to be isocyanide (Scheuer,1992), but the actual structure of isocyanide was established by Lindermann and Wiegrebe in 1930 (Edenborough, 1988). Isocyanide is an isomer of cyanide. Isocyanide is also called isonitrile and the term isocyano is used as prefix. Isocyano function is unique as carbon is attached to a single atom nitrogen like oxygen in carbon monoxide.

Isocyanides are commonly prepared by (i) the reaction of amine with chloroform in the presence of alkali, this reaction is also used for the detection of primary amine (carbylamine test); (ii)

reaction of *N*-alkyl-/aryl- formamide with $POCl_3$ in presence of pyridine; (iii) reaction of alkyl or aryl halide with silver cyanide; (iv) reduction of isocyanate by Cl_3SiH/Et_3N (Baldwin, 1983).

The repelling vile odour of volatile isocyanide keeps the chemists away to work much with them. Toxicity of isocyanide is lesser than inorganic cyanides. Toxicity study by a German chemical and pharmaceutical company (Farbenfabriken Bayer AG) showed that 0.5g to 5.0 g/kg can be tolerated by mice for oral or subcutaneous doses.

General structure of isocyanide ($R\text{-}N^+\equiv C^-$) claims strong Lewis basicity of carbon which is proved by the formation of H-bond between acetylenic hydrogen of phenylacetylene and phenyl isocyanide (Ferstanding, 1962). Isocyanides behave initially as nucleophile or base and then as electrophile and this dual character makes isocyanide attractive to the chemists in organic synthesis. 1,1-Addition of halogen (to $RNCX_2$), addition of sulphur to isothiocyanate (RNCS) and ready oxidation by HgO to isocyanate (RNCO) are some examples of dual character of isocyanide. Greater thermodynamic stability of cyanides over isocyanides is manifested from the thermal rearrangement of alkyl isocyanide to alkyl cyanide.

2. Natural Occurrence of Isocyanides

Naturally occurring isocyanides can be classified into two main categories depending on their resources: (a) Terrestrial isocyanides and (b) Marine isocyanides.

2.1. Terrestrial isocyanides. Terrestrial isocyanides are classified into four classes depending on their structural varieties: (i) Xanthocillin type, (ii) Cyclopentenyl type, (iii) Having indole skeleton and (iv) Miscelleneous.

2.1.1. Xanthocillin type. Naturally occurring isocyanide xanthocillin was discovered in 1957 almost 100 years after the discovery of isocyanide in the laboratory. Xanthocillin **1** was isolated from *Penicillium notatum*, which is also the source of penicillin discovered by Alexander Flemming in 1929. Later many varieties of xanthocillin eg Xanthcillin-X, Xanthcillin-Y_1, Xanthcillin-Y_2, and Xanthcillin-Z were isolated. But structure of Xanthocillin Z is not yet assigned (Table 1, entries 1-3) (Edenborough, 1988). Another xanthocillin type antibiotic is MK 4588 (**2**) (Scheuer, 1992) (entry 4). Xanthoascin **3** (entry 5) was also isolated (Takahashi, 1976).

2.1.2. Cyclopentenyl type. The second type of terrestrial isocyanide is structurally related to cyclopentenyl isocyanides. Dermadin **4** is the first member of of this class and was isolated from a soil fungus *Trichoderma viride* (entry 6) (Pyke, 1966). 'Ovine ill thrift' is a disease which makes the sheep shrinks. This disease is common in those places where the grassy fields are

found to contain a large amount of *Trichoderma* species, which secrete bioactive metabolites like dermidin **4** and trichoviridine **5** (entry7). These metabolites inhibit the growth of cellulose-digesting bacteria in the rumen (first part of stomach) of sheep and are probably the cause of this disease. *Trichoderma viride* is also a fungicide, when it is introduced along with seed or at root-zones, the seedlings are survived from soil-borne pathogens. Isonitrin A **6**, Isonitrin B **7**, Isonitrin D **8** were also isolated from Trichoderma species (entries 8-10). Homothallin I **9** and Homothallin II **10** are another set of cyclopentenyl isocyanide that induce production of oospores (entries 11-12) (Edenborough, 1988).

2.1.3. Having Indole skeleton. The third type of terrestrial isocyanide involves indole skeleton in their structures. Indoleacrylo isocyanide **11** obtained from *pseudomonus* acts as antibiotic towards *Staphylococcus aureus* (entry 13). Hapalindole **12** was isolated from cultured blue-green alga *Hapalasiphon fontinalis* (entry 14) (Bornemann, 1988).

2.1.4. Miscelleneous. Mannitol diester **13** is a member of this class. It is an antibiotic (A32390A) and acts as an inhibitor for dopamine-β-hydroxylase (entry 15). A broad spectrum antibiotics Hazamycin factors have been isolated from *Micromonospora echinospora*. From a complex mixture of Hazamycin factors only two compounds Hazamycin factor 5 (a racemic mixture) (RR and SS forms of **14**) and Hazmycin factor 6 (*meso* form) (**15**) have been isolated (entries 16-17) (Edenborough, 1988).

2.2. Marine Isocyanides. The first reported marine isocyanide is axisonitrile-1 (**16**), an isocyanosesquiterpene, isolated from marine sponge *Axinella cannabina* (Table 2, entry 1) (Cafieri, 1973). Marine isocyanides are commonly terpene-based isocyanides involving sesquiterpene and diterpenes. Unlike terrestrial isocyanides marine isocyanides often appear as triad system of isocyanide, isothiocyanate and *N*-formylamine.

Axisonitrile-2 (**17**), Axisonitrile-3 (**18**) and Axisonitrile-4 (**19**) are also isolated from the same marine sponge (entries 2-4) (Di Blasio, 1976). Acanthellin-1 (**20**), another sesquiterpene isocyanide, isolated from *Axinella Cannabina* exhibits antimicrobial activity (entry 5) (Ciminiello, 1984). Kalihinol A **21**, a tricyclic isocyanoditerpene, has been isolated from *Acanthella acuta* (entry 6). Kalihinol B **22**, Kalihinol C **23**, Kalihinol E **24**, Kalihinol F **25** were also isolated (entries 7-10) (Patra, 1984). Kalihinol F **25** exhibited antibacterial activity. The other isocyanoditerpene Kalihinene **26** and Isokalihinol **27** were isolated from *Acanthella klethra* (entries 11-12) (Fusetani, 1990). Isolation of metabolites **28** and **29** having antimicrobial

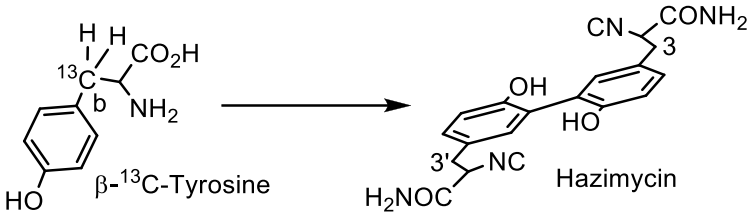
activities from *Halicondria* species have been reported (entries 13-14) (Burreson, 1975). Diisocyanoadociane **30**, an isocyanoditerpene isolated from *Adocia* species exhibited marked activity towards Gram+ve and Gram-ve bacteria (entry 15) (Baker, 1976). Many isocyanides have been isolated as minor components and all structures could not be determined. Another diisocyanoditerpene **31** isolated from *Hymeniacidon amphilecta* inhibits the growth of *Staphylococcus aureus, Bacillus subtilis* and *Candida albicans* (entry 16) (Wratten, 1978).

An interesting observation on nudibranchs led to the discovery of another class of marine isocyanides. Nudibranchs are shell-less mollusk and some are colourful but surprisingly they are rarely eaten by their predators except carnivorous opisthobranch. *Phyllidia varicosa*, a class of such nudibranch secretes mucous which are neutral and having a bad smell. A 0.2% solution of such mucous can kill the crustaceans in the aquarium. While collecting *Phyllidia vericosa* at Pupukea, Oahu, it was observed that this nudibranch was feeding upon a *Ciocalypta* species of marine sponge. This marine sponge became the source of the active material in larger amount (Burreson, 1975). This active material was finally established to be 9-isocyanopupukeanane **32** named after the place of finding this marine sponge.

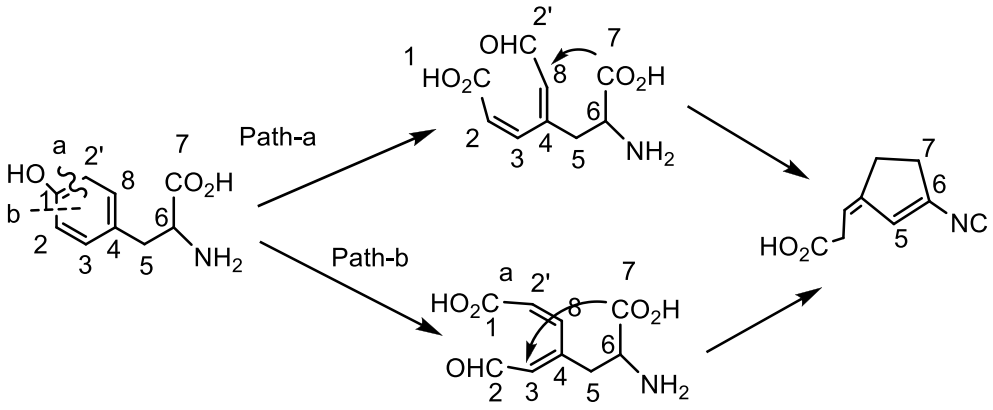
3. Biosynthesis of natural isocyanides

3.1. Biosynthesis of terrestrial isocyanides. Terestrial isocyanides are supposed to generate from amino acids whereas the marine isocyanides are terpenoid-based. Considering the structures of terrestrial isocyanides, they can be correlated to different amino acids. As for example xanthocillin **1**, hazimycin factors **14** and **15** can be correlated to tyrosine; indolylacrylo isonitrile **11** and hapalindole A **12** can be correlated to tryptophan and mannitol diester **13** to valine. From all these structural relations, it may be assumed that all terrestrial isocyanides are derived from the metabolism of appropriate amino acids. Based on this idea many experiments have been conducted but an unambiguous metabolic pathway could not be predicted**.**

3.1.1. Biosynthesis of xanthocillin and Hazimycin: Regarding biosynthesis of xanthocillin it was concluded from labeling experiments that 'N' of isocyano function and rest of the carbon framework of xanthocillin comes from tyrosine, but the source of 'C' in isocyano function could not be ascertained. Whereas generation of hazimycins from tyrosine was established by using DL-[β-^{13}C]tyrosine. Labeled ^{13}C was well incorporated in hazimycin factors at their 3- and 3'-positions (Scheme 1).



Scheme 1. Incorporation of labeled carbon of tyrosine into 3, 3'-position of Hazimycin



Scheme 2. Biosynthetic pathway for the generation of cyclopentenyl isocyanide

3.1.2. Biosynthesis of cyclopentenyl isocyanides: Regarding the biosynthesis of cyclopentenyl isocyanides, it seems from their structural considerations that they may not be derived from amino acids. But it is observed that cyclopentenyl isocyanides are formed following a polyketide route with the cleavage of hydroxyphenyl ring of tyrosine (Scheme 2). Cyclisation to cyclopentenyl ring system occurs involving the carbon of carboxylic acid of α–amino acid moiety and the α–carbon of α,β–unsaturated aldehyde.

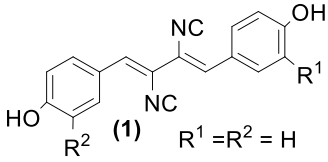
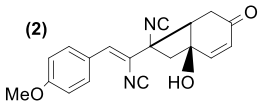
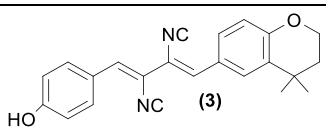
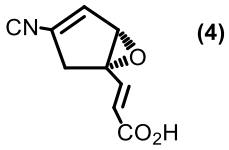
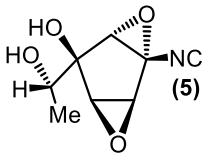
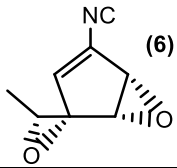
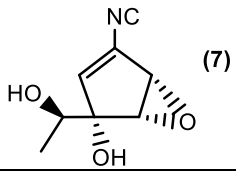
3.1.3. Biosynthesis of mannitol diester: Regarding the biosynthesis of mannitol diester **13**, it was observed that a mixture of glucose and sucrose acted better as a source of mannitol than the addition of mannitol itself. Valine acts as a source of the acid part of the diester (Edenborough, 1988).

3.1.4. Biosynthesis of indole isocyanide: Biosynthesis of indole isocyanide **11** and **12** were not studied but anticipated to be derived from tryptophan.

3.2. Biosynthesis of marine isocyanides. Marine isocyanides are generally associated with corresponding isothiocyanate and formamide. It has been proved that isocyanide was not formed by dehydration of corresponding *N*-substituted formamide in the system but reverse may take place by hydration. From the structures of the marine isocyanides it has been observed that

marine isocyanides are appropriately functionalized sesquiterpenoids or diterpenoids. These genaralizations have been varified successfully with respect to axisonitrile-1 **16** (Adinolfi, 1977) and 9-isocyanopupukeanane **31**(Hogadone, 1984). Biosynthesis of isonitriles in marine sponges differ fundamentally from those of micro-organism in terrestrial isocyanides.

Table 1. Terrestrial Isocyanides

Entry	Terrestrial isocyanides	Structure	Source	Activities
1	Xanthocillin X	 (1) $R^1 = R^2 = H$	*Penicillium notatum*	Antibiotic activity against Gram +ve, Gram –ve bacteria, pathogenic fungi, yeasts and are effective against micro organisms which are resistant to Penicillin and sulfonamides
2	Xanthocillin Y_1	$R^1 = OH, R^2 = H$		
3	Xanthocillin Y_2	$R^1 = R^2 = OH$		
4	Xanthocillin type	 (2)		Antibiotic MK4588
5	Xanthoascin	 (3)	*Aspergillus candidus*	Exhibited hepato- and cardio- toxicity and teratogenicity in experimental animals.
6	Dermadin	 (4)	*Trichoderma viride and T. koningii*	Antibiotic activity against Gram +ve, Gram –ve bacteria and wide variety of fungi
7	Trichoviridine	 (5)	*Trichoderma viride and T. koningii*	Fungicide. Active against *Escherichia coli* and Trichophytonasteroides.
8	Isonitrin A	 (6)	*Trichoderma harzianum*	
9	Isonitrin B	 (7)	*Trichoderma hamatum and T. koningii*	Active against Gram +ve, Gram –ve bacteria.

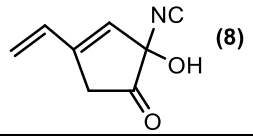
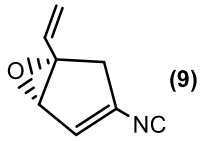
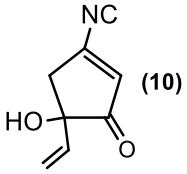
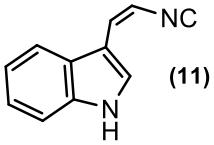
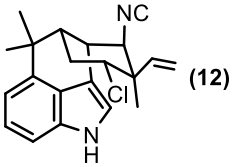
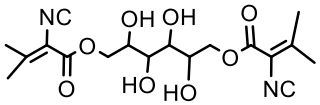
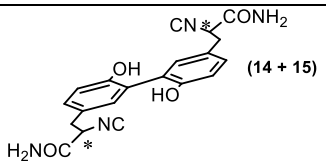
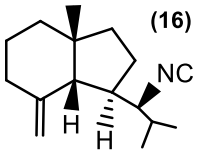
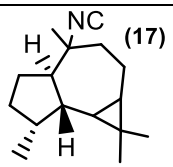
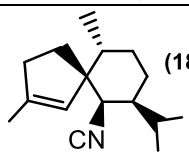
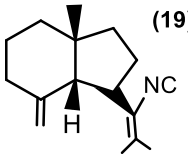
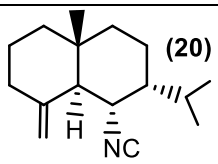
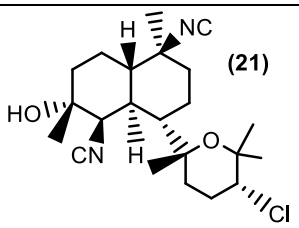
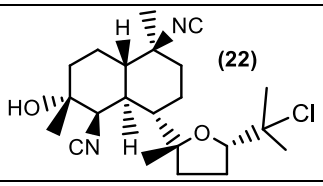
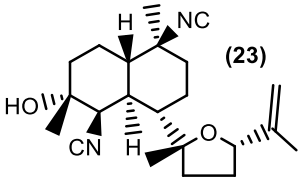
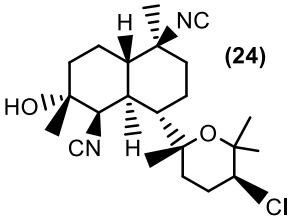
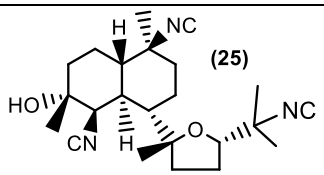
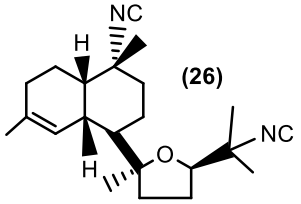
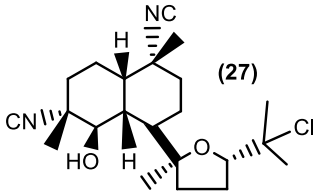
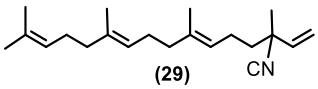
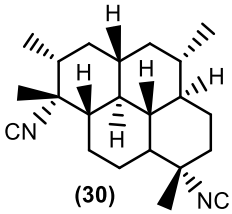
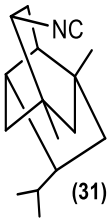
10	Isonitrin D	 (8)	*Trichoderma harzianum*	
11	Homothallin I	 (9)	*Trichoderma koningii*	Induce production of oospores in *Phytopthera cinnamoni*
12	Homothallin II	 (10)		
13	Indolylacrylo isonitrile	 (11)	*Pseudomonus sp.*	Active against *Staphylococcus aureus*
14	Hapalindole A	 (12)	*Hapalasiphon fontinalis*	Antibiotic
15	Mannitol diester	 (13)	*Pyrenochaeta sp.*	Antibiotic A32390A against Gram +ve bacteria; Inhibits dopamine-β-hydroxylase, fungistatic towards pathogen *Candida albicans*
16	Hazimycin5 (**14**) (*racemic*) (RR +SS)	 (14 + 15)	*Micro--monospora echinospora*	Broad spectrum antibiotic
17	Hazimycin6 (**15**) (*meso*) (RS)			

Table 2. Marine Isocyanides

Entry	Marine isocyanides	Structure	Source	Activities

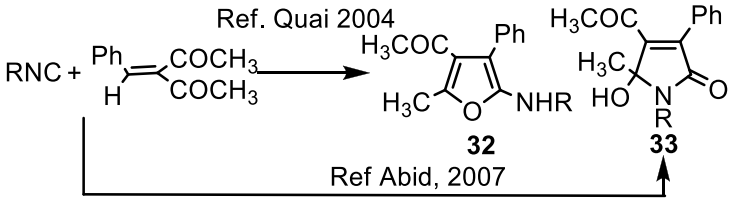
1	Axisonitrile 1	 (16)	*Axinella cannabina*	Tested as feeding deterant to marine and fresh water fish. They are toxic to fishes. Antibiotic activity.
2	Axisonitrile 2	 (17)		
3	Axisonitrile 3	 (18)		
4	Axisonitrile 4	 (19)		
5	Acanthellin 1	 (20)	*Axinella cannabina*	Antimicrobial activity.
6	Kalihinol A	 (21)	*Acanthella acuta*	Active against *Bacillus subtilis, Staphylococcus aureus* and *Candida albicans*
7	Kalihinol B	 (22)	*Acanthella sp.*	
8	Kalihinol C	 (23)	*Acanthella sp.*	
9	Kalihinol E	 (24)	*Acanthella sp.*	

10	Kalihinol F	 (25)	*Acanthella sp.*	Active against *Bacillus subtilis*, *Staphylococcus aureus* and *Candida albicans*
11	Kalihinene	 (26)	*Acanthella klethra*	Induce production of oospores in *Phytopthera cinnamoni*
12	Isokalihinol B	 (27)	*Acanthella klethra*	
14	Isocyano diterpene	 (29)	*Halicondria spp.*	
15	Diisocyano adociane	 (30)	*Adocia sp.*	Marked activity against Gram +ve bacteria.
16	Isocyano- -pupukaenane	 (31)	Genus *Hymeniacidon*	

4. Application of isocyanide in synthesis:

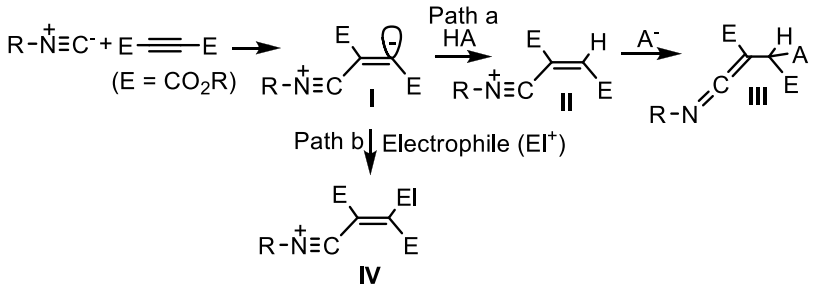
The general structural representation for isocyanide ($R\text{-}N^{+}\equiv C^{-}$) clearly demonstrates its nucleophilic / basic character; after exhibiting the nucleophilic or basic nature it captures E^{+} or H^{+} to form $R\text{-}N^{+}\equiv C\text{-}E$/ $R\text{-}N^{+}\equiv C\text{-}H$ and becomes an electrophile. This basic principle is exhibited in most of the reactions of isocyanide. Till date many reports on the application of isocyanide in organic synthesis have appeared in the literature. To make a general survey, common reactions of isocyanide are classified into a few classes for the ease of understanding.

4.1. Reaction of isocyanide with α, β–unsaturated carbonyl compound: Reaction of isocyanide with benzylidene acetylacetone was initially reported to form 2-aminofuran derivative **32** (Quai, 2004), but later the structure was revised to be pyrroline-2-one **33** (Scheme 3). Addition of triplet oxygen on **32** followed by rearrangement and cleavage of peroxo linkage leads to **33** (Abid, 2007).



Scheme 3. Reaction of isocyanide with α, β–unsaturated carbonyl compound

4.2. Reaction of isocyanide involving dialkyl acetylenedicarboxylate: Isocyanides react with dialkyl acetylenedicarboxylate (CO_2R is represented by E) to form **I**, which can react in two ways: (i) Abstracts a proton from HA and then A^- attacks the electron deficient centre (Path-a); (ii) Intermediate **I** interacts with an electrophile (Path-b) (Scheme 4):

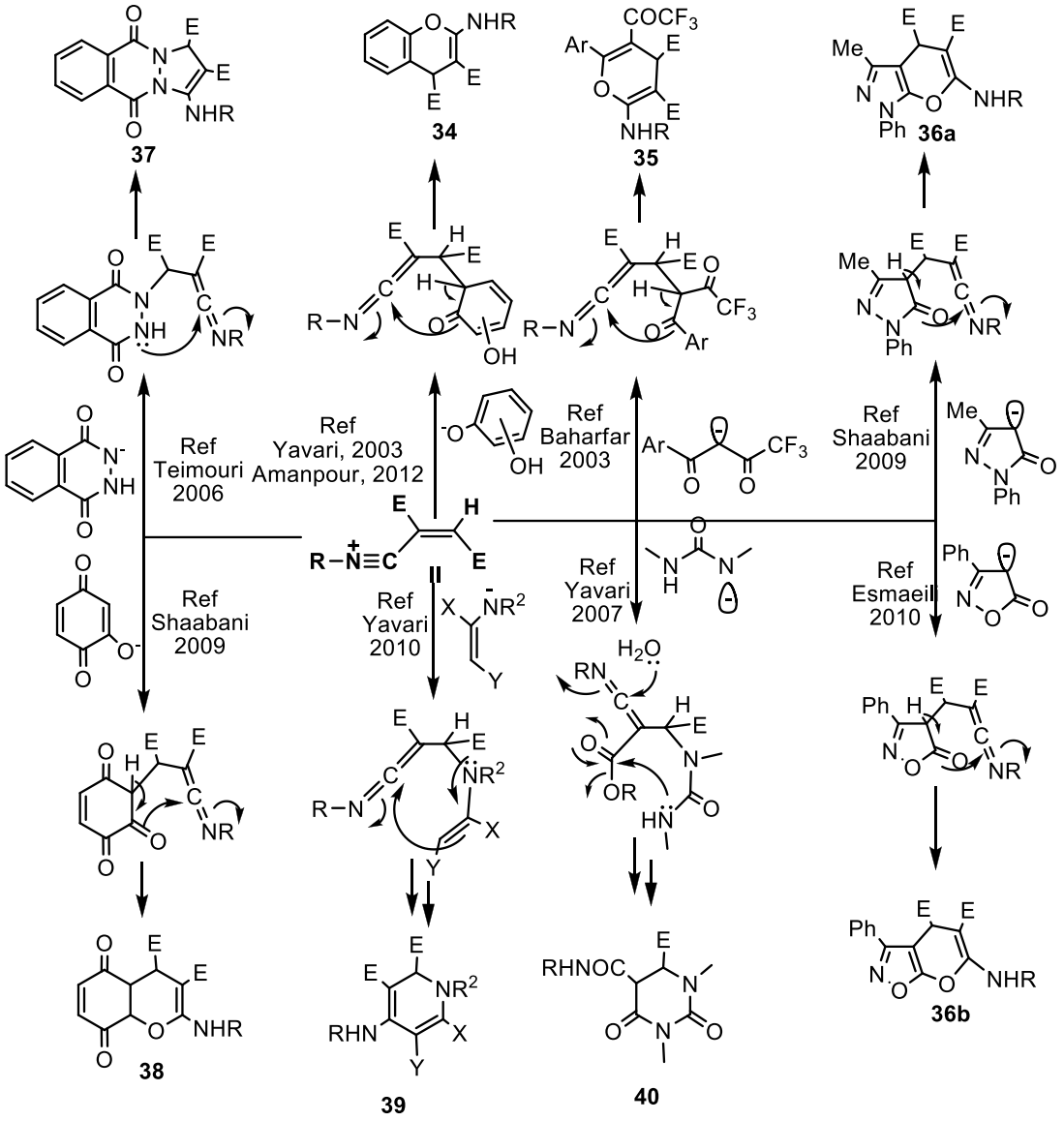


Scheme 4. Reactions of isocyanide involving dialkyl acetylenedicarboxylate

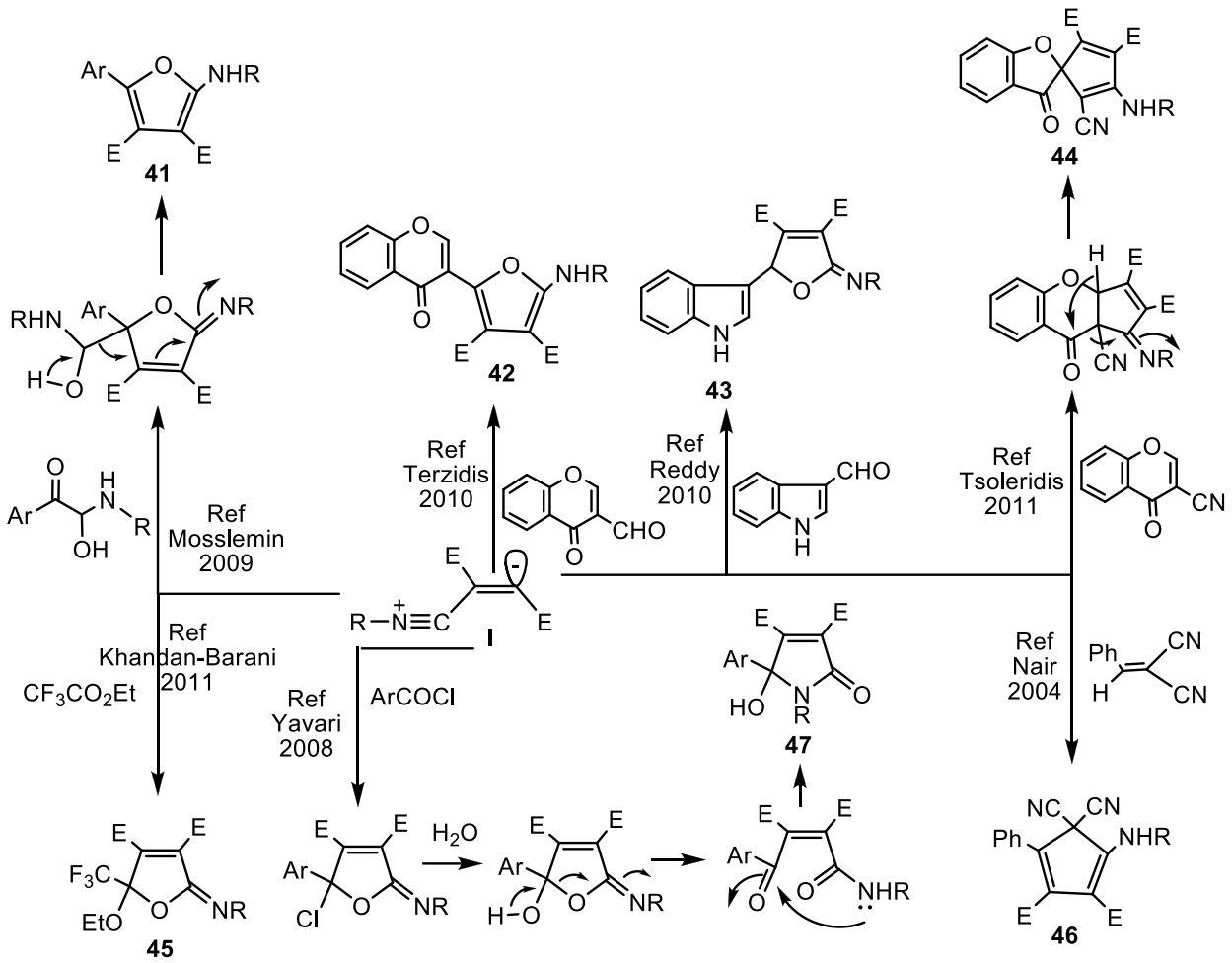
(i) Intermediate **I** can take up a proton from compound (HA) having acidic hydrogen to form **II** (Path-a) (Scheme 4), which is then readily attacked by the conjugate base A^- to form ketenimine **III**. This ketenimine **III** can transform itself into different heterocycles depending on the nature of conjugate base ($\mathbf{A^-}$). A few reactions of the intermediate **II** with different conjugate bases bearing negative charge on oxygen (enolate type), nitrogen and carbon are depicted with corresponding references (Scheme 5).

(ii) Another mode of reaction is that the carbanion **I** (Scheme 4, path-b) can attack electrophiles (El^+). α, β–Unsaturated -carbonyl, -nitriles, alkylidene malononitrile, α–hydroxyketone, reactive ester, acid chloride are used as electrophilic species. Mostly heterocycle-based α, β–unsaturated -carbonyls and -nitriles are exploited. Initial attack of

carbanion **I** followed by cyclisation leads to densely substituted heterocyclic compounds. Different reactions with references are depicted in Scheme 6.



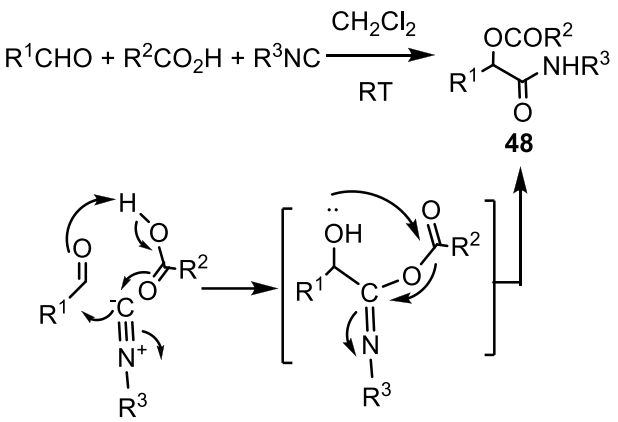
Scheme 5. Reactions of the intermediate **II** with different conjugate bases



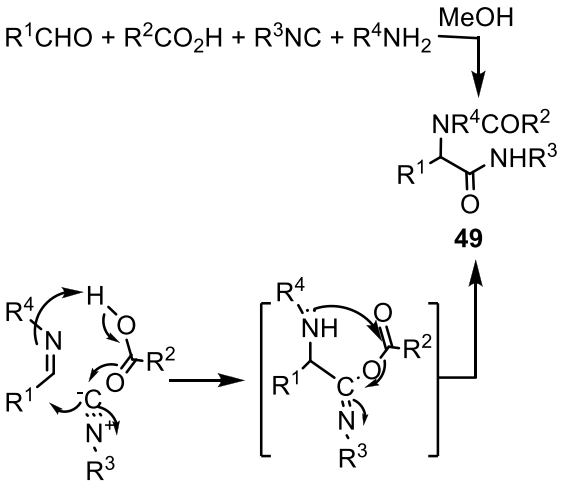
Scheme 6. Reactions of the carbanion **I** with different electrophiles

4.3. Passerini reaction and Ugi reaction:

During 1920s Mario Passerini first introduced an isocyanide-induced three component reaction (Passerini-3CR) involving aldehyde or ketone and carboxylic acid as the other two components to produce α-acyloxycarboxamide **48**. This reaction was found to be faster in aprotic solvent than in protic solvent and supports a non-ionic mechanism (Scheme 7). The development of a chiral centre in this reaction demands for stereoselective synthesis. The involvement of all three molecules in the transition state predicts a diastereoselective Passerini reaction by incorporation of a chiral centre in any one of these components and indeed asymmetric synthesis involving Passerini reaction has been accomplished.



Scheme 7. Passerini 3-Component Reaction



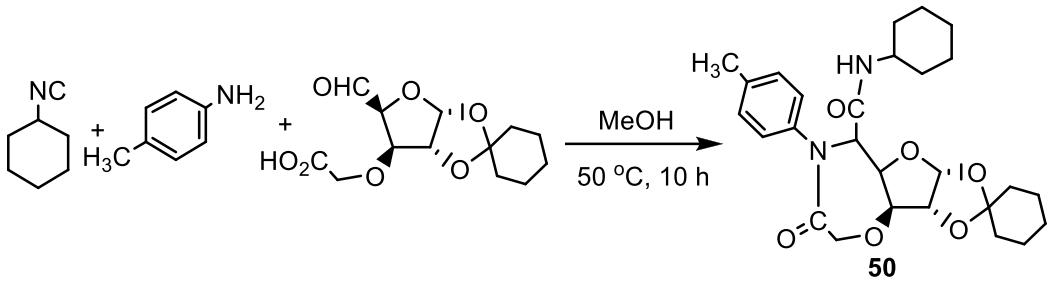
Scheme 8. Ugi 4-Component Reaction

In 1959, Ivary Ugi developed a four componment reaction (Ugi-4CR) involving isocyanide, carbonyl compound, carboxylic acid and amine to produce α-acylaminocarboxamide **49** (Ugi, 1962). Although the mechanism of this reaction is still a matter of debate, a plausible mechanism is depicted in scheme 8. The structure of compound **49** appears to be a dipeptide involving R^2CO_2H, $R^1CH(NHR^4)CO_2H$ and R^3NH_2 where the R^2CO_2H and R^3NH_2 are the acid and amine parts of other two aminoacids. This reaction has also been extended to diastereoselective reactions by using appropriate chiral components and helps study peptidomimetics. Ugi reaction has drawn much attention for its wide range of synthetic application. A few variations of this methodology are mentioned here.

4.3.1. Having two functional groups on a single component: Use of suitable substrate having two of the four required functional groups in Ugi reaction would lead to the formation of cyclic compound.

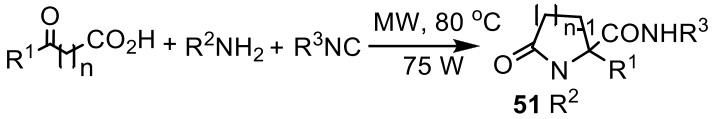
(a) The mostly studied system is with molecules having carbonyl group and carboxylic acid functionalities in the same molecule.

3-Carboxy-tethered sugar aldehyde with arylamine and isocyanide produces furo-oxazepine derivative (Scheme 9) (Reddy, 2012).



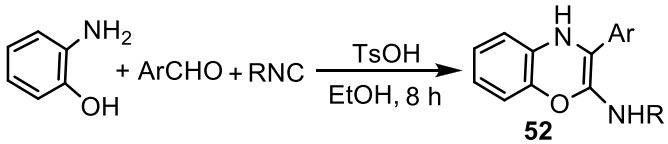
Scheme 9. Ugi reaction involving **c**arboxy-tethered aldehyde, arylamine and isocyanide

Formation of five or six membered lactams **51** have been reported by solvent-free MW-irradiation (Scheme 10) (Jida, 2010).[9]

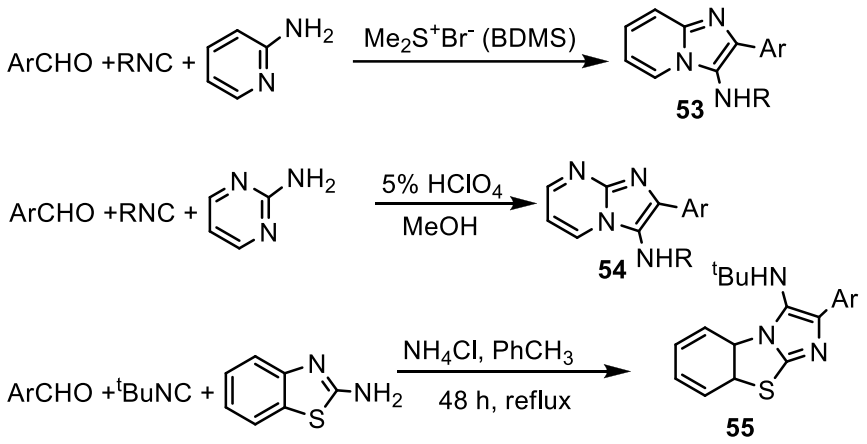


Scheme 10. Solvent-free Ugi reaction involving **c**arboxy-tethered ketone, amine and isocyanide

(b) Amine and carboxylic acid in the same molecule would not produce any effective ring other than their lactam formation. But use of *o*-aminophenol with aldehyde and isocyanide produces benzoxazine **52** (Scheme 11) (Heravi, 2009).



Scheme 11. Ugi reaction involving aminophenol, aldehyde and isocyanide

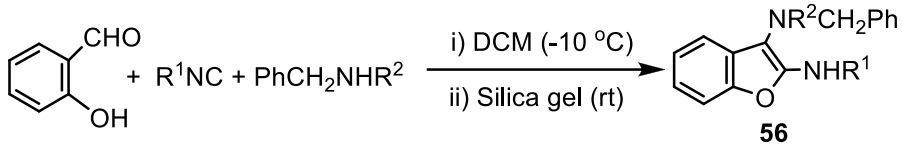


Scheme 12. Multicomponent reaction involving aldehyde, isocyanide and amidine moieties

4.3.2. Different types of amine used in Ugi-type reaction:

(a) 2-Aminopyridine, 2-aminopyrimidine or 2-aminobenzthiazole having an in-built amidine moiety produce pyrido-imidazoles **53** (Khan, 2012), pyrimido-imidazoles **54** (Bienayme, 1998), or benzthiazolo-imidazole **55** (Sun, 2008) (Scheme 12).

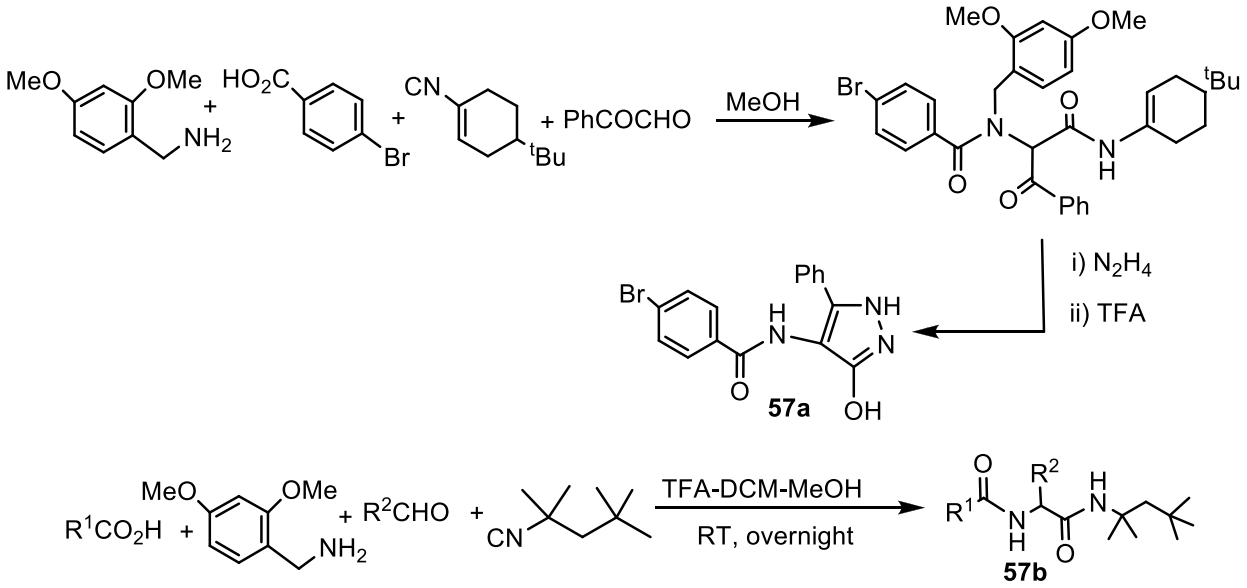
(b) Secondary amine has been employed with salicylaldehyde and isocyanide to produce benzofuran **56** (Scheme 13) (Ramazani, 2009).



Scheme 13. 3-component reaction involving salicylaldehyde, isocyanide and secondary amine

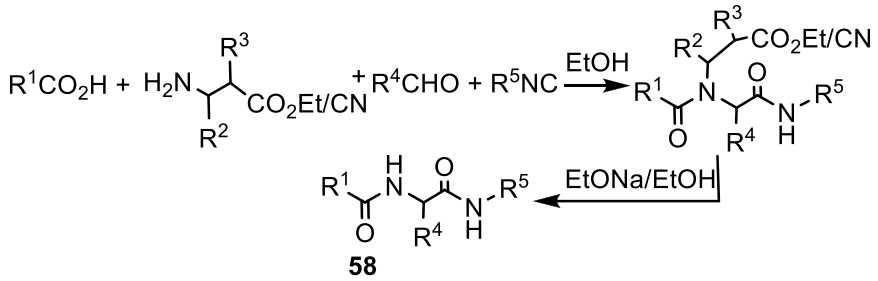
4.3.3. Use of synthetic equivalent of ammonia and hydrogen isocyanide:

(a) Synthetic equivalent of ammonia: It is to be mentioned that substituted benzyl amines are employed in Ugi reaction as masked ammonia. Debenzylation (demasking) of Ugi product is commonly accomplished by trifluoroacetic acid (TFA) (Scheme 14) (Shaw, 2012).



Scheme 14. Use of benzylamine derivative as masked ammonia in Ugi reaction

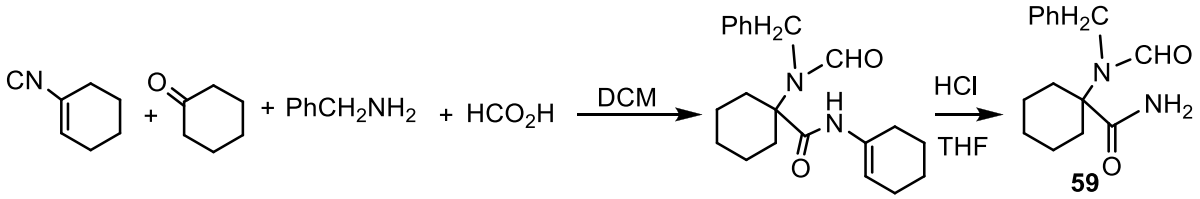
β-Aminoester or nitrile can also be considered as synthetic equivalent of ammonia (Scheme 15) (Marcaccini, 2005).



Scheme 15. Use of β-aminoester or nitrile as masked ammonia in Ugi reaction

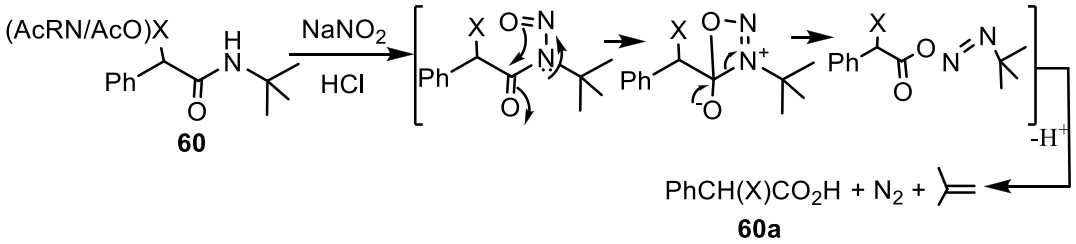
(b) Synthetic equivalent of hydrogen isocyanide:

Armstrong (Keating, 1995) first established cyclohexene-1-yl isocyanide as masked hydrogen isocyanide (Scheme 16).



Scheme 16. Use of cyclohexene-1-yl isocyanide as masked hydrogen isocyanide in Ugi reaction

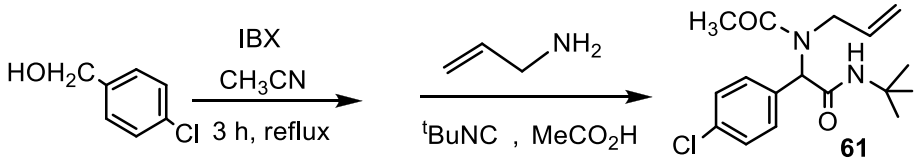
Use of *tert*-butyl isocyanide in Passerini or Ugi reaction forms *N*-tert-butyl amide **60**, which can be converted into carboxylic acid **60a** by nitrosation (Scheme 17) (Le, 2011).



Scheme 17. Conversion of *N*-tert-butyl amide into carboxylic acid by nitrosation

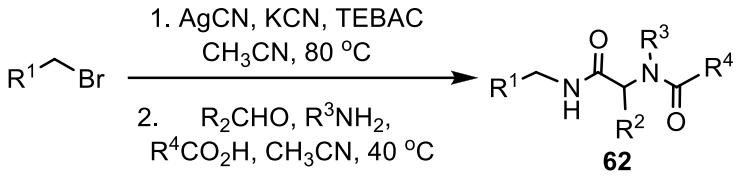
4.3.4. Ugi reactions involving precursors of some components:

(a) Using primary alcohol as a precursor of aldehyde (Scheme 18) (Drouet, 2013).



Scheme 18. Use of primary alcohol as a precursor of aldehyde in Ugi reaction

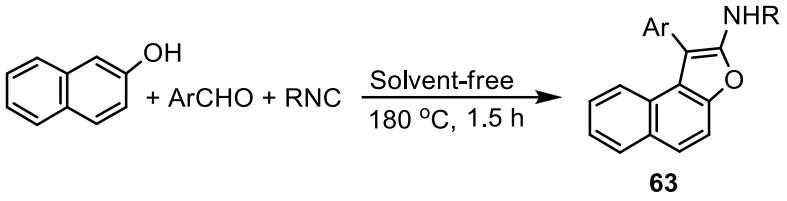
(b) *In situ* generation of isocyanide has been accomplished by using alkyl halide and AgCN (Scheme 19, TEBAC stands for triethyl benzyl ammonium chloride) (Kaim, 2009).



Scheme 19. *In situ* generation of isocyanide in Ugi reaction

4.3.5. Passerini type reactions replacing some original components:

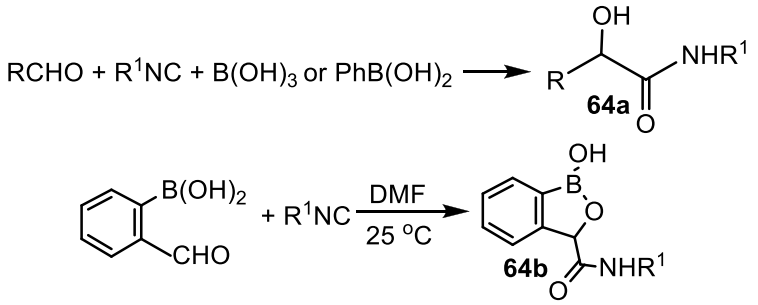
(a) Use of phenolic compound in place of acid: β-Naphthol was used in place of carboxylic acid in a Passerini type reaction to produce 2-aminonaphthofuran **63** (Scheme 20) (Adib, 2009).



Scheme 20. Use of phenols in place of carboxylic acid in Passerini reaction

(b) Use of boron acids in place of carboxylic acid:

Use of boric acid or phenyl boronic acid in modified Passerini reaction produces α-hydroxyamide **64a** whereas 2-formylphenyl boronic acid yields dihydrobenzooxaborole **64b** (Scheme 21) (Kumar, 2010).



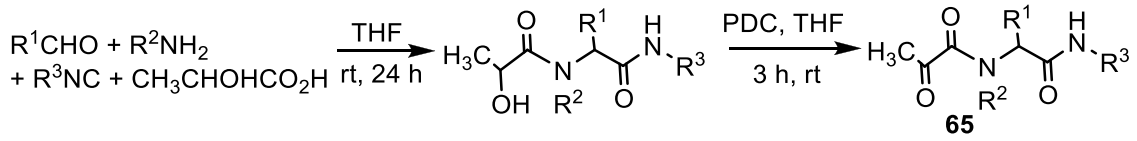
Scheme 21. Use of boron-acids in place of carboxylic acid in Passerini reaction

4.3.6. Post Passerini- and Ugi- condensation modifications:

Passerini-3CR and Ugi-4CR have opened many avenues for the construction of wide variety of organic molecules. Three components (acid, aldehyde and isocyanide) in Passerini-3CR and four components (acid, aldehyde, amine and isocyanide) in Ugi-4CR can be chosen in such a manner that after formation of α-acyloxyamide in Passerini-3CR and α-acylaminoamide in Ugi-4CR

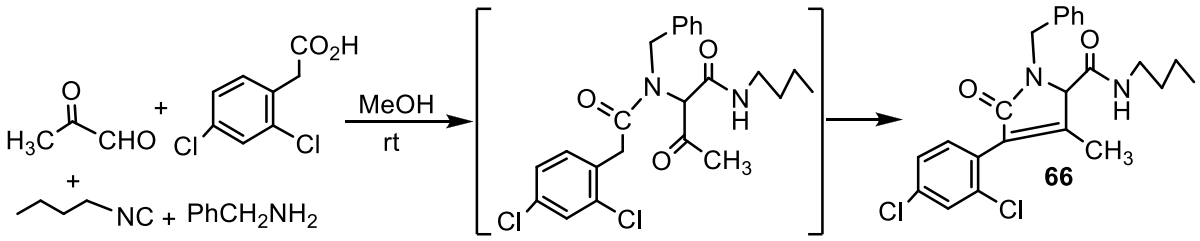
possibility of a secondary reaction in them arises. Depending on the nature of this secondary reaction, post Passerini-3CR and Ugi-4CR modifications have been classified as follows:

4.3.6.1. Ugi-4CR followed by oxidation: Ugi-4CR was accomplished using lactic acid as carboxylic acid component and the product was subsequently oxidized to get pyruvamide **65** by a one-pot two-step reaction (Scheme 22) (Nakamura, 2000).[63]



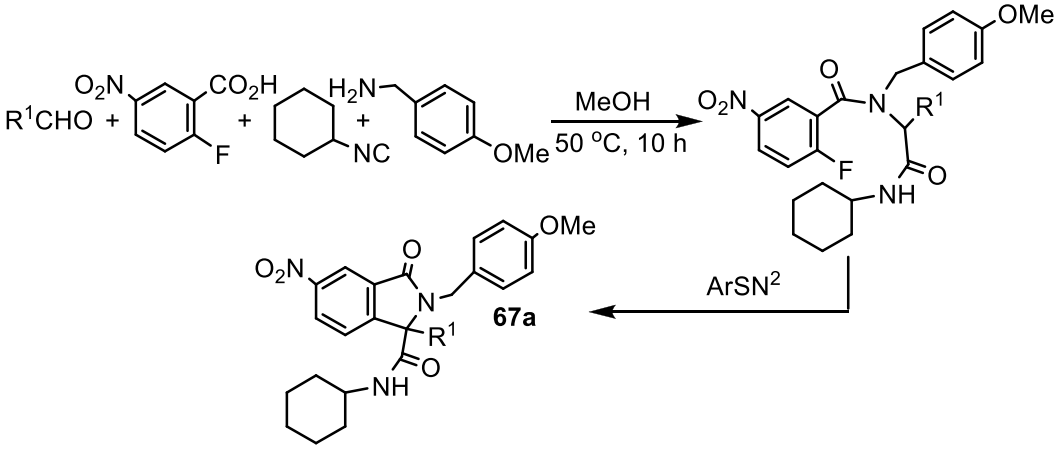
Scheme 22. Ugi-4CR followed by oxidation

4.3.6.2. Ugi-4CR followed by aldol condensation: Aldehyde having another carbonyl group at a suitable position facilitates aldol condensation in the Ugi condensation product to produce pyrroline derivative **66** (Scheme 23) (Xu, 2013).

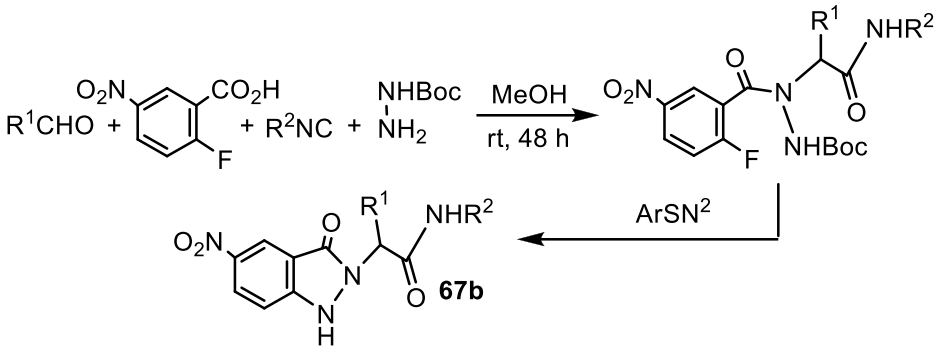


Scheme 23. Ugi-4CR followed by aldol condensation

4.3.6.3. Ugi-4CR followed by ArSN^2 reaction: The acid component has been decorated for an aromatic nuclephilic substitution in the following reactions (Scheme 24a) (Trifilenkov, 2007).



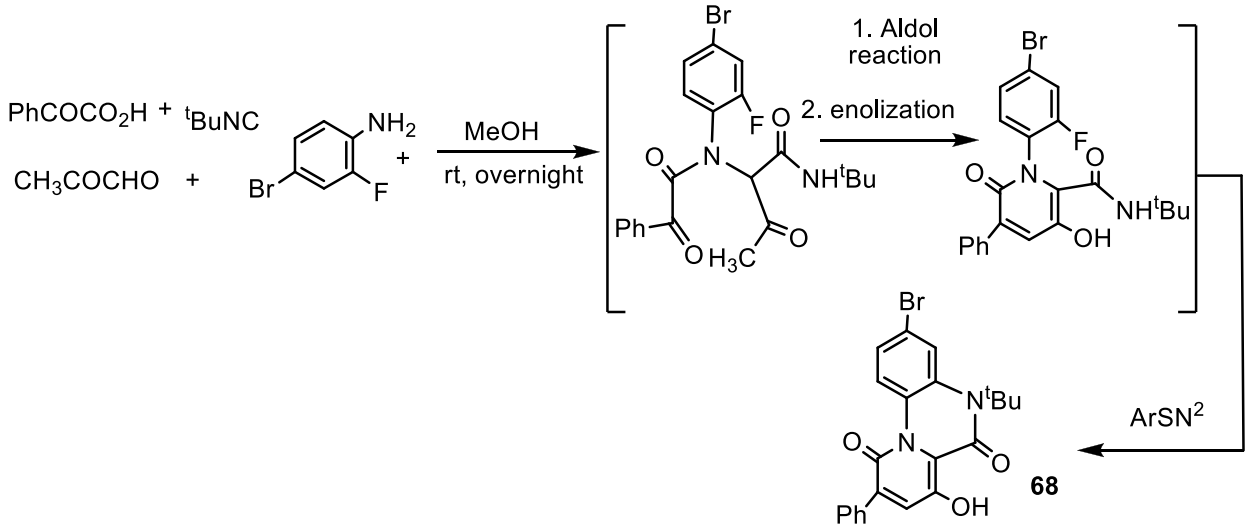
Scheme 24a. Ugi-4CR followed by ArSN^2 reaction using C-nucleophile



Scheme 24b. Ugi-4CR followed by $ArSN^2$ reaction using N-nucleophile

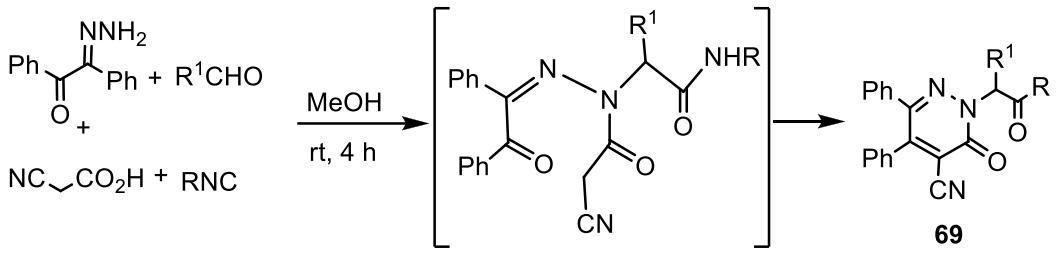
Use of suitable hydrazine derivative as amine component gives indazolinone **67b,** where second NH-function of hydrazine acts as nucleophile (Scheme 24b) (Tempest, 2001).

4.3.6.4. Ugi-4CR followed by aldol condensation and $ArSN^2$ reaction: Appropriate substitutions on carboxylic acid component and aldehyde component facilitate aldol reaction and suitably substituted amine favours the $ArSN^2$ reaction to form **68** (Scheme 25) (Marcos, 2003).



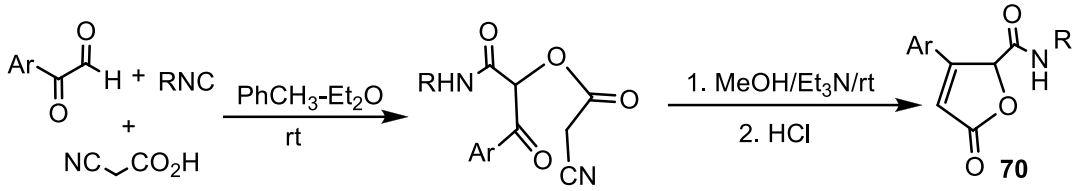
Scheme 25. Ugi-4CR followed by aldol condensation and $ArSN^2$ reaction

4.3.6.5. Ugi-4CR followed by Knoevenagel reaction: Use of benzilmonohydrazone and cyanoacetic acid as amine and acid components respectively in an Ugi reaction produced a skeleton which is susceptible towards Knoevenagel reaction to produce 2,3-dihydrooxopyridazine **69** (Scheme 26) (Bossio, 1994).



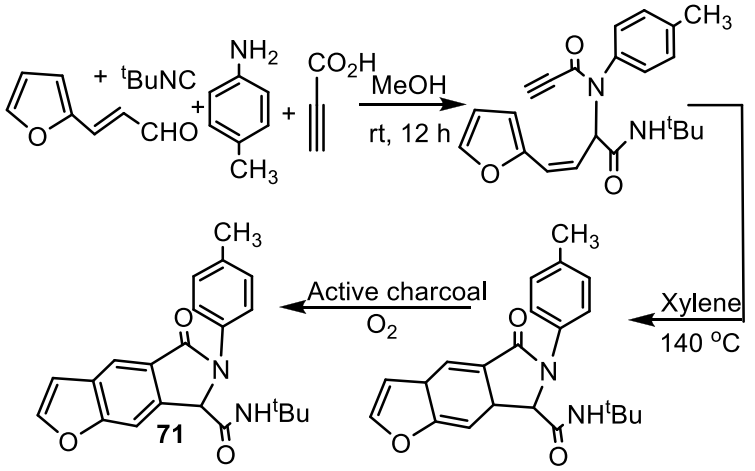
Scheme 26. Ugi-4CR followed by Knoevenagel reaction

4.3.6.6. Passerini-3CR followed by Knoevenagel reaction: Passerini-3CR followed by Knoevenagel reaction has been performed using arylglyoxal, isocyanide and cyanoacetic acid to produce butenolide **70** (Scheme 27) (Bossio, 1993).



Scheme 27. Passerini-3CR followed by Knoevenagel reaction

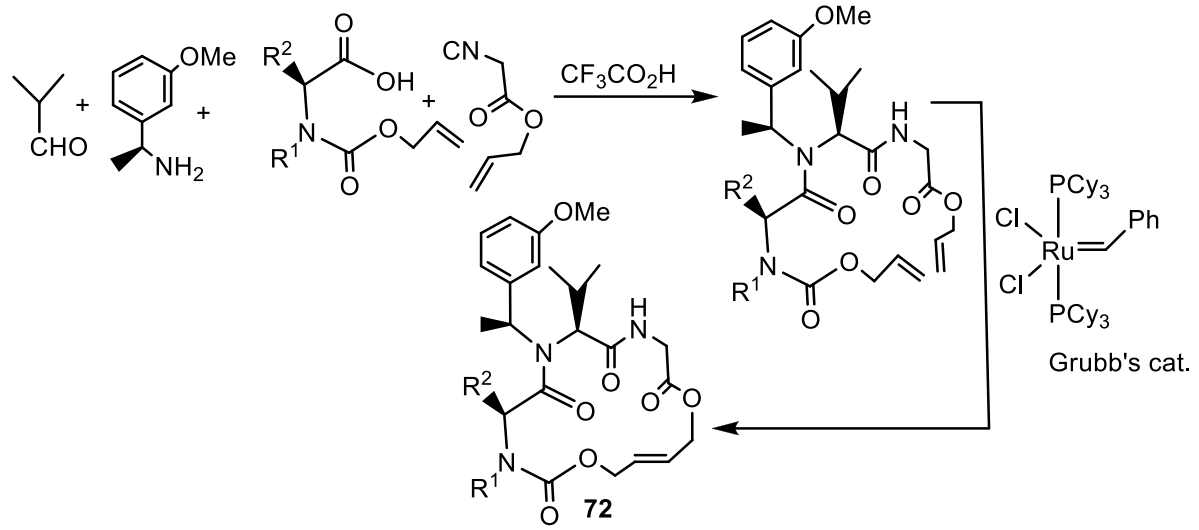
4.3.6.7. Ugi-4CR followed by Diels-Alder reaction: A diene in the aldehyde component and an alkyne in the carboxylic acid component of Ugi-4CR lead to the formation of Ugi condensation product which undergoes intramolecular Diels-Alder reaction followed by oxidation to form **71** (Scheme 28) (Lu, 2005).



Scheme 28. Ugi-4CR followed by Diels-Alder reaction

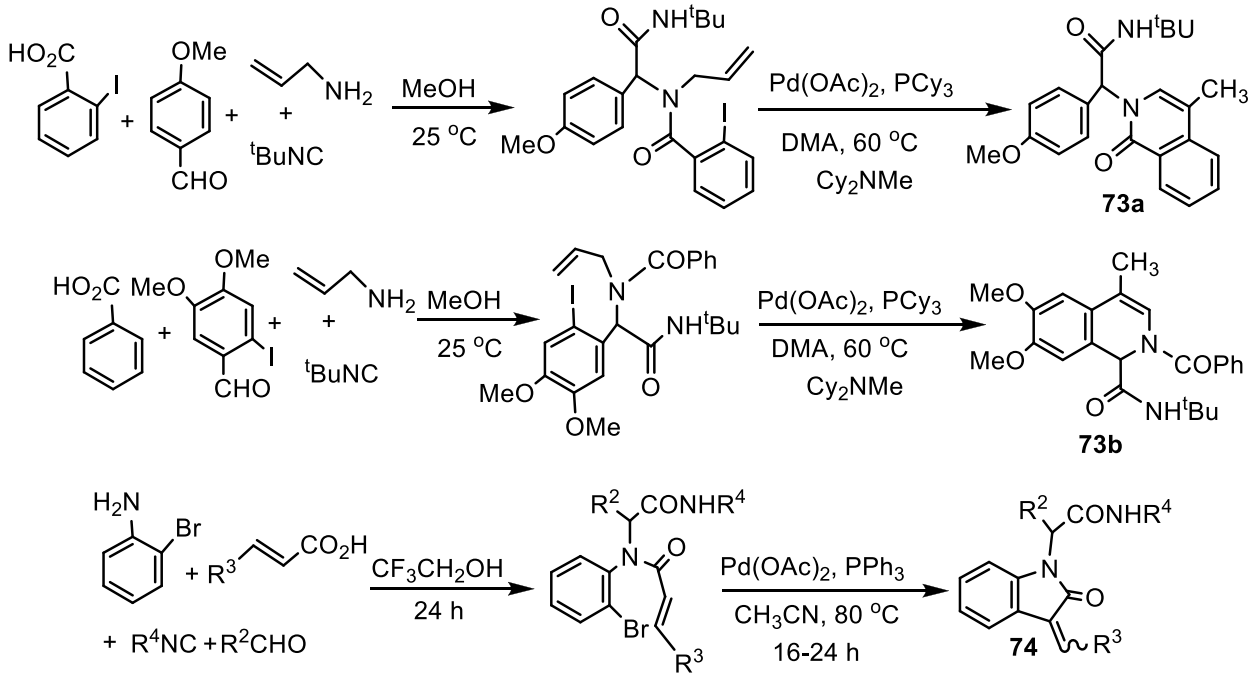
4.3.6.8. Ugi-4CR followed by ring closing metathesis (RCM): Suitably placed functional groups in different components of Ugi-4CR can form such a Ugi product which is

further prone towards RCM reaction in the presence of Grubb's catalyst to form macrocyclic compound **72** (Scheme 29) (Hebach, 2003).



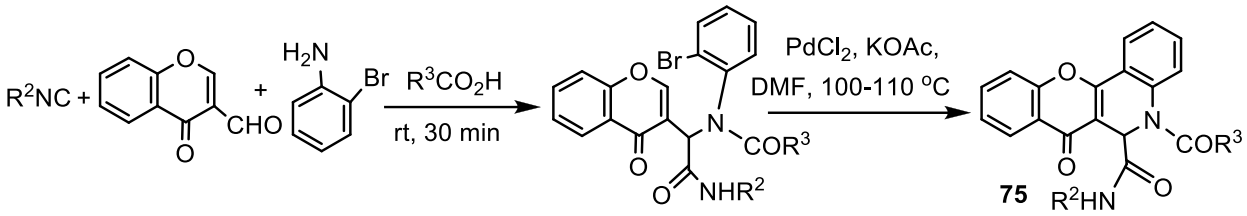
Scheme 29. Ugi-4CR followed by ring closing metathesis (RCM)

4.3.6.9. Ugi-4CR followed by Heck coupling: A considerable number of reports on Ugi-4CR followed by Heck reaction have appeared in the literature. The halogen atom may be suitably placed on the acid or aldehyde (Umkehrer, 2006) or amine (Xiang, 2004) component and olefinic bonds are placed mostly on amine component (Umkehrer, 2006) or in acid component (Xiang, 2004) (Scheme 30).



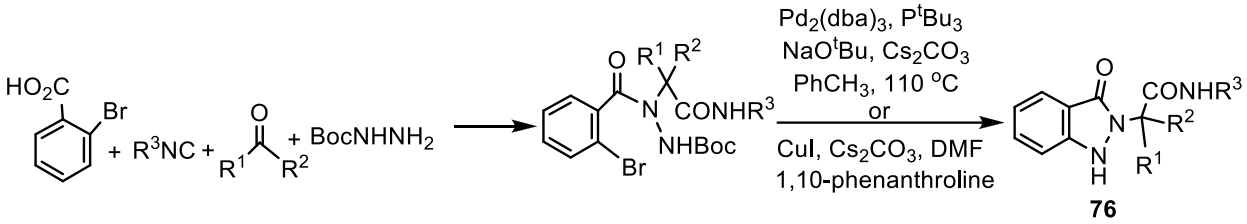
Scheme 30. Ugi-4CR followed by Heck coupling

From the author's group such reaction involving 3-formylchromone having double bond on the aldehyde part and halogen on the amine part has been accomplished and a ligand-free Pd-catalyzed intramolecular arylation of chromone has been reported for the synthesis of chromenoquinoline **75** (Scheme 31) (Ghosh, 2013).



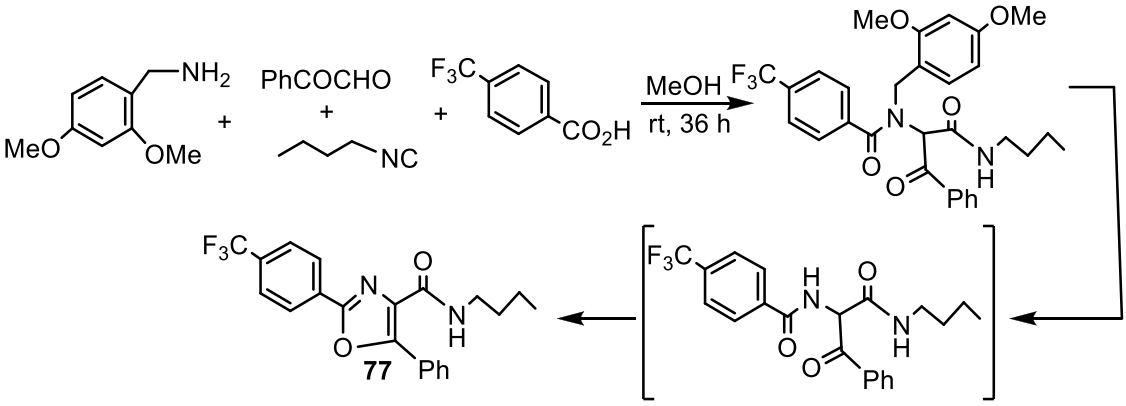
Scheme 31. Ugi-4CR followed by C-C bond formation

4.3.6.10. Ugi-4CR followed by C-N bond formation: Formation of C-N bond on Ugi product has been considered earlier by $ArSN^2$ reaction (section 4.3.6.3). In this section transition metal-catalyzed C-N bond formation has been considered (Scheme 32) (Welsch, 2012).



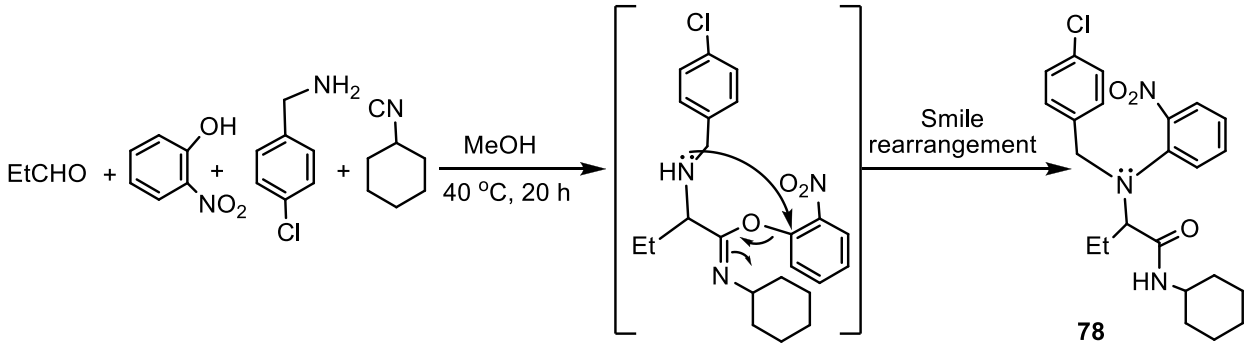
Scheme 32. Ugi-4CR followed by C-N bond formation

4.3.6.11. Ugi-4CR followed by Robinson Gabriel synthesis: 2,4-Dimethoxybenzylamine has been utilized as synthetic equivalent of ammonia (section 4.3.3. a). In this section this chemistry has been utilized for further cyclization of the Ugi product. Ugi product was formed using arylglyoxal as aldehyde source along with isocyanide, carboxylic acid and the aforementioned amine. The formed Ugi product on debenzylation forms α–*N*-acylaminoketone which on cyclodehydration readily undergoes Robinson-Gabriel synthesis of oxazole **77** in the presence of H_2SO_4 (Scheme 33) (Shaw, 2012).



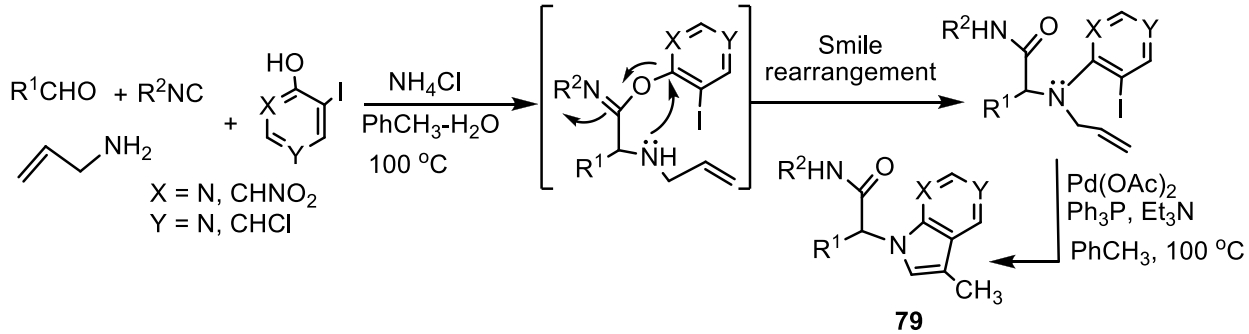
Scheme 33. Ugi-4CR followed by Robinson Gabriel synthesis

4.3.6.12. Ugi-4CR followed by Smile rearrangement: Use of *o*-nitrophenol as the acid component in Ugi-4CR leads to such a product which becomes prone towards Smile rearrangement (Scheme 34) (Kaim, 2010).



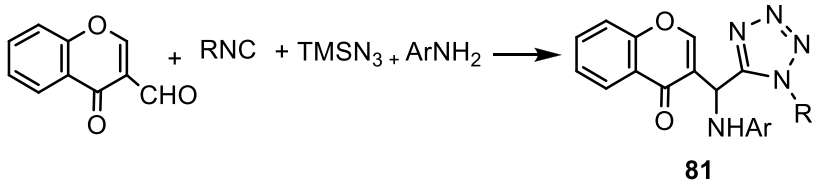
Scheme 34. Ugi-4CR followed by Smile rearrangement

4.3.6.13. Ugi-4CR followed by Smile rearrangement and then Heck reaction: Halogen substituted *o*-nitrophenol or 2-hydroxypyridine or 2-hydroxypyrimidine can participate as acid component and allyl amine as an amine component along with aldehyde and isocyanide in Ugi-4CR. The product arises from Smile rearrangement of the Ugi product bears suitably disposed halogen and olefin to undergo Heck reaction (Scheme 35) (Kaim, 2008).



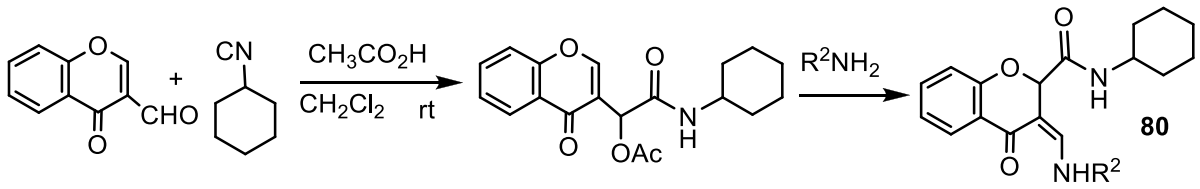
Scheme 35. Ugi-4CR followed by Smile rearrangement and then Heck reaction

4.3.6.14. Ugi-4CR followed by cyclization involving azide group: $TMSN_3$ is used in Ugi-4CR in place of carboxylic acid resulting a tetrazole (Scheme 36) (Cano, 2014).



Scheme 36. Ugi-4CR followed by cyclization involving azide group

4.3.6.15. Passerini-3CR followed by nucleophilic substitution: The authors group has shown that the Passerini condensation product arising from 3-formylchromone, cyclohexyl isocyanide and acetic acid undergoes nucleophilic substitution of acyloxy group with primary aliphatic amine associated with a rearrangement. This rearrangement takes place by amine induced pyran-ring opening followed by cyclization with the expulsion of acetoxy group (Scheme 37) (Ghosh, 2016).

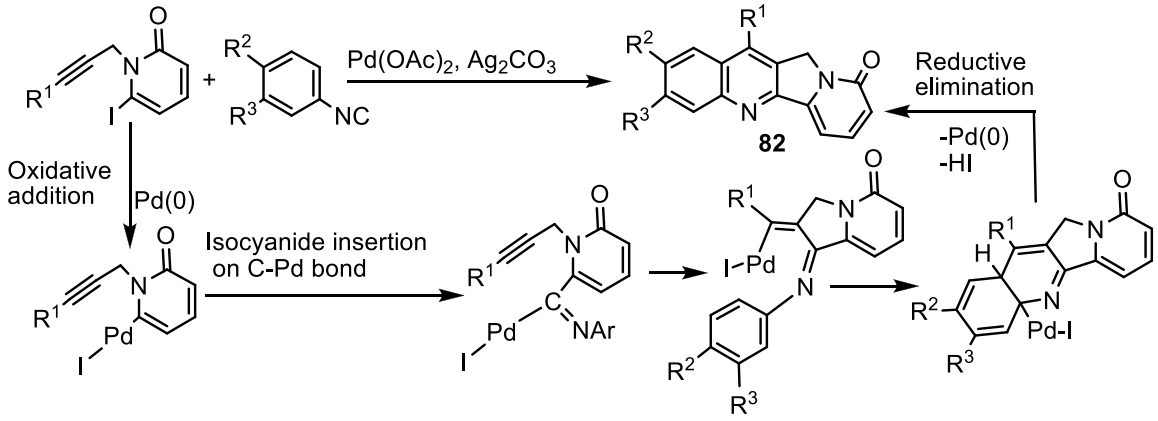


Scheme 37. Passerini-3CR followed by nucleophilic substitution

4.4. Isocyanide insertion reaction:

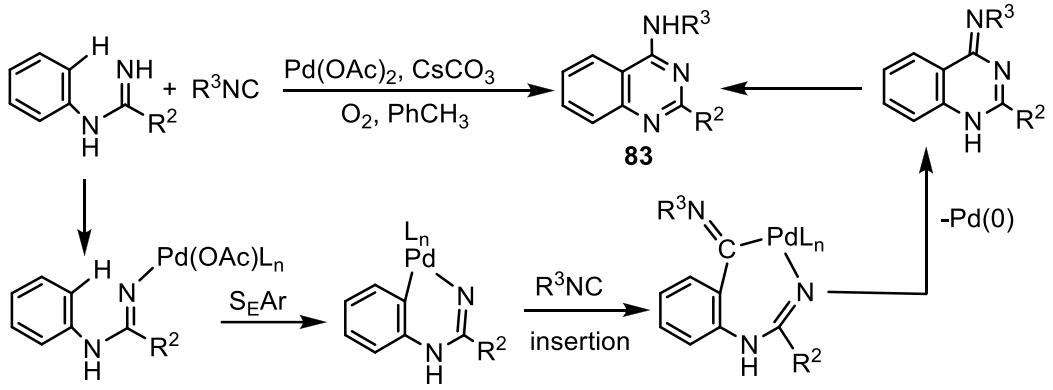
Isocyanide is isoelectronic with carbon monoxide. Akin to carbon monoxide, isocyanide also undergoes insertion reaction. Isocyanide insertion often becomes a substitute of CO insertion. Commonly such reactions are accomplished by Pd-catalyst.

4.4.1. Isocyanide insertion on C-halogen bond: It is depicted in scheme 38 (Curran, 2002).



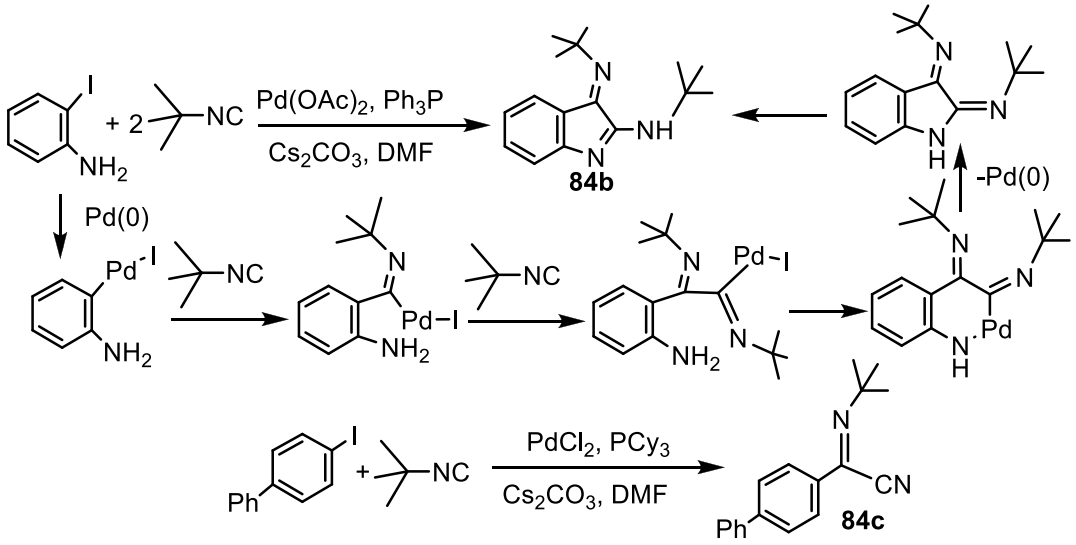
Scheme 38. Isocyanide insertion on C-halogen bond

4.4.2. Isocyanide insertion *via* C-H activation: Properly functionalized aromatic nucleus undergoes C-H activation by various transition metal catalysts and undergoes suitable functionalization at the C-H bond. The *ortho* hydrogen *N*-arylamidine is activated by palladium catalyst and undergoes isocyanide insertion and finally cyclises to quinazoline derivative **83** (Scheme 39) (Wang, 2011).



Scheme 39. Isocyanide insertion *via* C-H activation

4.4.3. Double isocyanide insertion reaction: Isocyanides often polymerise in presence of transition metals. But control insertion of double isocyanide has now become a challenge to the organic chemists. A few reports of isocyanide double insertion have appeared for the synthesis of heterocycles and α-iminonitrile. Palladium-catalyzed synthesis of 3-iminoindol-2-amines **84a** (Pan, 2015) and α-iminonitriles **84b** (Chen, 2016) from aryl halides *via* isocyanide double insertion reaction has been reported (Scheme 40).



Scheme 40. Double isocyanide insertion reaction

5. Conclusion.

In conclusion, this short report on isocyanide is only a tip of the ice-berg of complete isocyanide history. Attempts are made to reflect a glimpse regarding its natural resources, biosynthesis, biological activities and chemical application in synthesis.

Acknowledgements. The author gratefully acknowledges the college authority for providing facilities.

References

1. Abid, M., Mahdavi, M., Noghani, M. A., Bijanjadeh, H. R. 2007. Reaction between isocyanides and chalcones: an efficient solvent-free synthesis of 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones. *Tetrahedron Lett*, 48: 8056-8059.
2. Adib, M., Mahdavi, M., Bagherzadeh, S., Bijanzadeh, H. R. 2009. Efficient and direct solvent-free synthesis of naphtho[1,2-*b*]furans, naphtho[2,1-*b*]furans, and furo[3,2-*c*]chromenes. *Synlett*, 20: 2542-2544.
3. Adinolfi, M., De Napoli, L., Di Blasio, B., Iengo, A., Pedone, C., Santacroce, C. 1977. The absolute configuration of the axane sesquiterpenes from the sponge *axinella cannabina*. *Tetrahedron Lett*, 18: 2815-2816.
4. Baharfar, R., Hosseini, J. 2003. The reaction between *tert*-butyl isocyanide and acetylenic esters in presence of 2-thenoyltrifluoroacetone: A synthesis of highly functionalized-4*H*-Pyrans, *J. Chem. Res*, 27: 616-617.
5. Baker, J. T., Wells, R. J., Oberhansli, W. E., Hawes, G. B. 1976. A new diisocyanide of novel ring structure from a sponge. *J. Am. Chem. Soc*, 98: 4010-4012.
6. Baldwin, J. E., Drome, A. E., Riordan, P. D. 1983. Deoxygenation of isocyanates to isonitriles: A mechanistic study by nuclear magnetic resonance. *Tetrahedron*, 39: 2989-2994.
7. Bienayme, H., Bouzid, K. 1998. A new heterocyclic multicomponent reaction for the combinatorial synthesis of fused 3-aminoimidazoles. *Angew. Chem. Int. Ed*, 37: 2234-2237.
8. Bornemann, V., Patterson, G. M. L., Moore, R. E. 1988. Isonitrile biosynthesis in the cyanophyte *Hapalosiphon fontinalis*. *J. Am. Chem. Soc*, 110: 2339-2340.

9. Bossio, R., Marcaccini, S., Pepino, R. 1994. Studies on isocyanides and related compounds: A novel Synthesis of pyrroles *via* Ugi reaction, *Synthesis*, 26: 765-766. 55
10. Bossio, R., Marcaccini, S., Pepino, R., Torroba, T. 1993. Studies on isocyanides and related compounds: A novel synthetic route to furan derivatives. *Synthesis*, 25: 783-785.
11. Burreson, B. J., Christophersen, C., Scheuer, P. J. 1975. Cooccurrence of a terpenoid isocyanide-formamide pair in the marine sponge *Halichondria* species. *J. Am Chem. Soc*, 97: 201-202.
12. Burreson, B. J., Scheuer, P. J., Finer, J., Clardy, J. 1975. 9-Isocyanopupukeanane, a marine invertebrate allomone with a new sesquiterpene skeleton. *J. Am Chem. Soc*, 97: 4763-4764.
13. Cafieri, F., Fattorusso, E., Magno, S., Santacroce, C., Sica, D. 1973. Isolation and structure of axisonitrile-1 and axisothiocyanate-1 two unusual sesquiterpenoids from the marine sponge *Axinella cannabina*, *Tetrahedron*, 29: 4259-4262.
14. Cano, P. A., Islas-Jacome, A., Gonzalez-Marrero, J., Yepez-Mulia, L., Calzada, F. Gamez-Montano, R. 2014. Synthesis of 3-tetrazolylmethyl-4*H*-chromen-4-ones *via* Ugi-azide and biological evaluation against *Entamoeba histolytica, Giardia lamblia* and *Trichomona vaginalis*. *Bioorg. Med Chem*, 22: 1370-1376.
15. Chen, Z.-B., Zhang, Y., Yuan, Q., Zhang, F.-L., Zhu, Y.-M., Shen, J.-K. 2016. Palladium-catalyzed synthesis of α-iminonitriles from aryl halides *via* isocyanide double insertion reaction. *J. Org. Chem*, 81: 1610-1616.
16. Ciminiello, P., Fattorusso, E., Magno, S., Mayol, L. 1984. New nitrogenous sesquiterpenes from the marine sponge *Axinella cannabina*, *J. Org. Chem*, 49: 3949-3951.
17. Curran, D. P., Du, W. 2002. Palladium-promoted cascade reactions of isonitriles and 6-iodo-*N*-propargylpyridones: synthesis of mappicines, camptothecins and homocamptothecins. *Org. Lett*, 4: 3215-3218.
18. Di Blasio, B., Fattorusso, E., Magno, S., Mayol, L., Pedone, C., Santacroce, C., Sica, D. 1976. Axisonitrile-3, axisothiocyanate-3 and axamide-3. Sesquiterpenes with a novel spiro[4,5]decane skeleton from the sponge *Axinella cannabina*, *Tetrahedron*, 32: 473-478.

19. Drouet, F., Masson, G., Zhu, J. 2013. Ugi four-component reaction of alcohols: stoichiometric and catalytic oxidation/MCR sequences. *Org. Lett*, 15: 2854-2857.
20. Edenborough, M. S. and Herbert, R. B. 1988. Naturally occurring isocyanides. *Nat. Prod. Rep*, 5: 229-245.
21. Esmaeili, A. A., Hosseinabadi, R., Habib, A. 2010. Synthesis of highly functionalized 4*H*-Pyrano[3,2-*d*]isoxazoles *via* isocyanide-based three-component reaction. *Synlett*, 21: 1477-1480.
22. Ferstanding, L. I. 1962. Carbon as a hydrogen bonding base and carbon-hydrogen-carbon bonding. *J. Am. Chem. Soc*, 84: 3553-3557.
23. Fusetani, N., Yasumuro, K., Kawai, H., Natori, T., Brinen, L., Clardy, J. 1990. Kalihenene and isokalihinol B, cytotoxic diterpene isonitriles from the marine sponge *Acanthella klethra. Tetrahedron Lett*, 31: 3599-3602.
24. Ghosh, J., Biswas, P., Maiti, S., Sarkar, T., Drew, M. G. B., Bandyopadhyay, C. 2013 Ligand-free palladium-catalyzed intramolecular arylation of chromones: an expedient synthesis of 1-benzopyrano[3,2-*c*]quinolones. *Tetrahedron Lett*, 54: 2221-2225.
25. Ghosh, J., Panja, S. K., Maiti, S., Biswas, P., Sarkar, T., Bandyopadhyay, C. 2016. Synthesis of 3-aminomethylidenechroman-2-carboxamides by a sequential one-pot three component reaction and by post-Passerini condensation modification. *J. Heterocycl. Chem*, 53: 449-456.
26. Hebach, C., Kazmaier, U. 2003. *Via* Ugi reactions to conformationally fixed cyclic peptides. *Chem. Commun*, 596-597.
27. Heravi, M. M., Baghernejad, B., Oskooie, H. A. A novel three-component reaction for the synthesis of 3-aryl-4*H*-benzo[1,4]oxazin-2-amine. *Mol. Diversity*, 13: 395-398.
28. Hogadone, M. R., Scheuer, P. J., Holm, A. 1984. On the origin of the isocyano function in marine sponges. *J. Am. Chem. Soc*. 106: 2447-2448.
29. Jida, M., Malaquin, S., Deprez-Poulani, R., Laconde, G., Deprez, B. 2010. Synthesis of five- and six-membered lactams *via* solvent-free microwave Ugi reaction. *Tetrahedron Lett*, 51: 5109-5111.
30. Kaim, L. E., Gizzi, M., Grimaud, L. 2008. New MCR−Heck−isomerization cascade toward indoles. *Org. Lett*, 10: 3417-3419.

31. Kaim, L. E., Grimaud, L. Schiltz, A. 2009. “Isocyanide-free” Ugi reactions. *Org. Biomol. Chem*, 7, 3024-3026.
32. Kaim, L. E., Grimaud, L., Purumandla, S. R. 2010. Ugi-Smiles couplings in water, *Tetrahedron Lett*, 51: 4962-4964.
33. Keating, T. A., Armstrong, R. W. 1995. Molecular diversity *via* a convertible isocyanide in the Ugi four-component condensation. *J. Am. Chem. Soc*, 117: 7842-7843.
34. Khan, A. T., Sidick, R. Lal, M. 2012. Bromodimethylsulfonium bromide (BDMS) catalyzed synthesis of imidazo[1,2-*a*]pyridine derivatives and their fluorescence properties. *Tetrahedron Lett*, 53: 2211-2217.
35. Khandan-Barani, K., Saghsovdhou, M. T., Habibi-Khorasani, S. M., Hazeri, N. Sajadikah, S. S. 2011. Three-component reaction between alkyl (aryl) isocyanides and dialkyl acetylenedicarboxylates in the presence of ethyl trifluoroacetate. *J. Chem. Res.* 35: 231-233.
36. Kumar, J. S., Jonnalogadda, S. C., Mereddy, V. R. 2010. An efficient boric acid-mediated preparation of α-hydroxyamides. *Tetrahedron Lett*, 51: 779-782; Soeta, T., Kojima, Y., Ukaji, Y., Inomata, K. 2011. Borinic acid catalyzed α-addition to isocyanide with aldehyde and water. *Tetrahedron Lett*, 52: 2557-2559.
37. Le, H. V., Fan, L., Ganem, B. 2011. A practical and inexpensive ‘convertible’ isonitrile for use in multicomponent reactions. *Tetrahedron Lett*, 52: 2209-2211.
38. Lu, K., Luo, T., Xiang, Z., You, Z., Fathi, R., Chen, J., Yang, Z. 2005. A concise and diversity-oriented strategy for the synthesis of benzofurans and indoles *via* Ugi and Diels−Alder Reactions. *J. Comb. Chem*, 7: 958-967.
39. Marcaccini, S., Torroba, T., Post-condensation Modifications of the Passerini and Ugi Reactions. 2005. In: *Multicomponent Reactions,* ed. by J. Zhu and H. Bienayme. *Chap. 2*, pp 33-75. Wiley-VCH.
40. Marcos, C. F., Marcaccini, S., Pepino, R., Polo, C., Torroba, T. 2003. Studies on isocyanides and related compounds: A facile synthesis of functionalized 3(2*H*)-pyridazinones *via* Ugi four-component condensation. *Synthesis*, 35: 691-694.
41. Mosslemin, M. –H., Anary-Abbasinejad, M., Anaraki-Ardakani, H. 2009. Reaction between isocyanides, dialkyl acetylenedicarboxylates and 2-hydroxy-1-aryl-2-

(arylamino)ethanones: one-pot synthesis of highly functionalized 2-aminofurans. *Synlett*, 20: 2676-2678.

42. Nair, V., Menon, R. S., Beneesh, P. B., Sreekumar, V., Bindu, S. 2004. A novel multicomponent reaction involving isocyanide, dimethyl acetylenedicarboxylate (DMAD), and electrophilic styrenes: facile synthesis of highly substituted cyclopentadienes. *Org. Lett*, 6: 767-769.
43. Nakamura, M., Inoue, J., Yamada, T. 2000. A two-step, one-pot synthesis of diverse *N*-pyruvoyl amino acid derivatives using the Ugi reaction. *Bioorg. Med. Chem. Lett*, 10: 2807-2810.
44. Pan, Y.–Y., Wu, Y.-N., Chen, Z.-Z., Hao, W.-J., Li, G., Tu, S.-J., Jiang, B. 2015. Synthesis of 3-iminoindol-2-amines and cyclic enaminones *via* palladium-catalyzed isocyanide insertion-cyclization. *J. Org. Chem*, 80: 5764-5770.
45. Patra, A., Chang, C. W. J., Scheuer, P. J., van Duyne, G. D., Matsumoto, G. K., Clardy, J. 1984. An unprecedented triisocyano diterpenoid antibiotic from a sponge. *J. Am. Chem. Soc*, 106: 7981-7983.
46. Pyke, T. R. and Dietz, A. 1966. U-21,963, a new antibiotic: I, discovery and biological activity, *Appl. Microbiol*, 14: 506-510.
47. Quai, M., Frattini, S., Vendrame, U., Mondoni, M., Dossena, S. Cereda, E. 2004. 5-Hydroxy-2*H*-pyrrol-2-ones and not 2-aminofurans are the cycloaddition products between alkyl isocyanides and benzyliden-1,3-diketones. *Tetrahedron Lett*, 45: 1413-1416.
48. Ramazani, A., Mahyari, A. T., Rouhani, M., Rezaei, A. 2009. A novel three-component reaction of a secondary amine and a 2-hydroxybenzaldehyde derivative with an isocyanide in the presence of silica gel: an efficient one-pot synthesis of benzo[*b*]furan derivatives. *Tetrahedron Lett*, 50: 5625-5627.
49. Reddy, B. V. S., Majumder, N., Prabhakar Rao, T., Sridhar, B. 2012. A novel sugar based intramolecular Ugi 3CC for the *N*-alkyl-3-oxo-4-aryl-octahydrofuro[2,3-*f*][1,4]oxazepine-5-carboxamides, *Tetrahedron Lett*, 53: 2273-2276.
50. Reddy, B. V. S., Reddy, A. M., Somasekhar, D., Yadav, Y. S., Sridhar, B. 2010. Three-component one-pot synthesis of 3-(2-furanyl)indoles from acetylenedicarboxylate, isocyanide, and 3-formylindole. *Synthesis*, 42: 2571-2576.

51. Scheuer, P. J. 1992. Isocyanides and cyanides as natural products. *Acc. Chem Res*, 25: 433-439.
52. Shaabani, A., Ghadari, R., Sarvary, A., Rezayan, A. H. 2009. Synthesis of highly functionalized bis(4*H*-chromene) and 4*H*-Benzo[*g*]chromene derivatives *via* an isocyanide-based pseudo-five-component reaction. *J. Org. Chem*, 74: 4372-4374.
53. Shaabani, A., Sarvary, A., Rezayan, A. H., Keshipour, S. 2009. Synthesis of fully substituted pyrano[2,3-*c*]pyrazole derivatives *via* a multicomponent reaction of isocyanides. *Tetrahedron*, 65: 3492-3495.
54. Shaw, A. Y., McLaren, J. A., Nichol, G. S., Hulme, C. 2012. Hydrazine-mediated cyclization of Ugi products to synthesize novel 3- hydroxypyrazoles. *Tetrahedron Lett*, 53: 2592-2594; Thompson, M. J., Chen, B. 2008. Versatile assembly of 5-aminothiazoles based on the Ugi four-component coupling. *Tetrahedron Lett*, 49: 5324-5327.
55. Shaw, A. Y., Xu, Z., Hulme, C. 2012. Ugi/Robinson-Gabriel reactions directed toward the synthesis of 2, 4, 5-trisubstituted oxazoles. *Tetrahedron Lett*, 53: 1998-2000.
56. Sun, C., Ji, S. J., Liu, Y. 2008. A novel, simple and efficient synthesis of 3-amino-benzo[*d*]imidazo[2,1-*b*]thiazole derivatives *via* a multicomponent procedure. *J Chin. Chem. Soc*, 55: 292-296.
57. Takahashi, C., Sekita, S., Yoshihira, K., Natori, S. 1976. The structures of toxic metabolites of *Aspergillus candidus*. II. The compound B (Xanthoascin), a hepato- and cardio-toxic xanthocillin analog. *Chem. Pharm. Bull*, 24: 2317-2321.
58. Teimouri, M. B. 2006. One-pot three-component reaction of isocyanides, dialkyl acetylenedicarboxylates and phthalhydrazide: synthesis of highly functionalized 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones. *Tetrahedron*, 62: 10849-10853.
59. Tempest, P., Ma, V., Kelly, M. G., Jones, W., Hulme, C. 2001. MCC/S_NAr methodology. Part 1: Novel access to a range of heterocyclic cores. *Tetrahedron Lett*, 42: 4963-4968.
60. Terzidis, M. A., Stephanidou-Stephanatou, J., Tsoleridis, C.A. 2010. One-pot synthesis of chromenylfurandicarboxylates and cyclopenta[*b*]chromenedicarboxylates involving zwitterionic intermediates. A DFT investigation on the regioselectivity of the reaction. *J. Org. Chem*, 75: 1948-1955; Reddy, B. V. S., Somasekhar, D., Reddy, A. M., Yadav, Y. S., Sridhar, B. 2010. PEG 400 as a reusable solvent for 1,4-dipolar cycloadditions *via* a three-component reaction. *Synthesis*, 42: 2069-2074.

61. Trifilenkov, A. S., Ilyin, A. P., Kysil, V. M., Sandulenko, Y. B., Ivachtchenko, A. V. 2007. One-pot tandem complexity-generating reaction based on Ugi four component condensation and intramolecular cyclization. *Tetrahedron Lett*, 48: 2563-2567.
62. Tsoleridis, C.A. Kostakis, G. E. 2011. One-pot synthesis of functionalized spirobenzofuranones *via* MCR involving 3-cyanochromones. *J. Org. Chem*, 76: 9008-9014.
63. Ugi, I. 1962. The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions, *Angew Chem. Int. Ed*, 1: 8-21.
64. Umkehrer, M., Kalinski, C., Kolb, J., Burdack, C. 2006. A new and versatile one-pot synthesis of indol-2-ones by a novel Ugi-four-component-Heck reaction. *Tetrahedron Lett*, 47: 2391-2393.
65. Wang, Y., Wang, H., Peng, J., Zhu, Q. 2011. Palladium-catalyzed intramolecular C(sp2)–H amidination by isonitrile insertion provides direct access to 4-aminoquinazolines from *N*-arylamidines. *Org. Lett*, 13: 4604-4607.
66. Welsch, S. J., Kalinski, C. Umkehrer, M., Ross, G., Kolb, J. Burdack, C. Wessjohann, L. A. 2012. Palladium and copper catalyzed cyclizations of hydrazine derived Ugi products: facile synthesis of substituted indazolones and hydroxytriazafluorendiones, *Tetrahedron lett*, 53: 2298-2301.
67. Wratten, S. J., Faulkner, D. J., Hirotsu, K., Clardy, J. 1978. Diterpenoid isocyanides from the marine sponge *Hymeniacidon amphilecta. Tetrahedron Lett*, 19: 4345-4348.
68. Xiang, Z., Luo, T., Lu, K., Cui, J., Shi, X., Fathi, R., Chen, J., Yang, Z. 2004. Concise synthesis of isoquinoline *via* the Ugi and Heck reactions. *Org. Lett*, 6: 3155-3158.
69. Xu, Z., De Moliner, F., Cappelli, A. P., Hulme, C. 2013. Aldol reactions in multicomponent reaction based domino pathways: A multipurpose enabling tool in heterocyclic chemistry. *Org. Lett*, 15: 2738-2741.
70. Yavari, I., Bayat, M. J., Sirouspour, M., Souri, S. 2010. One-pot synthesis of highly functionalized 1,2-dihydropyridines from primary alkylamines, alkyl isocyanides, and acetylenic esters. *Tetrahedron*, 66: 7995-7999.
71. Yavari, I., Djahaniani, H., Nasiri, F. 2003. Reaction between alkyl isocyanides and dimethyl acetylenedicarboxylate in the presence of polyhydroxybenzenes. Synthesis of 4*H*-chromene derivatives. *Tetrahedron*, 59: 9409-9412; Amanpour, T., Mirzaei, P.,

Bazgir, A. 2012. Isocyanide-based four-component synthesis of benzo[*a*]pyrano[2,3-*c*]phenazines. *Synthesis*, 44: 235-240.

72. Yavari, I., Karimi, E., Djahaniani, H. 2007. Isocyanide-based multicomponent synthesis of functionalized 2,6-dioxohexahydropyrimidines in 1 M aqueous glucose. *Synth. Commun*, 37: 2593-2599.
73. Yavari, I., Mokhtarporyani-Sanandaj, A., Moradi, L., Mirazaei, A. 2008. Reaction of benzoyl chlorides with Huisgen's zwitterion: synthesis of functionalized 2,5-dihydro-1*H*-pyrroles and tetrasubstituted furans. *Tetrahedron*, 64: 5221-5225.