

MICRO-REVIEW

Cyanoethylation: A Vital Reaction in the Synthesis of Biologically Active Heterocycles

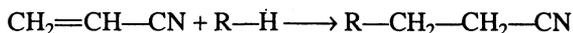
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Cyanoethylation is a vital reaction in the field of organic chemistry to incorporate a cyanoethyl group in a molecule. This review highlights the various methods of synthesizing cyanoethyl compounds by using various catalysts and the conversion of potential nitrile function to triazoles and tetrazoles.

Key Words: Cyanoethylation, Synthesis, Biologically active heterocycles.

INTRODUCTION

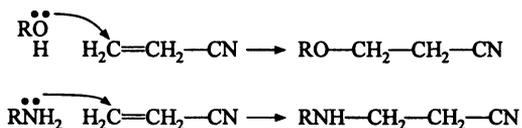
The reaction in which a compound possessing an active hydrogen adds across the double bond of acrylonitrile is termed as cyanoethylation¹⁻³. It provides a convenient route for incorporating the propionitrile moiety into a molecule. This propionitrile residue —CH₂—CH₂—CN is known as β-cyanoethyl or 2-cyanoethyl group.



If only one cyanoethyl group is attached to active hydrogen containing compound then it is called monocyanoethylation. If more than one cyanoethyl groups are attached to the active hydrogen containing compound then it is called multiple cyanoethylation.

Cyanoethylation process can be adopted easily for alcohols and amines; however it is also applicable for esters, phenols, thiols and ammonia.

In general, primary and secondary aliphatic amines react readily with acrylo-



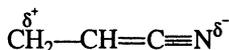
nitrile in the absence of catalysts to give high yields of aminopropionitriles, but some of the heterocyclic amines like carbazole, indole and pyrrole react only in presence of basic catalysts⁴. Thus cyanoethylation is a base catalyzed reaction.

Strong bases in aprotic medium are used as catalyst for cyanoethylation because it generates a high concentration of the mesomeric anion of the nitrile,

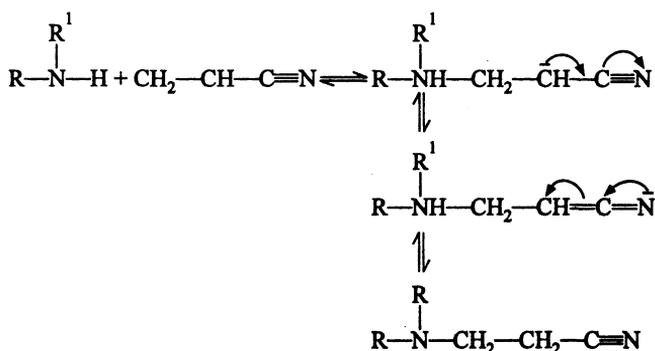
which restricts the degree of dialkylation^{5,6}. Strong bases like anion exchange resins of the quaternary ammonium hydroxide type [Zerolit FF of Amberlite (IRA-400)] are used as catalysts for cyanoethylation of alcohols⁷.

Mechanism of Cyanoethylation

Nitrile group is a powerful electron withdrawing group; hence the β -carbon atom of acrylonitrile is rendered relatively positive and nitrile portion of the molecule is rendered relatively negative.



Therefore the nucleophile will attack the β -position of the molecule.



Generally acidic catalysts or basic catalysts can be employed for cyanoethylation reaction. The basic strength of amine is the major factor determining whether acidic or basic catalysis is required.

Acid catalysts probably operate through the cyano group or the acrylonitrile and promote the development of an electron deficiency upon the β -carbon atom.

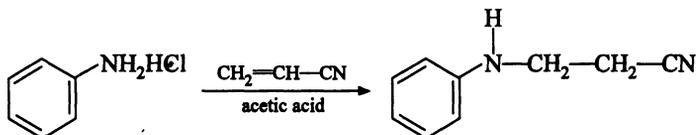
Basic catalysts function by removal of a proton from the aniline and subsequent attack of the anion upon the β -carbon atom of acrylonitrile.

The cyanoethylation reaction can be successfully attained by the following catalysts:

1. Acetic acid
2. Cuprous chloride and acetic acid
3. Sodium acetate, acetic acid and cuprous chloride
4. Acetic anhydride
5. Aniline salts
6. Exchange reaction of aromatic amine with 3-diethyl amino propionitrile
7. Choline catalysed monocyanoethylation reaction
8. Cupric acetate monhydrate
9. Triethylamine
10. Diethyl butyl ammonium hydroxide
11. Zinc chloride and *p*-toluene sulphonic acid
12. Aqueous pyridine
13. Triethylbenzyl ammonium hydroxide.
14. Triton B (benzyl trimethyl ammonium hydroxide)

1. Acetic Acid Catalyzed Cyanoethylation Reaction

Cyanoethylation of a variety of aromatic amines are reported to proceed readily with acetic acid catalysts⁸⁻¹². N-2-Cyanoethylaniline has been prepared by heating aniline hydrochloride, acrylonitrile and acetic acid in an autoclave for 10 h¹³⁻¹⁶.



Major drawback observed with acetic acid as catalyst was that it would not be sufficiently active to produce acceptable yields of cyanoethylated derivatives from sterically hindered (*ortho*-substituted) or deactivated (negatively substituted) aromatic amines even when employed in large excess and at high temperatures for long periods of time.

2. Cuprous Chloride Catalyzed Cyanoethylation Reaction

It has been reported that copper salts, particularly cuprous chloride, have a beneficial effect when employed in conjunction with acetic acid¹⁷⁻²⁰. Addition of cuprous chloride to acetic acid considerably enhances the catalytic activity, but frequently produces undesired mixtures of mono and dicyanoethylated derivatives, even when the acrylonitrile was not employed in excess. The other copper salts like cupric sulphate, copper powder, cupric oxalate and cupric borate are found to be completely ineffective as catalyst for cyanoethylation. Formation of the by-product acetanilide is the disadvantage of this reaction. Synthesis of N-benzyl-N-cyanoethyl-aniline from N-benzyl aniline is an example of such reaction.

3. Cyanoethylation Using Sodium Acetate, Acetic Acid and Cuprous Chloride

It was observed that addition of sodium acetate to the acetic acid-cuprous chloride mixture caused an improvement in yield over that obtained by either acetic acid or the acetic acid-cuprous chloride catalyst. Sodium acetate, effective in improving yields when added to cuprous chloride-acetic acid mixture, had no catalytic activity, nor did polyphosphoric acid or stannic chloride.

4. Acetic Anhydride Catalyzed Cyanoethylation Reaction

Cyanoethylation of certain aromatic amines are also reported to proceed in presence of acetic anhydride²¹.

5. Aniline Salts Catalyzed Cyanoethylation Reaction

Bekhli *et al.*²² reported the cyanoethylation of aromatic amines by aniline salts.

6. Cyanoethylation by Exchange Reaction of an Aromatic Amine with 3-Diethyl Aminopropionitrile

This reaction is called as Cymerman-Craig exchange reaction. This reaction has been considered to occur *via* an S_N² reaction involving attack of the arylamino

nitrogen upon the β -carbon of the cyanoethyl group rather than an S_N1 elimination-addition reaction²³⁻²⁷. This reaction was also reported to suffer from producing acceptable yields of cyanoethylated derivatives due to sterically hindered or deactivated aromatic amines even when employed in large excess and at high temperatures for long period of time.

7. Choline Catalysed Cyanoethylation Reaction

Pietra²⁸ has reported that good yields of arylamino propionitriles can be obtained by the base, choline catalyzed reaction of acrylonitrile and certain substituted aromatic amines.

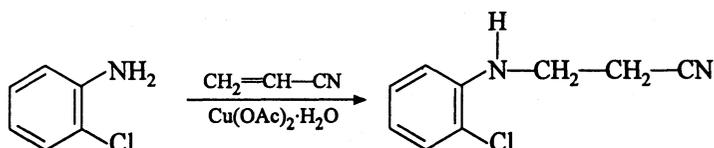
8. Cupric Acetate Catalysed Cyanoethylation Reaction

Cupric acetate monohydrate has been reported as a highly effective catalyst for the monocyanoethylation of a variety of aromatic amines. Several major advantages of using cupric acetate as catalyst in cyanoethylation process are

1. Improved yields
2. Rapid reaction and short reaction time.
3. The action of the catalyst is not inhibited by the presence of *ortho* or *N*-substituents²⁹ on the amines to be cyanoethylated as they do with other methods of carrying out the cyanoethylation of aromatic amines.
4. Ready cyanoethylation of the chloranilines, *p*-bromoaniline and *m*-nitroaniline in good yields with cupric acetate demonstrates the ability of the catalyst to promote cyanoethylation of even some negatively-substituted anilines.
5. Even under vigorous conditions like excess acrylonitrile, 10% cupric acetate and 12 h reflux, dicyanoethylation will not occur, which contrasts with the action of cuprous chloride which appears to favour dicyanoethylation in majority cases.
6. Formation of by-product acetanilide, sometimes reported to occur with acetic acid or acetic acid-cuprous chloride catalysts, has not been observed.

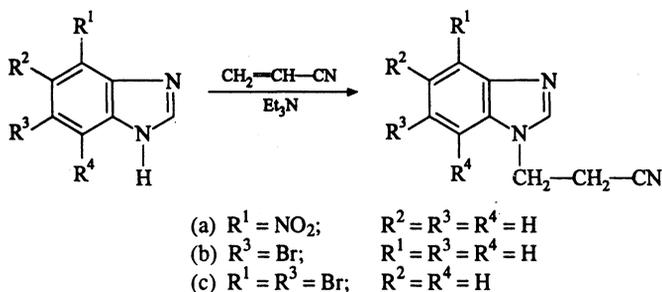
It was found that anhydrous cupric acetate was identical with the monohydrate in catalytic activity.

Heninger³⁰ reported the synthesis of 3-(*o*-chloroanilino)propionitrile from *o*-chloroaniline using cupric acetate monohydrate as catalyst. The yield of the product was found to be 90–94% based on *o*-chloroaniline and 50–53% based on acrylonitrile.



9. Triethylamine Catalysed Cyanoethylation Reaction

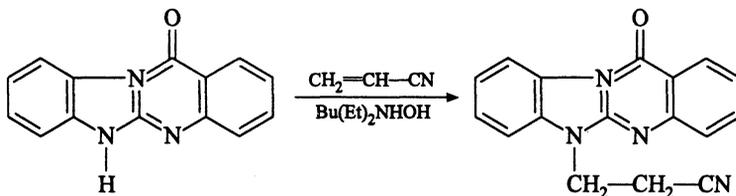
Vijayakumar *et al*³¹ synthesized some new 1-(β -cyanoethyl) benzimidazoles through cyanoethylation reaction, where triethylamine was used as a catalyst.



Toshiba *et al.*³² synthesized 3-nitro benzonitrile by reacting 3-nitro benzaldehyde oxime and triethylamine in dichloromethane.

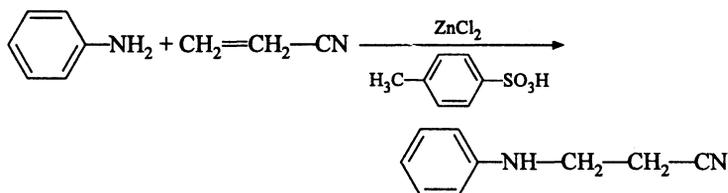
10. Diethyl Butylammoniumhydroxide Catalyzed Cyanoethylation Reaction

Popou *et al.*³³ synthesized 5-(β -cyanoethyl)benzimidazole by refluxing a mixture of benzimidazole(2,1-b)-quinazolinones, acrylonitrile, diethyl butylammonium hydroxide and dimethyl formamide.



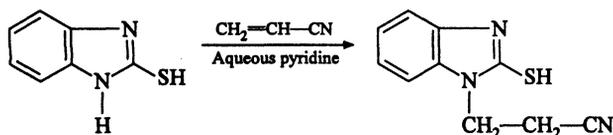
11. *p*-Toluene Sulphonic Acid and Zinc Chloride Catalyzed Cyanoethylation

Haruo Morita *et al.*³⁴ prepared *N*-cyanoethyl anilines by heating a mixture of aniline, acrylonitrile, *p*-toluene sulphonic acid and zinc chloride in water at 90–100°C for 10 h.



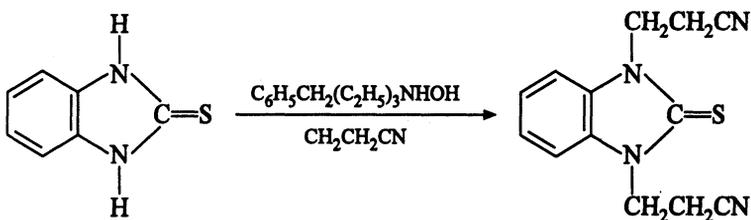
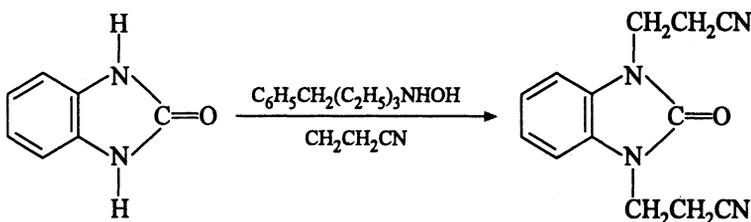
12. Aqueous Pyridine Catalyzed Cyanoethylation Reaction

Khalifa Mohamed *et al.*³⁵ reported the cyanoethylation of 2-mercapto benzimidazoles with acrylonitrile in aqueous pyridine medium to yield the cyanoethylated benzimidazole.



13. Triethylbenzylammoniumhydroxide Catalyzed Cyanoethylation Reaction

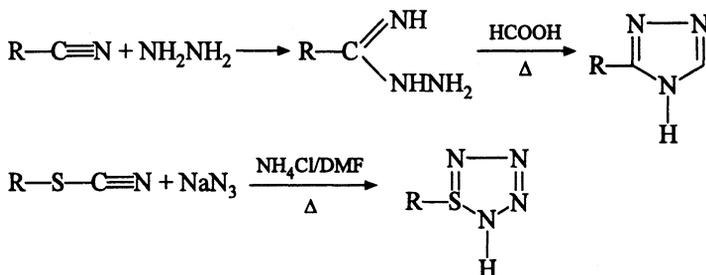
Cyanoethylation of benzimidazolone and mercaptazole in the presence of a quarternary base, triethylbenzylammonium hydroxide at a temperature of 40–50°C was reported by Efros³⁶. It was also reported that in the absence of triethylbenzylammonium hydroxide or in the presence of 33% caustic soda the cyanoethylation of benzimidazolone and mercaptobenzimidazole does not occur. Two acrylonitrile radicals will enter into the benzimidazolone or mercaptobenzimidazole molecule if equimolar quantities of reactants were used.



14. Triton B Catalyzed Cyanoethylation Reaction

Cyanoethylation of phenothiazine and 1,2,3,4-tetrahydrocarbazole using Triton B (Benzyl trimethyl ammonium hydroxide) was reported^{37, 38}.

Application of Cyanoethylation Reaction in Organic Synthesis



Nitrile function in cyanoethyl group is a potential function which can be easily converted into important heterocycles like triazole³⁹ and tetrazole^{40, 41} imidazole; benzimidazole³, oxazole and isoxazole and hence it can be useful in the synthesis of various heterocyclic compounds.

Syutkin *et al*⁴² and Efros⁴³ have reported the exclusive formation of 1-(β -cyanoethyl)-5-methyl/6-nitro benzimidazoles from the reaction of 5(6)-methyl/5(6)-nitro benzimidazoles with acrylonitrile. 1-(β -cyanoethyl)-5-nitro-benzimidazole have reported to possess positive effect on photosynthesis and plant growth and an adverse effect on caterpillar hatching⁴⁴⁻⁴⁶

Conclusion

Cyanoethylation of some heterocyclic compounds containing an amino or imino hydrogen has been especially used for building up novel heterocyclic systems. Preparation of series of arylaminopropionitriles can be effected by making use of both acidic and basic catalyts. But the use of acidic catalyts was found to be ineffective in producing consistently good yields of monocyanoethylated aromatic amines.

From the review of literature on cyanoethylation reactions, it may be concluded that:

1. Cyanoethylation of amine with electron-donating substituents is readily accomplished with acid catalyts such as acetic acid.
2. Sterically hindered amines (those with *ortho* or N-substituents) react less readily and require catalysis with cuprous chloride-acetic acid mixtures, or, preferably, cupric acetate.
3. Negatively substituted amines may require either acidic or basic catalyts depending upon the location of the substituent groups.
4. The role of copper catalyts in cyanoethylation reaction may be due to the formation of cupric or cuprous ions complex, since both the amino group and the cyano group of acrylonitrile are capable of forming complexes with these ions. The relative efficiency of the acetate compared with other salts of copper is probably due to its greater solubility in the reaction mixture.

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