Malononitrile: A Versatile Active Methylene Group

R. S. Dhivare^{1, a *}, S. S. Rajput^{2, b}

¹Department of Chemistry, J.J.T. University, Jhunjhunu, Rajasthan, India

²Department of Chemistry, SVS's Dadasaheb Rawal College, Dondaicha, Maharashtra, India

E-mail address: ^aravii_1978@rediffmail.com, ^brajputss65@gmail.com

Keywords: Malononitrile, Active methylene group

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.

Contents:

1. Introduction
2. Concept of active methylene group in malononitrile
3. Methods of synthesis of malononitrile derivatives
4. Chemical reactions of malononitriles
5. Miscellaneous Reactions with malononitrile
6. Conclusion

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 ^[1]. Some of the malononitrile derivatives shows the significant antimicrobial ^[2] such as antibacterial ^[3] and antifungal ^{[4] [5]}, anti-proliferative activities on human breast adenocarcinoma, ovarian adenocarcinoma and lymphoblastic leukemia cell ^[6]. They also acts as anticancer ^[7], molluscicidal ^[8], anti-inflammatory ^[9] and anti-oxidant ^[10] agents. Besides these the definite complex molecules of malononitrile derivatives by copper metal confers the virtuous anticancer activities ^[11] and similarly acts as G protein-coupled receptor 35 (GPR₃₅) agonists ^[12].

2. CONCEPT OF ACTIVE METHYLENE GROUP IN MALONONITRILE:

Active methylene group of malononitrile **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 ^[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 ^[14]. In the photochemical study of malononitrile **1** measured by the photo absorption and fluorescence excitation in vacuum UV region by Rydberg states. It was proved that CN ($B^2\Sigma^+$) and CN ($A^2\Pi$) photo fragments increases by decreasing the wavelength excitation in fluorescence spectrum ^[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**)

Scheme - 01

Gupta R. et al ^[17] have build up 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 60°C temperature in methylene dichloride solvent; furnished compound **6(a-l)** gave high quality and yields. (**Scheme – 02**)

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**)

Scheme - 03

Scheme - 04

3.2 Synthesis using aldehydes:

Bhuiyan M. M. H. et al ^[19] synthesized arylidene 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)

Scheme - 05

Sheibani H. and Saljoog A. S. ^[20] 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)

Scheme - 06

Rajendran A. et al ^[21] 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)

Scheme - 07

Pal R. ^[22] 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 malonic nitrile **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)

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 Na_2CO_3 catalyst under grindstone method afforded aryl-methylidene **21**. (**Scheme – 09**)

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**)

Scheme - 10

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

Scheme - 11

Basude M. et al. ^[26] have prepared the methylene-dinitrile derivatives **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**)

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**)

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**)

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**)

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**)

Scheme -16

Lashgari N. et al ^[31] 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)

Scheme - 17

Katrizky A. R. et al ^[32] 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 malononitrile 1 under DMSO readily converted into corresponding 1-alkyl-3-cyanomethylideneindol-2-ones 47(a-g). (Scheme – 18)

Scheme - 18

3.4 Using cyclopentadienones:

Andrew T. L. et al ^[33] 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)

Scheme - 19

3.5 Using ninhydrin and naphthalen-2,3-diamine:

Taherkhani M. ^[34] reported the indenobenzoquinoxaline **53** in microwave assisted solvent free one pot synthesis. The quinoxalines **53** derivatives was synthesized by the mixture of ninhydrin **51** and naphthalen-2,3-diamine **52** counterparts of malononitrile **1** with few drops of DMSO in solvent free microwave conditions. (Scheme – 20)

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)

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 ^[37] have formulated pyrrolo[2,3-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 ^[38] 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**)

Scheme - 24

4. CHEMICAL REACTIONS:

Jayachandran M. and Shriram K. ^[39] have fortified the 5,5'-(aryalkene-1,1-diyl) bis(1H-tetrazoles) **70(a-b)** derived from (aryalkene)malononitrile **69(a-b)** intermediates. The (aryalkene) 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 ^[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-ylidene) 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

Dandia A. et al ^[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]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

Abdel-megid M. et al ^[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

Karimi-Jaberi Z. and Pooladian B. ^[43] have constructed a novel synthesis of 2-amino-4H-pyran-3-carbonitrile **84(a-q)** series by facile one pot reaction of α,α' -bis(arylidene)cycloalkanones **83(a-q)** and malononitrile **1** were refluxed under alcoholic condition by using K_2CO_3 catalyst. (Scheme – 29)

Scheme - 29

Manikannan R. et al ^[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)

Scheme - 30

Shi F. et al ^[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)

Scheme - 31

Datta B. and Pasha M. A. ^[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_2CO_3 catalyst, the polysubstituted dicyanoaniline **93** afforded in a very short time. (Scheme – 33)

Scheme - 32

Desale K. R. et al ^[47] developed the candid one-pot multicomponent microwave synthesis. In these neat reaction, the combination mixture of methylenedinitrile **1**, aromatic aldehydes **94** and 1-naphthol **95** were catalysed by p-dimethylaminopyridine which produces 2-amino-2-chromenes **96** derivatives. (Scheme – 33)

Scheme - 33

Beheshtia Y. S. et al ^[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)

Scheme - 34

Heravi M. M. et al ^[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 naphthols **101** in a single pot reaction. (Scheme – 35)

Scheme - 35

Hasaninejad A. et al ^[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)

Scheme - 36

Ahmadi S. A. and Maddahi M. ^[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)

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-arylpyridazine-4-carbonitril **118** series by using arylglyoxal **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 benzoate 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-tetrahydra-carbazoles **123** and malononitrile **1** with anhydrous ethanol in presence of sodium hydride catalyst refluxed under desicated benzene. (**Scheme – 42**)

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)

Scheme - 43

El-Emary T. I. et al ^[58] have synthesized a novel spiro segregated indole substituted heterocyclic compounds like 3-benzoylcyanomethylidene-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 phsphoryl chloride catalyst. (Scheme – 44)

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)

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**)

Scheme - 46

5. MISCELLANEOUS REACTIONS:

Hamam 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 $\text{CH}_2(\text{CN})_2$ **1**, $\text{NH}=\text{C}(\text{NH}_2)_2 \cdot \text{HCl}$ **147**, $\text{CN}-\text{CH}_2\text{COOEt}$ **149**, PhNHNH_2 **151** in presence of ammonium acetate afforded pyroles, pyridine, pyrimidine, pyrazoline derivatives. (**Scheme – 47**)

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 Al_2O_3 catalyst. (**Scheme – 48**)

Rajput S. S. ^[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. ^[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 K₁₀ 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.

References:

- [1] Lin Z., Zhang W., Wang L., Yu H. and Wu C., Mechanism of the synergistic toxicity of malononitrile and p -nitrobenzaldehyde with photobacterium phosphoreum, *Toxicology mechanism and methods*, 13(4), (2003), 241-245
- [2] Hussein A. H. M., Gad-Elkareem M. A. M., El-Adasy A. A. A. M., Khames A. A., and Othman I. M. M., β -oxoanilides in heterocyclic synthesis: synthesis and antimicrobial activity of pyridines, pyrans, pyrimidines and azolo, azinopyrimidines incorporating antipyrine moiety, *International Journal of Organic Chemistry*, 2, (2012), 341-351
- [3] Al-Adiwish W. M., Yaacob W. A., Adan D. and Nazlina I., Synthesis and antibacterial activity of thiophenes, *International Journal on Advanced Science Engineering Information Technology*, 2(4), (2012), 27-30
- [4] Mandour A. H., El-Sawy E. R., Ebaid M. S. and Hassan S. M., Synthesis and potential biological activity of some novel 3-[(N-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano(2,3-c)pyrazole-5-carbonitriles and 3,6-diamino-4-(N-substituted indol-3-yl)pyrano(2,3-c)pyrazole-5-carbonitriles, *Acta Pharm*, 62, (2012), 15–30
- [5] Mungra D. C., Patel M. P. and Patel R. G., An efficient one-pot synthesis and *in vitro* antimicrobial activity of new pyridine derivatives bearing the tetrazoloquinoline nucleus, *ARKIVOC*, xiv, (2009), 64-74
- [6] Rao M. S., Chhikara B. S., Tiwari R., Shirazi A. N., Parang K. and Kumar A., A greener synthesis of 2-aminochromenes in ionic liquid and evaluation of their anti-proliferative activities, *Chemistry and Biology Interface*, 2(6), (2012), 362-372
- [7] El-Shekeil A., Obeid A. O. and Al-Aghbari S., Anticancer activity studies of some cyclic benzimidazole derivatives, *European Journal of Chemistry*, 3(3), (2012), 356-358
- [8] Hassaneen H. M., Abunada N. M. and Hassaneen H. M., Synthesis of some new indeno[1,2-e]pyrazolo[5,1-c]-1,2,4-triazin-6-one and indeno[2,1-c]pyridazine-4-carbonitrile derivatives, *Natural Science*, 2, (2010), 1349-1355
- [9] Niranjane K. D. and Kale M. A., Synthesis and anti-inflammatory activity of some novel derivatives of 2-amino-3-cyano-14-imino-10-methoxy-4-methylthio pyrimido [2,1-b] pyrazolo [4,5-d] pyrimido [2,1-b] benzothiazole, *Der Pharmacia Lettre*, 3(2), (2011), 276-283
- [10] Fadda A. A., Berghot M. A., Amer F.A., Badawy D.S. and Bayoumy N.M., Synthesis and Antioxidant and Antitumor Activity of Novel Pyridine, Chromene, Thiophene and Thiazole Derivatives, *Archiv Der Pharmazie*, 345(5), (2012), 378-385
- [11] El-fiky B. A., Aly S. A., El-Sayed I. H., El-Abd S. F. and Abo-Ella S. S., Study the Antitumor Activity of Copper (II) Complex of 4-Azomalononitrile Antipyrine on Mice Induced with Earlich Ascites Carcinoma Cells, *Journal Environmental Bioremediation and Toxicology*, 2(2), (2014), 42-47
- [12] Deng H., Hu H., He M., Hu J., Niu W., Ferrie A. M. and Fang Y., Discovery of 2-(4-Methylfuran-2(5H)-ylidene)malononitrile and Thieno[3,2-b]thiophene-2-carboxylic Acid Derivatives as G Protein-Coupled Receptor 35 (GPR35) Agonists, *J. Med. Chem.*, 54, (2011), 7385–7396
- [13] Dove M. T., Farelly G., Rae A. I. M. and Wright L., The re-entrant phase transitions in malononitrile: specific heat capacity measurements, *J. Phys. C: Solid State Phys.*, 16, (1983), L195-L198.

-
- [14] Binev Y. I., Tsenov J. A., Juchnovski I. N. and Binev I. G., Ab initio, DFT and experimental studies on the IR spectra and structure propanedinitrile (malononitrile) and its carbanion, *Journal of Molecular Structure (Theo-chem)*, 625, (2003), 207-214
- [15] Uchida S., Tabayashi K., Tanaka M., Takahashi O., Saito K., Kono M. and Ibuki T., Photoabsorption and fluorescence excitation of malononitrile in the vacuum UV region, *Chemical Physics Letters*, 282, (1998), 375-380
- [16] Wang G. and Cheng G., Solvent free and aqueous Knoevenagel condensation of aromatic ketones with malononitrile, *ARKIVOC*, ix, (2004), 4-8
- [17] Gupta R., Gupta M., Paul S. and Gupta R., Silica supported ammonium acetate: an efficient and recyclable heterogeneous catalyst for Knoevenagel condensation between aldehydes or ketones and active methylene group in liquid phase, *Bull. Korean Chem. Soc.*, 30(10), (2009), 2419-2421
- [18] Elison M. N., Feducovich S. K., Lizunova T. L. and Nikishin G. I., Electro chemical transformation of malononitrile and carbonyl compounds into functionally substituted cyclopropanes: Electrocatalytic variant of the Wiedemann reaction, *Tetrahedron*, 56, (2000), 3063-3069.
- [19] Bhuiyan M. M. H., Hossain M. I., Ashraful A. M. and Mahmud M. M., Microwave assisted Knoevenagel condensation: synthesis and antimicrobial activities of some arylidene-malononitriles, *Scientific Journals, Chemistry Journal*, 02(01), (2012), 30-36.
- [20] Sheibani H. and Saljoogi A. S., A high-speed and eco-friendly catalytic system for Knoevenagel condensation of aldehydes with malononitrile and ethylcyanoacetate in aqueous media, *Heteroletters*, 2(4), (2012), 389-393
- [21] Rajendran A., Karthikeyan C. and Rajathi K., An efficient synthesis of arylmethylidene derivatives promoted by pyridinium salicylate ionic liquid, *International Journal of ChemTech Research*, 3(2), 2011, 858-863
- [22] Pal R., Visible light induced Knoevenagel condensation: A clean and efficient protocol using aqueous fruit extract of *tamarindus indica* as catalyst, *International Journal of Advanced Chemistry*, 2 (1), (2014), 27-33
- [23] Pasha M. A., Manjula K. and Jayashankara V. P., Sodium carbonate: A versatile catalyst for Knoevenagel condensation, *Indian Journal of Chemistry*, 49B, (2010), 1428-1431
- [24] Tamami B. and Fadavi A., A Polymeric Heterogeneous Catalyst Based on Polyacrylamide for Knoevenagel Reaction in Solvent Free and Aqueous Media, *Iranian Polymer Journal*, 15 (4), (2006), 331-339
- [25] Lin Q., Chen. P., Fu. Y., Zang Y., Shi B., Zang P. and Wei T., A green synthesis of simple chemosensor that could instantly detect cyanide with high selectivity in aqueous solution, *Elsevier, Chinese Chemical Letters*, 24, (2013), 699-702.
- [26] Basude M., Sunkara P. and Puppala V. S., ZnO catalyst for Knoevenagel condensation in aqueous medium at ambient temperature, *Journal of Chemical and Pharmaceutical Research*, 5(9), (2013), 46-50
- [27] Jain S., Bhimireddy N. R. and Kolisetty S. R., L-proline catalyzed Knoevenagel condensation: Synthesis of some new indole derivatives and Biological activities, *International Journal of ChemTech Research*, 3(2), (2011), 817-824
- [28] Gutch P. K., Kumar P., Suryanarayana M. V. S. and Malhotra R.C., Structure-biological Activity Relationship of Analogues of 2-Chlorobenzylidenemalononitrile-A Riot-control Agent, *Defense Science Journal*, 55(4), (2005), 447-457
- [29] Gouda M. A. and Abu-Hashem A. A., An eco-friendly procedure for the efficient synthesis of arylidinemalononitriles and 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) in aqueous media, *Green Chemistry Letters and Reviews*, 5(2), (2012), 203-209
- [30] Riyaz S. D., Indrasena A., Naidu A. and Dubey P. K., Knoevenagel condensation of isatin with nitriles and 1,3-diketones, *Indian Journal of chemistry*, 53B, (2014), 120-123

- [31] Lashgari N., Ziarani G. M., Badiei A. and Gholamzadeh P., Knoevenagel condensation of isatins with malononitrile/ethyl cyanoacetate in the presence of sulfonic acid functionalized silica (SBA-Pr-SO₃H) as a new nano-reactor, *European Journal of Chemistry*, 3(3), (2012), 310-313
- [32] Katritzky A. R., Fan W., Liang D. and Li ., Novel dyestuffs containing dicyanomethylidene groups, *Novel Dyestuffs, University of Florida*, 26, (1989), 1541-1545
- [33] Andrew T. L., Cox J. R. and Swager T. M., Synthesis, Reactivity and Electronic properties 6,6-dicyanofulvenes, *American Chemical Society, Organic Letters*, 12(22), (2010), 5302-5305.
- [34] Taherkhani M., Microwave-assisted one-pot synthesis of two derivatives of indenobenzoquinoxaline under solvent free conditions, *Int. J. Res. Chem. Environ.*, 2(4), (2012), 215-219
- [35] Asiri A. M., Synthesis and absorption spectral properties of bis-methine dyes exemplified by 2, 5-bis-arylidene-1-dicyanomethylene-cyclopentanone, *Journal of chemical Society of Pakistan*, 26(1), (2004), 57-60
- [36] Sidhu A., Sharma J.R. and Rai M., Chemoselective reaction of malononitrile with imine-ones and antifungal potential of products, *Indian Journal of Chemistry*, 49B (2), (2010), 247-250.
- [37] Hammam A. S., Abdel-Rahman M. A. and Hassan A. A., Synthesis and Characterization of Pyrrolo[2,3-*f*] Indole-3,7-Dicarbonitriles, *International Journal of Advance in Medical Science (AMS)*, 1(1), (2013), 11-17
- [38] Diez-Barra E., Hoz. A. de la, Moreno A. and Sanchez-Verdu P., Phase transfer catalysis without solvent: selective mono- or di-alkylation of malononitrile, *J. Chem. Soc. Perkin Trans. 1*, 1991, 2589-2592
- [39] Jeyachandran M. and Shriram K., Synthesis Of Antibacterial Ethyl 3-Aryl/Alkyl-2-(1H-tetrazole-5-Yl)Enoates and 5, 5'-(2-Arylalkene-1, 1-Diyl)Bis (1H-tetrazoles), *International Journal of Applied Biology and Pharmaceutical Technology*, 2(2), (2011), 349-353
- [40] Dodiya D. K., Trivedi A. R., Jarsania S. H., Vaghasia S. J. and Shah, V. H., Characterization and biological evaluation of some novel pyrazolo[3',4':4,5]thieno[2,3-*d*]pyrimidin-8-ones synthesized via the Gewald reaction, *J. Serb. Chem. Soc.*, 73 (7), (2008), 683-690
- [41] Dandia A., Singh R., Sachdeva H., Gupta R. and Paul S., Microwave promoted and improved thermal synthesis of Spiro-[indole-pyranobenzopyrans] and Spiro-[indole-pyranoimidazoles], *Journal of Chinese Chemical Society*, 50, (2003), 273-278.
- [42] Abdel-Megid M., Ahmed Ibrahim M., Gabr, El-Gohary N. M. and El-Hossain Y. A., Synthesis and Antimicrobial Activity of Some New Nitrogen Bridge-head Pyrido[1,2-*b*][1,2,4]triazepines Incorporating 6-Methylchromone Moiety, *15th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-15)*, 2011, 1-30
- [43] Jaber Z. K. and Pooladian B., A facile synthesis of new 2-amino-4H-pyran-3-carbonitriles by a one pot reaction of α, α' -bis(arylidene) cycloalkanones and malononitrile in the presence of K₂CO₃, *The Scientific World Journal*, (2012), 1-5
- [44] Manikannan R., Muthusubramanian S., Yogeeswari P. and Sriram D., Selective one-pot multicomponent synthesis and anti-tubercular evaluation of 5-(aryl/cyclohexylsulfanyl)-2-alkoxy-4,6-diaryl nicotinonitriles, *Bioorganic and Medicinal Chemistry Letters*, 20, (2010), 3352-3355
- [45] Shi F., Tu S., Fang F. and Li T., One-pot synthesis of 2-amino-3-cyanopyridine derivatives under microwave irradiation without solvent, *ARKIVOC*, (i), (2005), 137-142
- [46] Datta B. and Pasha M. A., I₂/K₂CO₃: An efficient catalyst for the synthesis of 5-aryl-2, 6-dicyano-3-methylanilines, *J. Chem. Sci.*, 125(2), (2013), 291-294.
- [47] Desale K. R., Nandre K. P. and Patil S. L., *p*-Dimethylaminopyridine (DMAP): A highly efficient catalyst for one pot, solvent free synthesis of substituted 2-amino-2-chromenes under microwave irradiation, *Org. Commun.*, 5(4), (2012), 179-185

- [48] Beheshtia Y. S., Khorshidi M., Heravi M. M. and Baghernejad B., DABCO as a novel and efficient catalyst for the synthesis of pyridine dicarbonitriles, *Journal of Scientific Research and Reviews*, 2(3), (2013), 030-033
- [49] Heravi M. M., Baghernejad B. and Oskooie H. A., A Novel and Efficient Catalyst to One-pot Synthesis of 2-Amino-4H-chromenes by Methanesulfonic Acid, *Journal of the Chinese Chemical Society*, 55, (2008), 659-662
- [50] Hasaninejad A., Jafarpour N. and Mohammadnejad M., Synthesis of Benzo[b]pyrane Derivatives Using Supported Potassium Fluoride as an Efficient and Reusable Catalytic System, *E-Journal of Chemistry*, 9(4), (2012), 2000-2005
- [51] Sayed A. A. and Maddahi M., Synthesis of 2-Amino-4hydroxy-1H-pyrrole-3-carbonitrile from Glycine under Microwave Irradiation, *International journal of Advanced Biological and Biomedical Research*, 1(11), (2013), 1364-1367
- [52] Ghodsi Mohammadi Ziarani, Sakineh Faramarzi, Shima Asadi, Alireza Badiei, Roya Bazi and Massoud Amanlou, Three-component synthesis of pyrano[2,3-d]-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO₃H) and their docking and urease inhibitory activity, *DARU Journal of Pharmaceutical Sciences*, 21(3), (2013), 1-13.
- [53] Kibou Z., Cheikh N., Choukchou-Braham N., Mostefa-Kara B., Benabdellah M. and Villemin D., A new route for the synthesis of 2-aminopyridines, *St. Cerc. St. CICBLA*, 12 (2), (2011), 121-126
- [54] Khalafy J., Rimaz M., Farajzadeh S. and Ezzati M., A Simple Three-component Synthesis of 3-Amino-5-arylpyridazine-4-carbonitriles, *S. Afr. J. Chem.*, 66, (2013), 179-182
- [55] Kiyani H., Samimi H. A., Ghorbani F. and Esmaili S., One-pot, four-component synthesis of pyrano[2,3-c]pyrazoles catalyzed by sodium benzoate in aqueous medium, *Current Chemistry Letters*, 2, (2013), 197-206
- [56] Danish I. A. and Prasad K. J. R., An Elegant Synthetic Route to 3-Cyano-5,6-dihydro-2-ethoxy-4-phenyl-pyrido[2,3-a]carbazoles, *Z. Naturforsch*, 59b, (2004), 106-108
- [57] Varela J. A., Castedo L. and Saa C., One-step synthesis of spiropyridines, a novel class of C₂-symmetric chiral ligands, by cobalt(i)-catalyzed [2 + 2 + 2] cycloadditions between bis-alkynenitriles and alkynes, *Organic Letters*, 1(13), (1999), 2141-2143
- [58] El-Emary T. I., Ahmed R. A. and Bakhite E. A., Synthesis of Some New Spiro, Isolated and Fused Heterocycles Based on 1H-indole-2-one, *Journal of the Chinese Chemical Society*, 48, (2001), 921-927
- [59] Makarem S., Mohammadi A. A. and Fakhari A. R., A multi-component electro-organic synthesis of 2-amino-4H-chromenes, *Tetrahedron Letters*, 49, (2008), 7194-7196
- [60] Fringuelli F., Piermatti O. and Pizzo F., One-Pot Synthesis of 7-Hydroxy-3-carboxycoumarin in Water, *Journal of Chemical Education*, 81(6), (2004), 874-876
- [61] Hammam A. E. G., Sharaf M. A. and El-Hafez N. A., Synthesis and anticancer activity of pyridine and thiazolopyrimidine derivatives using 1-ethylpiperidone as a synthon, *Indian Journal of Chemistry*, 40 (B), (2001), 213-221.
- [62] Shaker R. M., Mahmoud A. F. and Abdel-Latif, Facile one pot microwave assisted solvent-free synthesis of novel spiro- f. f. fused pyran derivatives via the three-component condensation of ninhydrin with malononitrile and active methylene compounds, *Journal of the Chinese Chemical Society*, 52, (2005), 563-567
- [63] Rajput S. S., Synthesis and Characterization of Bis-Heterocyclic derivatives of 1-(3-Chlorophenyl)-Pyrrolidine-2, 5-Dione, *International Journal of Advances in Pharmacy, Biology and Chemistry*, 1(2), (2012), 242-246.
- [64] Ameta K.L., Rathore N.S. and Kumar B., Synthesis of some novel chalcones and their facile one-pot conversion to 2-aminobenzene-1, 3-dicarbonitriles using malononitrile, *Analele University Din Bucuresti-Chimie (Serie Noua)*, 20(1), (2011), 15-24.