Malononitrile: A Versatile Active Methylene Group

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Abstract: The title role of malononitrile in the development of Knoevenagel condensation of organic synthesis and their new findings are explored in this review. The active methylene group of malononitriles is very important attacking part in the heterocyclic conversions and also having a great potency towards several microbial and biological systems.

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1. INTRODUCTION:
In the earlier periods, the nitrile derivative differs and proved their multiple practices in the heterocyclic synthesis. Furthermore they performed as an intermediary part in a number of reaction conversions. The malononitrile derivatives exhibits the synergistic toxicity in the toxic-dynamic and toxic-kinetic interactions with aldehyde components \cite{1}. Some of the malononitrile derivatives shows the significant antimicrobial \cite{2} such as antibacterial \cite{3} and antifungal \cite{4} \cite{5}, anti-proliferative activities on human breast adenocarcinoma, ovarian adenocarcinoma and lymphoblastic leukemia cell \cite{6}. They also acts as anticancer \cite{7}, mollucidal \cite{8}, anti-inflammatory \cite{9} and anti-oxidant \cite{10} agents. Besides these the definite complex molecules of malononitrile derivatives by copper metal confers the virtuous anticancer activities \cite{11} and similarly acts as G protein-coupled receptor 35 (GPR\textsubscript{35}) agonists \cite{12}.

2. CONCEPT OF ACTIVE METHYLENE GROUP IN MALONONITRILE:
Active methylene group of malononitrile \textup{1} analogs plays a vital and attacking role in the heterocyclic synthesis. Malononitrile innumerate the unique interest in the organic synthesis due to the conversion of different functional groups such as ketones, aldehydes, esters, Oxo and amines corresponding carbanions of malononitrile molecule causes very essential for structural and spectral changes \cite{13}. The Knoevenagel condensation reaction offers most of the conversion between carbonyl carbons with active methylene group of the nitrile analogs. Their molecular crystal acts as phase transfer in the specific heat capacity at low temperature \cite{14}. In the photochemical study of malononitrile \textup{1} measured by the photo absorption and fluorescence excitation in vacuum UV region by Rydberg states. It was proved that CN (B\textsubscript{2}^\Sigma^+) and CN (A\textsubscript{2}^\Pi) photo fragments increases by decreasing the wavelength excitation in fluorescence spectrum \cite{15}. 
3. METHODS OF SYNTHESIS OF MALONONITRILE:

3.1 Synthesis using ketones:
Wang G. and Cheng B. \(^{[16]}\) have synthesized the arylidene 3(a-c) malononitrile analogs by uniform mixture of substituted ketones 2 (a-c) and dicyanomethane 1 catalyzed by ammonium acetate or silica gel under the microwave assisted solvent free synthesis. (Scheme-01)

Gupta R. et al \(^{[17]}\) have buildup the simple and efficient silica supported method of Knoevenagel condensation method. Identical molar mixture of different substituted ketones 4(a-f) and malononitrile 5(a-b) were reacted in presence of silica supported ammonium acetate catalyst refluxed on 60ºC temperature in methylene dichloride solvent; furnished compound 6(a-l) gave high quality and yields. (Scheme – 02)

Elison M. N. et al \(^{[18]}\) have synthesized the different substituted tetracyanopropanes by the electrolysis of malononitrile and carbonyl groups (ketones / aldehydes) in presence of sodium bromide undivided electrolytic cell reaction. (Scheme – 03 and Scheme – 04)
3.2 Synthesis using aldehydes:
Bhuiyan M. M. H. et al. \cite{ref19} synthesized aryldene malononitrile derivatives 11(a-k) by parallel mixture of substituted aromatic aldehydes 10(a-k) and malononitrile 1 using catalytic amount of ammonium acetate under microwave irradiation. (Scheme -05)

Sheibani H. and Saljoog A. S. \cite{ref20} have reported the ecofriendly high speed Knoevenagel condensation synthesis. In the reaction condition, counterpart mixture of the substituted aldehydes 12(a-v) and nitrile groups 13(a-b) were carried out under ethanol-aqueous media in presence of KOH or NaOH catalyst at 50-60°C temperature afforded the productive 14(a-t) derivatives. (Scheme – 06)

Rajendran A. et al. \cite{ref21} have reported the simple efficient and rapid Knoevenagel condensation synthesis by using ionic liquid media. The mixture of aromatic aldehyde 15(a-f) and dicyanomethane 1 were evenly carried out in pyridinium salicylate ionic liquid refluxed on 40°C for few minutes occupied the malononitrile 16(a-f) derivatives. (Scheme – 07)

Pal R. \cite{ref22} endured a new efficient method of Knoevenagel condensation reaction by using fruit juice accelerators. The Parallel mixture of different substituted aldehydes 17(a-d) and malononitrile 1 by tamarind juice catalyst in an aqueous media in presence visible light for few minutes afforded the malononitrile 18(a-d) analogous. (Scheme – 08)
Pasha M. A. et al. [23] have fabricated the solvent free grindstone method of Knoevenagel condensation. In the reaction condition, the substituted aldehyde 19 and nitriles 20 uniformly mixed with Na₂CO₃ catalyst under grindstone method afforded aryl-methylidene 21. (Scheme – 09)

Tamami B. and Fadavi A. [24] have synthesized the malononitrile derivatives 24 in presence of modified form of polyacrylamide catalyst heated under water by using equimolar mixture of aromatic aldehyde 22 and nitrile 23 analogs. (Scheme – 10)

Lin Q. et al. [25] have designed a novel chemosensor of cyanide analogous 26 by the condensation between napthaldehyde 25 with malononitrile 1 heated at 90°C fro 2 hrs in aqueous media via green synthesis. (Scheme – 11)

Basude M. et al. [26] have prepared the methylene-dinitrile derivaties 29(a-i) under water. An experimental section, substituted aryl aldehydes 27(a-i) reacts with malononitrile or ethyl cyanoacetate 28(a-b) in presence of ZnO catalyst in an aqueous condition at ambient temperature that gives end products (Scheme – 12)
Jain S. et al. [27] have established a new indole derivatives 32(a-t) promoted by L-proline catalyst. Indole aldehydes 30(a-d) evenly mixed with active methylene nitrile groups 31(a-e) under Knoevenagel condensation reaction catalyzed by L-proline refluxed on 60°C in ethanol. (Scheme – 13)

Gutch P. K. et al. [28] have formulated and reported the biologically active riot control agent benzylidene malononitrile 34 groups. These are synthesized by the mixture of substituted aromatic aldehydes 33 and malononitrile 1 in presence of highly alkaline catalyst like piperidine refluxed in cyclohexane solvent. They are bio-significant riot-control agents. (Scheme – 14)

Gauda M. A. and Abu-Hasan A. [29] have intended the eco-friendly synthesis of malononitrile derivatives 36, 38 in an aqueous media. In the Knoevenagel condensation synthesis of aromatic aldehydes 35, 37 and malononitrile 1 were equally mixed by using lithium hydroxide monohydrate catalyst which acts as dual-activator nature. (Scheme – 15)

3.3 Synthesis from indole-1,3-diketones:
Riyaz S. D. et al. [30] have formulated the different substituted isatins 41(a-s) were afforded by appropriate amount of substituted indole-1,3-diketone 40(a-s) reacts with active methylene malononitrile or ethyl cyanoacetate or cyanoacetic acid 39(a-c) in presence of piperidinium acetate catalyst heated at 100°C for 30 min in aqueous media. (Scheme – 16)
Lashgari N. et al \cite{Ref31} have reported the Knoevenagel condensation of isatins 44(a-h) in an aqueous condition. These products were synthesized by the parallel mixture of indoles 42(a-d) and nitriles 43(a-b) refluxed in presence of silica based sulphonic acid (SBA-Pr-SO₃H) catalyst under water. (Scheme – 17)

Katrizky A. R. et al \cite{Ref32} have formulated the novel dyestuffs. These compounds were carried out from isatin 45(a-g) refluxed with alkyl halides and DMF which gave N-alkylisatins 46(a-g); then further refluxed with malonitrile 1 under DMSO readily converted into corresponding 1-alkyl-3cyanomethylideneindol-2-ones 47(a-g). (Scheme – 18)

3.4 Using cyclopentadienones:

Andrew T. L. et al \cite{Ref33} have synthesized 6,6-dicyanofulvenes 49, 51 derived from monomeric and dimeric forms of cyclopentadienones 48, 50 with malononitrile 1 by using TiCl₄ and pyridine catalyst stirred from 0°C to room temperature in the methylene dichloride solvent. (Scheme – 19)
3.5 Using ninhydrin and napthalen-2,3-diamine:
Taherkhani M. [34] reported the indenobenzoquinaxoline 53 in microwave assisted solvent free one pot synthesis. The quinoxalines 53 derivatives was synthesized by the mixture of ninhydrin 51 and napthalen-2,3-diamine 52 counterparts of malononitrile 1 with few drops of DMSO in solvent free microwave conditions. (Scheme – 20)

3.6 Synthesis from chalcones:
Asiri A. M. [35] has synthesized the bis-methine dyes from chalcones and malononitrile. A solution of afforded chalcones 54(a-g) were refluxed with malononitrile 1 catalyzed by ammonium acetate and acetic acid under benzene, the 2,5-bis-arylidene-1-dicyanomethylene-cyclopentane 55(a-g) are produced. The afforded compounds have found promising antifungal activities. (Scheme – 21)

3.7 From 1-[4-(benzylideneamino)-phenyl] ethanones:
Sindhu A. et al [36] have assembled the chemoselective elimination of malononitrile derivatives. The 2-benzylidinemalononitrile 58 was performed by the condensation of malononitrile 1 and 1-[4-(benzylideneamino)-phenyl] ethanones 56 by the elimination of byproduct 59. (Scheme – 22)
3.8 Using chloranils: Hammam A. S. et al. have formulated pyrrolo[2,3-\text{f}]indole-3,7-dicarbonitrile 62 derivatives. These are gained by the reaction mixture chloranils 60 and malononitrile 61 (1:2) ration in presence of triethylamine catalyst refluxed in ethanolic conditions. The selected compounds possess the significant antimicrobial activities. (Scheme – 23)

3.9 From alkyl halides: Diez-Barra E. Et al have prepared the mono-alkyl-malononitrile 64 and di-alkyl-malononitriles 67 by using tetra-butyl ammonium bromide catalyst in solvent free basic medium. (Scheme – 24)

4. CHEMICAL REACTIONS: Jayachandran M. and Shriram K. have fortified the 5,5’-(arylalkene-1,1-diyl) bis(1H-tetrazoles) 70(a-b) derived from (arylalkene)malononitrile 69(a-b) intermediates. The (arylalkene) malononitriles were prepared by substituted ketones 68 and propane-di-nitrile 1 with piperidine refluxed in presence of ethanolic condition. Then further cyclization was done by using sodium azide with ammonium chloride catalyst heated in DMF solvent acquired the final products which reveals the significant antibacterial activities. (Scheme – 25)
Dodiya D. K. et al.\textsuperscript{[40]} have synthesized some novel pyrazolo[3',4':4,5]thieno[2,3-d] pyrimidine-8-ones 74(a-j) via malononitrile intermediates by three-step Gewald reaction. (5-methyl-2,4-dihydro-3H-pyrazol-3-ylide-ne) malononitrile 72(a-j) were afforded from 71(a-j) and 1 with the help of piperidyl acetate catalyst, then accomplished with sulphur morphine at 60°C for 6 min which form 73(a-j). By closing the final step, glacial acetic acid was catalyzed by the mixture of substituted aldehydes and 52(a-j) furnishes the novel pyrazolo-pyrimidine 53(a-j) synthons are positive antimicrobial agents. (Scheme – 26)

![Scheme - 26](image)

Dandia A. et al.\textsuperscript{[41]} have constructed a novel indole derivatives by solventless method. The new annulated 2-amino-3-carbonitrile-spiro[indeno-1,2,b]pyran-4(5H),3'-3(H)indole\textsuperscript{2',5(1'H)-diones} 78(a-b) were carried out by 3-dicyano/carboethoxycyanomethylene-2H-indol-2-ones 77 intermediates from malononitrile derivatives 76 and substituted indoles 75 titles. (Scheme – 27)

![Scheme - 27](image)

Abdel-megid M. et al.\textsuperscript{[42]} have developed diaminopyridone 82 of nitrogen substituted fused heterocyclic compounds derived from 1 and 79 starting components. The final derivatives 82 were gained by [(6-methyl-4-oxo-4H-chromene-3-yl)methylene] malononitrile 80 intermediates in presence of piperidine catalyst refluxed in ethanol. The synthesized products emphasized the substantial antimicrobial activities. (Scheme – 28)

![Scheme - 28](image)
Karimi-Jaberi Z. and Pooladian B.\textsuperscript{[43]} have constructed a novel synthesis of 2-amino-4H-pyran-3-carbonitrile 84(a-q) series by facile one pot reaction of $\alpha,\alpha'$-bis(arylidene)cycloalkanones 83(a-q) and malononitrile 1 were refluxed under alcoholic condition by using K$_2$CO$_3$ catalyst. (Scheme – 29)

\[
\begin{align*}
\text{Z} = & \text{CH}_2, \text{CH}_2\text{CH}_2, \text{CH(}\text{CH}_3)\text{CH}_2 \\
\text{Scheme - 29}
\end{align*}
\]

Manikannan R. et al\textsuperscript{[44]} have buildup the multicomponent synthesis of polysubstituted pyridines 87 by using equivalent mixture of substituted ketones 85, dicyanomethane 1 and aromatic aldehydes 86 in presence of alcoholic sodium hydroxide stirred for 10-60 min. Then the formulated compounds were screened their anti-tubercular activities on mycobactrium tuberculosis. These compounds were found more potent activities than the standards. (Scheme – 30)

\[
\begin{align*}
\text{Scheme - 30}
\end{align*}
\]

Shi F. et al\textsuperscript{[45]} have mounted the solvent free synthesis of 2-amino-cyanopyridines 90 by microwave assisted method. The substituted aromatic aldehydes 88, ketones 89 and propanedinitrile 1 are uniformly mixed with the addition of ammonium acetate catalyst was irradiated in a single component system intended the final products. (Scheme – 31)

\[
\begin{align*}
\text{Scheme - 31}
\end{align*}
\]

Datta B. and Pasha M. A.\textsuperscript{[46]} have reported the solvent free eco-friendly synthesis under thermal condition. Malononitrile 1, substituted ketones 92 and aromatic aldehydes 91 were heated with iodized K$_2$CO$_3$ catalyst, the polysubstituted dicyanoaniline 93 afforded in a very short time. (Scheme – 33)

\[
\begin{align*}
\text{Scheme - 32}
\end{align*}
\]

Desale K. R. et al\textsuperscript{[47]} developed the candid one-pot multicomponent microwave synthesis. In these neat reaction, the combination mixture of methylenedinitrile 1, aromatic aldehydes 94 and 1-napthol 95 were catalysed by p-dimethylaminopyridine which produces 2-amino-2-chromenes 96 derivatives. (Scheme – 33)
Beheshtia Y. S. et al. \cite{48} have introduced the novel DABCO catalyst in one pot multicomponent synthesis of pyridine dicarbonitrile 99 by the reaction mixture of paramethyl thiophenol 97, malonic nitrile 1 and substituted aromatic aldehydes 98. (Scheme – 35)

Heravi M. M. et al. \cite{49} have synthesized the novel 2-amino-4-H-chromene derivatives 102 and 103 in presence methanesulfonic acid catalyst refluxing with the mixture of aryl aldehydes 100, malononitrile 1 and α,β-disubstituted napthols 101 in a single pot reaction. (Scheme – 35)

Hasaninejad A. et al. \cite{50} alumina supported recyclable potassium fluoride catalyst were created and used for the synthesis of benzopyran 106 by using the uniform mixture malononitrile 1, substituted cyclohexane-1,3-dione 105 and aromatic aldehydes 104 were refluxed under ethanolic condition. (Scheme – 36)

Ahmadi S. A. and Maddahi M. \cite{51} have developed the 2-amino-4-hydroxy-1H pyrrole-3-carbonitrile 108 from the reaction mixture of glycine 107 and malononitrile 1 accelerated by piperidine under the microwave efficient conditions. (Scheme – 37)
Zirani G. M. et al. [52] have prepared the pyrano[2,3-d]-pyrimidine diones 111 by the three component reaction synthesis from barbituric acid 109, malononitrile 1 and substituted aldehydes 110 carried out with SBA-Pr-SO₃H nanocatalyst under the solvent free conditions. The final compounds possessed the considerable urease inhibitory activities. (Scheme – 38)

Kibon Z. et al. [53] have constructed the new 2-amino-3-cyanopyridines 155(a-d) through enaminonitriles 113 intermediate from substituted ketones 112 and malononitrile 1 by the solvent free microwave assisted method. (Scheme – 39)

Khalify J. et al. [54] have synthesized 3-amino-5-arylpripyrazidine-4-carbonitrile 118 series by using arylglyxal 116 and hydrazine hydrate 117 in presence of malononitrile 1 stirred for 30 min at room temperature under ethanol and water (1:1) ratio. (Scheme – 40)

Kiyani H. et al. [55] have developed the eco-friendly green facile four component reaction. In the synthesis part, pyranopyrazoles 122(a-q) were prepared by equimolar mixture of aromatic aldehydes 119(a-q), hydrazines 120, ethyl acetoacetate 121 and malononitrile 1 by using sodium acetoacetate catalyst stirred under water at room temperature. (Scheme – 41)

Danish I. A. and Prasad K. J. R. [56] have synthesized 3-cyano-5,6-dihydro-2-ethoxy-4-phenylpyrido[2,3-a]carbazoles 124 from the reaction mixture of 2-benzylidene-8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazoles 123 and malononitrile 1 with anhydrous ethanol in presence of sodium hydride catalyst refluxed under desicated benzene. (Scheme – 42)
Varela J. A. et al [57] have developed the novel series of spiropyridines 127 a symmetric chiral ligands obtained from dual-cyclization between bis-alkynenitriles 125 and substituted alkynes 126 by using cobalt catalyst under single pot reaction. (Scheme – 43)

El-Emary T. I. et al [58] have synthesized a novel spiro segregated indole substituted heterocyclic compounds like 3-benzoylcyanomethylidine-1(H)-indole-2-one 130, 3-thiosemicarbazide-1(H)-indole-2-one 132 and indoline-2,3-dione-3-cyanoacetic hydrazone 134 derivatives. They are procured by the condensation of 1-H-indole-2,3-dione 128 with benzoylacetonitrile 129, thiosemicarbazide 131 and cyanoacetic hydrazide 133 heated with phosphoryl chloride catalyst. (Scheme – 44)

Makarem S. et al [59] have developed the electrochemical induced multicomponent condensation reaction. In the experimental section, a mixture of resorcinol 135, substituted aldehydes 136(a-h) and malononitrile 1 were evenly condensed in propanol by using NaBr electrolytes resulting in the formation of 2-amino-4H-chromenes 137(a-h). (Scheme – 45)
Fringulli F. et al. [60] have developed the 7-hydroxy-3-carboxy coumarins 143 in a single pot reaction in aqueous media by equimolar amount mixture of 2, 4, dihydroxy benzaldehyde 138 and propane-dinitrile 1 were carried out under water in heterogeneous conditions. There are four types of fundamental reaction are stepwise carried out such as Knoevenagel, aldol condensation, Pinner reaction, acid catalyst, base catalyst and acid-base equilibrium synthesis simultaneously monitoring pH scales from starting medium to the final coumarins. (Scheme – 46)

5. MISCELLANEOUS REACTIONS:

Hammam A. E. G. et al. [61] have synthesized pyrazole 152, pyridine 150, pyrimidine 148 and malononitrile 145, 146 derivatives. In the beginning bis-chalcone 144 derivatives were treated with CH₂(CN)₂ 1, NH=C(NH₂)₂HCl 147, CN-CH₂COOEt 149, PhNHNH₂ 151 in presence of ammonium acetate affered pyroles, pyridine, pyrimidine, pyrazoline derivatives. (Scheme – 47)

Shaker R. M. et al. [62] have formulated the novel Spiro-fused pyran 157 derivatives by solvent less microwave assisted synthesis. These pyran derivatives were made by the cyclization of three components mixture of ninhydrin 154, malononitrile 1 and phenyl pyrazoline-3, 5-dione 153 irradiated in presence of the neutral Al₂O₃ catalyst. (Scheme – 48)
Rajput S. S. \cite{63} has reported the malononitrile derivatives azofluorenes 160, 162 furnished by the mixture of 4-chlorophenyl-succinimides 158, substituted aromatic aldehydes 159 and acetaldehyde 161 with methylene nitrile 1 by using piperidine catalyst refluxed under ethanolic conditions. (Scheme – 49)

Ameta K. L. et al. \cite{64} have synthesized malononitrile analogous 166 by the mixture of substituted aromatic aldehydes 164 and 2,4-dihydroxy-acetophenone 163 under microwave in presence of montmorillonite K$_{10}$ catalyst which form chalcones 165. On further treatment with malononitrile in presence of catalytic amount of morpholine furnishes the required product. (Scheme – 50).
6. CONCLUSION

This review has attempted to summarize the synthetic methods and reactions of malononitrile groups. Many biologically active heterocyclic compounds have been synthesized from that group. These reactions greatly extended synthetic possibilities in organic chemistry.

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