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Utility of 2-cyano-*N*-(2-hydroxyethyl) acetamide in heterocyclic synthesis

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ABSTRACT

This review presents a systematic and comprehensive survey of the method of preparation and the chemical reactivity of 2-cyano-*N*-(2-hydroxyethyl) acetamide. The target compounds are important intermediates for the synthesis of a variety of synthetically useful and novel heterocyclic systems.

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1. Introduction

Cyanoacetamides are polyfunctional compounds possessing both electrophilic and nucleophilic properties. Typical nucleophilic position at NH and CH_2. On the other hand, cyano acetamides possesses electrophilic positions, especially at the carbon of the cyano. These chemical properties have been used to design different heterocyclic moiety with difrerent ring sizes such as pyrole [1], thiophene [2], pyrazole [3], thiazole [4], thiadiazole [5], pyridine [6], pyridine [7], coumarin [8]. Moreover, cyanoacetamides and their related heterocyclic derivatives have generated great attention due to their interesting biological, therapeutic value and pharmaceutical activities e.g. as herbicidal [9], anti-inflammatory [10], anti-tumor [11], and analgesic properties [12]. Furthermore, 2-cyano-*N*-(2-hydroxyethyl)acetamide is a highly reactive compound. It is extensively utilized as reactant or reaction intermediate since the cyano function of this compound are suitably situated to enable reaction with common mono or bidentate to form a variety of heterocyclic compounds. Moreover, the active hydrogen on N and O atoms of this compound can take part in a variety of condensation and substitution reactions. There is no review summarizing the literature on the synthesis and chemistry of 2-cyano-*N*-(2-hydroxyethyl) acetamide.

2. Synthesis

The synthesis of 2-cyano-*N*-(2-hydroxyethyl)acetamide (**3**) may be carried out in several ways. The most versatile and economical method involves the treatment of ethanolamine (**1**) with (ethyl) methylcyanoacetate (**2**) using different reaction conditions to yield 2-cyano-*N*-(2-hydroxyethyl) acetamide (**3**). The following are some of the methods that have been used to synthesis of 2-cyano-*N*-(2-hydroxyethyl) acetamide (**3**).

2.1. Solvent-free methods

The solvent-free reaction of ethanolamine with (ethyl) methylcyanoacetate constitutes one of the most widely used methods for the preparation of 2-cyano-*N*-(2-hydroxy ethyl) acetamide (**3**). Thus, stirring of methylcyanoacetate with an ethanol amine at room temperature for 2 h afforded cyano acetanilide (**3**) [13]. Moreover fusion of ethanolamine with

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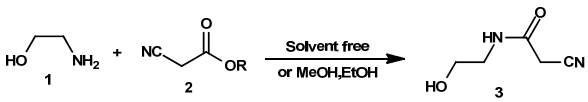
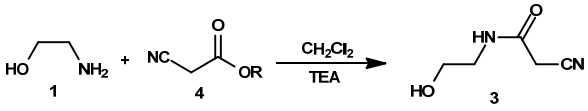
methylcyanoacetate at 100-120 °C [14] or 95-150 °C [15] afforded cyanoacetanilide derivative **3** (Scheme 1).



Scheme 1

2.2. Using different solvent

The reaction of ethanolamine (**1**) with ethyl (methyl) cyanoacetate (**2**) in boiling ethanol or methanol afforded 2-cyano-*N*-(2-hydroxyethyl) acetamide (**3**) (Scheme 1) [16-20]. Furthermore reaction of cyanoacetylchloride (**4**) with ethanol amine (**1**) in dichloromethane containing triethylamine as a basic catalyst afforded 2-cyano-*N*-(2-hydroxyethyl)-acetamide (**3**) (Scheme 2) [21].



Scheme 2

2.3. Reactivity

2-Cyano-*N*-(2-hydroxyethyl)acetamide have polyfunctions, possessing both electrophilic and nucleophilic properties. Typical nucleophilic positions are NH, OH and C-2. These chemical properties have been used to design different heterocyclic moiety with different ring sizes such as pyrrole, thiophene, oxazole, triazole, pyridine, quinolone, coumarin and diazepinone. On the other hand, 2-cyano-*N*-(2-hydroxyethyl) acetamide possesses electrophilic positions, especially at C-3, C-1 of 2-cyano-*N*-(2-hydroxyethyl)acetamide.

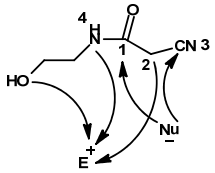


Figure 1. Reactivity of 2-cyano-*N*-(2-hydroxyethyl)acetamide (**3**).

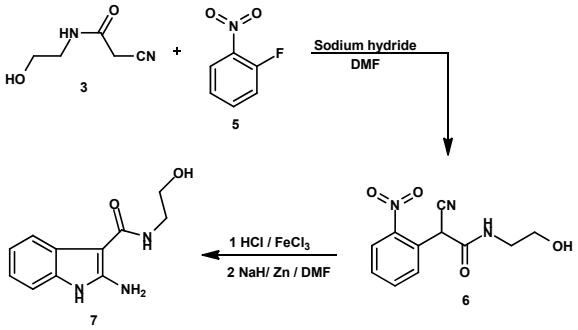
2.4. Synthesis of five membered rings

An efficient one-pot, two-step solution-phase synthetic method was developed to synthesize 2-amino-indole-3-carboxamide (**7**) from 2-halonitrobenzene (**5**) and cyano acetamide (**3**). In this sequence, first, intermediate 2-cyano-2-(2-nitrophenyl)acetamide (**6**) was generated under basic condition *via* nucleophilic aromatic substitution reaction; after direct addition of hydrochloric acid solution, $FeCl_3$, and Zn powder, indole (**7**) was generated *via* reduction/cyclization process (Scheme 3) [22].

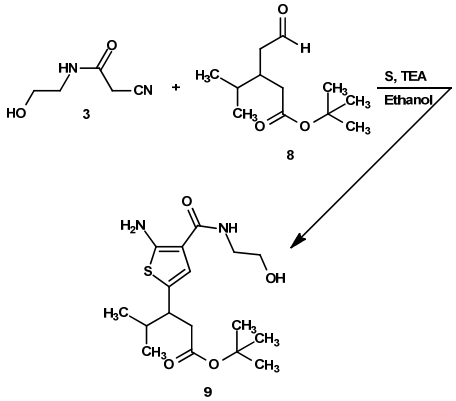
Gewald reaction of *t*-butyl 4-methyl-1-oxopentan-3-yl carbamate (**8**) with cyanoacetamide (**1**) in ethanol in presence of sulfur and triethylamine afforded the corresponding thiophene **9** (Scheme 4) [23].

Furthermore cyanoacetamide **3** reacted with butanal (**10**) and sulfur in DMF in presence of DEA under Gewald reaction condition in to give the corresponding 2-aminothiophene (**11**) (Scheme 5) [21].

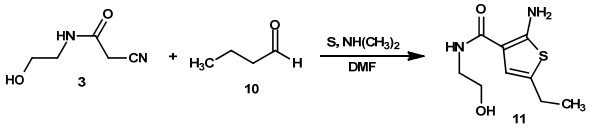
Cyanoacetamide (**3**) reacted with oxime derivative **12** in sodium ethanolate in ethanol to give the corresponding 5-aminooxazole (**13**). Furthermore isoxazoles **15** having a heterocycle at the omega-position of the side chain of compound **15** was prepared via heating of compound **13** with $SOCl_2$ in pyridine/$CHCl_3$, followed by heating the chloro derivative **14** in xylene containing sodium. Reduction of compound **14** with $LiAlH_4$ in MeOH afforded the oxazolone derivative **16** (Scheme 6) [24].



Scheme 3



Scheme 4



Scheme 5

Triazoles **20** are synthesized by reaction of azides **17** with cyanoacetamide (**3**) in methanolate followed by reaction of the formed triazole **18** with $SOCl_2$ in pyridine/$CHCl_3$ to give the chloroderivative **19** which cyclized in methanol containing sodium and sodium iodide to give the corresponding oxazoles **20** (Scheme 7) [20].

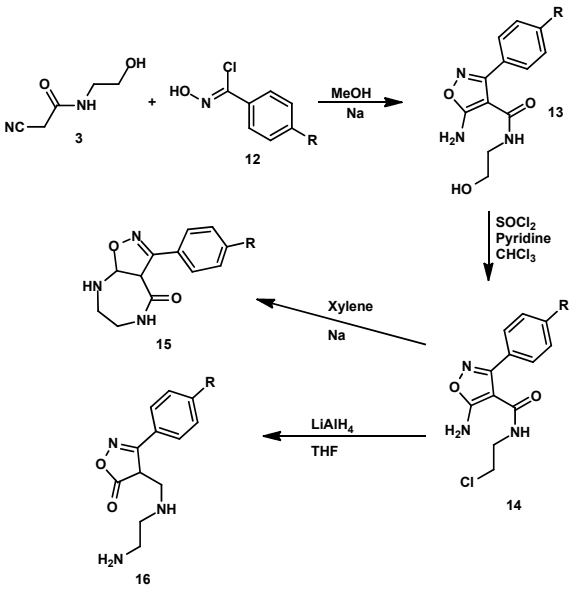
2.5. Synthesis of six membered rings

Knoevenagel condensation of cyanoacetamide (**3**) with 2, 4-dihydroxybenzaldehyde **21** in ethanol and piperidine afforded the corresponding iminocoumarin (**22**) which condensed with *p*-methoxyaniline (**23**) to give the corresponding *p*-methoxyphenyliminocoumarin (**24**) (Scheme 8) [25].

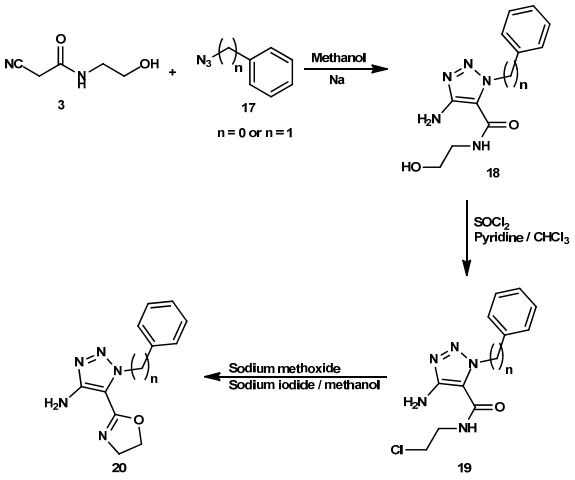
Furthermore Knoevenagel condensation of cyanamide **3** with 4-bromo (3-methoxy)-2-hydroxbenzaldehyde (**25**) in H_2O in presence of sodium carbonate afforded the corresponding iminocoumarin (**26**), which hydrolyzed with HCl to give coumarin **27** (Scheme 9) [26].

Whereas, Knoevenagel condensation of cyanamide **3** with 2-hydroxbenzaldehyde (**28**) in ethanol in presence of piper-

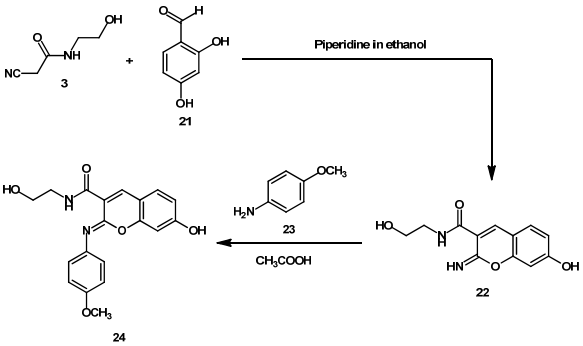
dine afforded the corresponding arylidine (**29**) (Scheme 10) [19].



Scheme 6

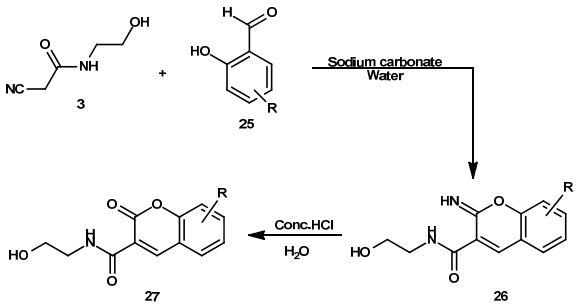


Scheme 7

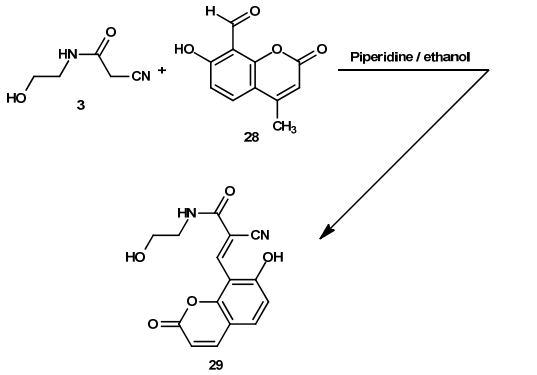


Scheme 8

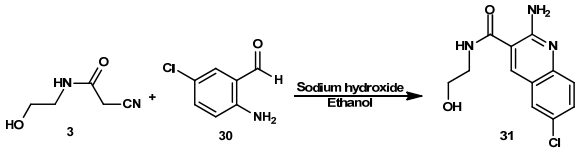
Condensation of 2-amino-5-chlorobenzaldehyde (**30**) with cyanoacetamide (**3**) in sodium hydroxide in ethanol afforded the aminoquinolone derivative **31** (Scheme 11) [13].



Scheme 9

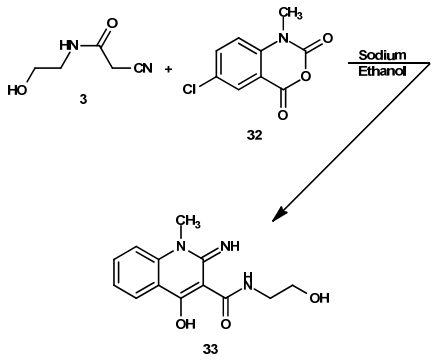


Scheme 10



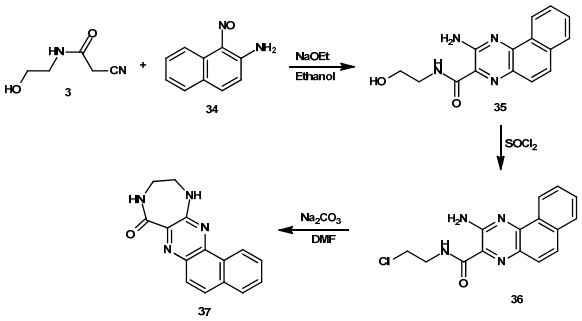
Scheme 11

6-Chloro-1, 2-dihydro-4-hydroxy-*N*-(2-hydroxyethyl)-2-imino-1-methyl-3-quinolinecarbox-amide (**33**) was prepared *via* condensation of 6-chloro-1,2-dihydro-4-hydroxy-*N*-(2-hydroxy-ethyl)-2-imino-1-methyl-3-quinoline- carboxamide (**32**) with 2-cyano-*N*-(2-hydroxyethyl)-acetamide (**3**) in ethanol containing sodium (Scheme 12) [27].



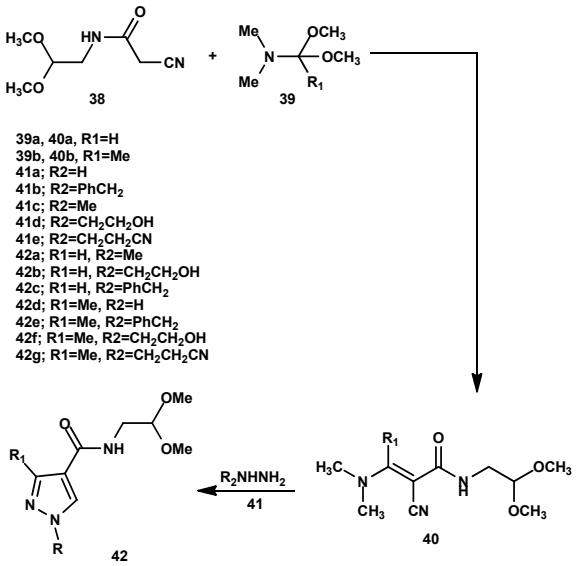
Scheme 12

Cyanoacetamide **3** reacted with oxime derivative **34** in sodium ethanolate in ethanol to give the corresponding 2-aminobenzo[5,6]quinoxaline (**35**). Heating of compound **35** with $SOCl_2$ followed by heating the chloro derivative (**36**) in DMF containing sodium carbonate afforded the corresponding diazepin-12-on derivative (**37**) (Scheme 13) [28].



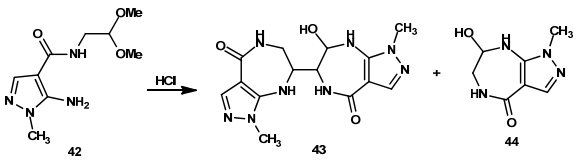
Scheme 13

Furthermore, 2-cyano-*N*-(2,2-dimethoxyethyl)-acetamide (**38**) which obtained from ethyl cyanoacetate and amino acetaldehyde di-methylacetal [29] reacted with dimethylform-(acet)amide dimethylacetals **39a** and **39b** to give 3-dimethyl amino-*N*-(2,2-dimethoxyethyl)- 2-cyanoacryl(croton) amides **40** and **40b**. Condensation of compound **40a** and **40b** with hydrazine hydrate (**41a**) or alkylhydrazines **41b**-**41e** in pyridine give amides **42a**-**42g** (Scheme 14) [30].



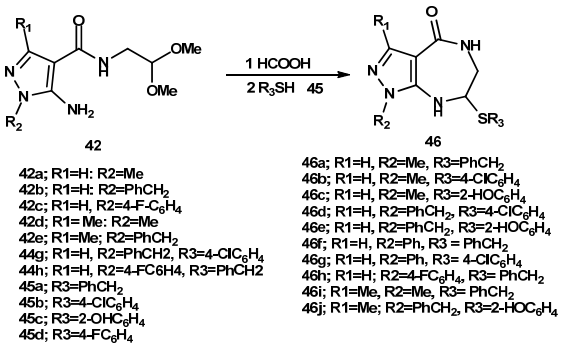
Scheme 14

Amide **42a** was converted into the corresponding pyrazolodiazepines (**43**) and (**44**) after boiling in water in the presence of hydrochloric acid (Scheme 15) [30].



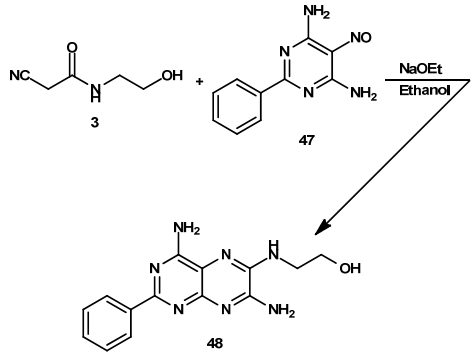
Scheme 15

Stirring of amides **42** in formic acid followed by addition of thiophenols (**45**) afforded 7-R-sulfanyl derivatives **46** (Scheme 16) [30].



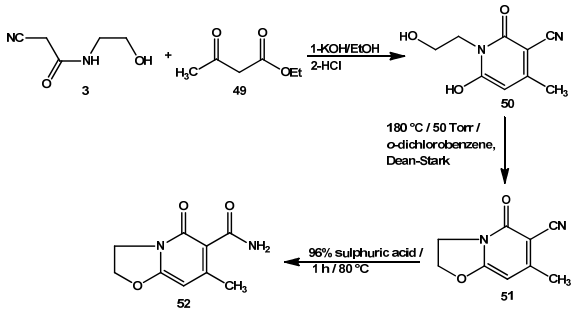
Scheme 16

Reaction of 4,6-diamino-2-substituted 5-nitrosopyrimidines (**47**) with *N*-substituted cyanoacetamide (**3**) in refluxing ethanol containing catalytic amounts of sodium afforded the 2-(4,7-diamino-2-phenylpteridin-6-ylamino)ethanol (Scheme 17) [31].



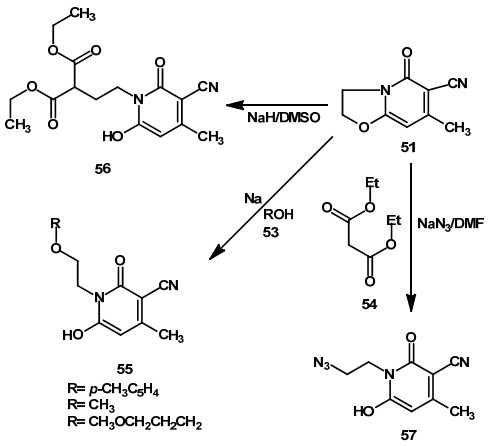
Scheme 17

Heating of cyanoacetamide **3** with ethylacetoacetate (**49**) in KOH/EtOH afforded 3-cyano-1-(hydroxyethyl)-6-hydroxy-4-methylpyrid-2(1H)-one (**50**). Cyclodehydration of compound **50** *via* heating in *o*-dichlorobenzene afforded 6-cyano-2, 3-dihydro-7-methyloxazolo[3, 2-a]pyrid-5(*H*)-one (**51**). Hydrolysis of compound **51** with sulfuric acid, afforded the carboxamide (**52**) (Scheme 18) [32].



Scheme 18

Furthermore condensation of compound **51** with alkoxides (**53**), carbanion of di-Et malonate (**54**) and sodium azide afforded the corresponding pyridines **55**-**57** (Scheme 19) [18].

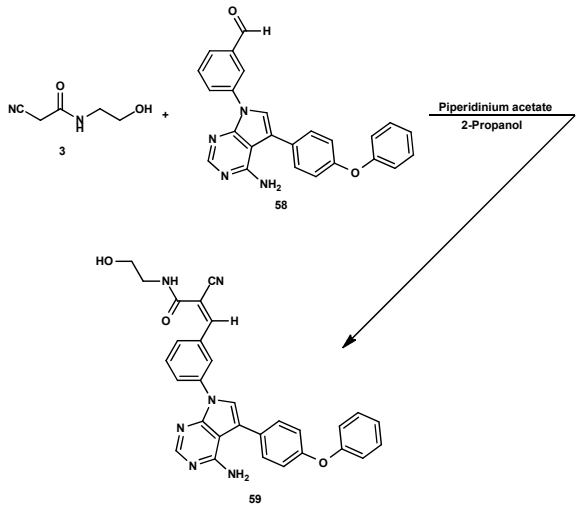


Scheme 19

2.6. Miscellaneous reaction

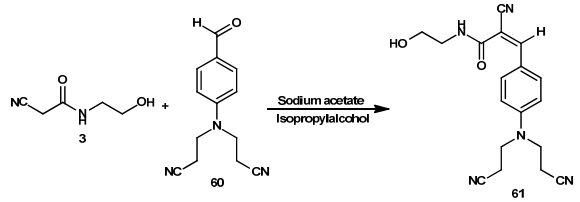
2.6.1. Reaction with aldehyde

3-(4-Amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2, 3-d]pyri midin7-yl)benzaldehyde (**58**) reacted with 2-cyano-*N*-(2-hydroxyethyl)acetamide (**3**) in presence of in piperidinium acetate to give the corresponding (*E*)-3-(3-(4-amino-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)phenyl)-2-cyano-*N*-(2-hydroxyethyl) acrylamide (**59**) (Scheme 20) [33].



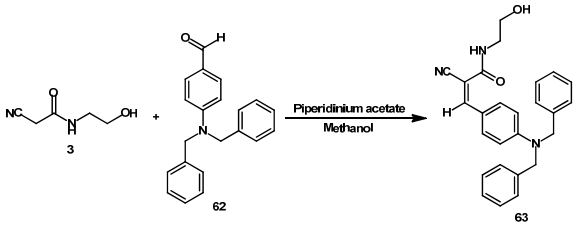
Scheme 20

Furthermore, treatment of *N*,*N*-(disubstituted amino) benzaldehyd (**60**) with 2-cyano-*N*-(2-hydroxyethyl)acetamide (**3**) in isopropyl alcohol in presence of sodium acetate gave the acrylamide (**61**) (Scheme 21) [15].



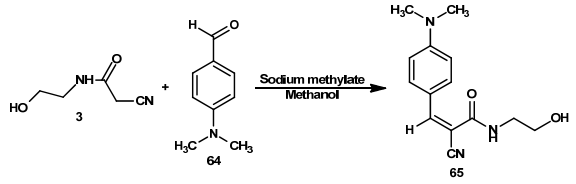
Scheme 21

Stirring of 4-(dibenzylamino)benzaldehyd (**62**) with 2-cyano-*N*-(2-hydrox-yethyl) acetamide (**3**) in methanol in presence of in piperidinium acetate gave the acrylamide (**63**) (Scheme 22) [15].



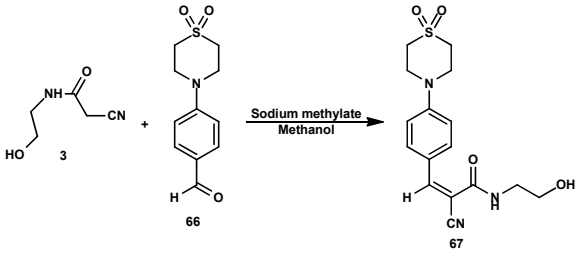
Scheme 22

Moreover, heating of 4-*N*,*N*-dimethylaminobenzaldehyde (**64**) with acetamide (**3**) in sodium methylate in methanol afforded the corresponding arylidene (**65**) (Scheme 23) [15].



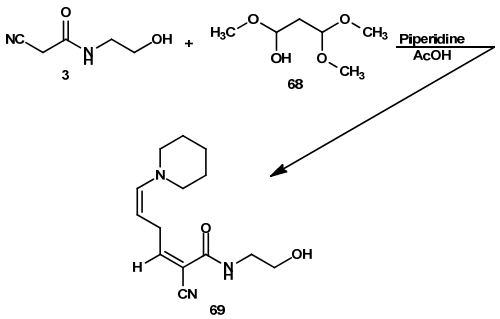
Scheme 23

Refluxing of cyanamide **3** with 4-piperdinylbenzaldehyde derivative (**66**) in methanol gave the corresponding acrylo nitrile (**67**) (Scheme 24) [15].



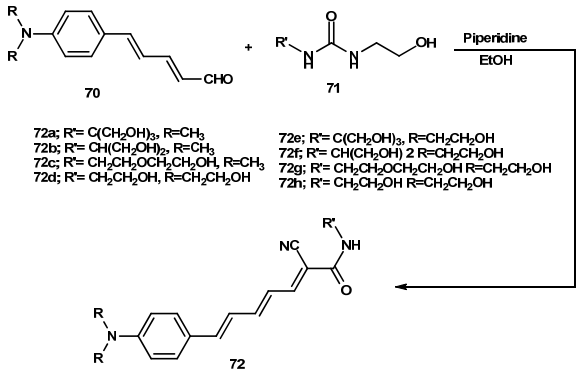
Scheme 24

Piperidine was condensed with 1,1,3,3-tetramethoxy propane (**68**) and 2-cyano-*N*-(2-hydroxyethyl)acetamide (**3**) in acetic acid, to afford the corresponding enamine **69** (Scheme 25) [32].



Scheme 25

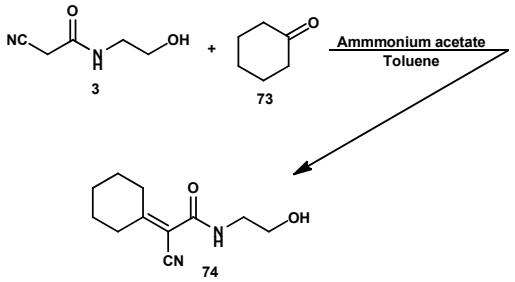
Eight hydroxyl functionalized donoreacceptor polyene chromophores (**72a-f**) were synthesized *via* Knoevenagel condensation reaction of aromatic polyenals (**70**) with 2-cyanoacetamide derivatives (**71**) (Scheme 26) [34].



Scheme 26

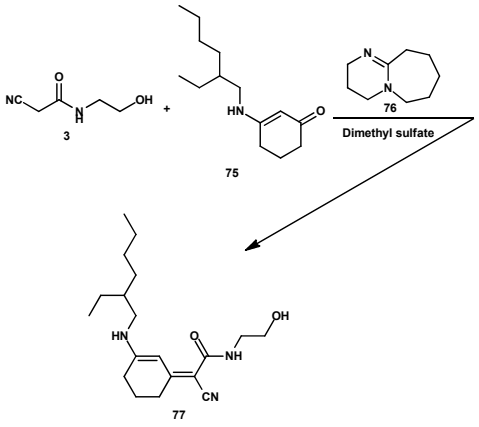
2.6.2. Reaction with ketones

2-Cyano-2-cyclohexylidene-*N*-(2-hydroxyethyl)acetamide (**74**) was prepared *via* Knoevenagel condensation of 2-cyano-*N*-(2-hydroxyethyl)-acetamide (**3**) with cyclohexanone (**73**) in acetic acid and ammonium acetate in toluene under reflux Dean-Stark (Scheme 27) [16].



Scheme 27

Furthermore acetamide **77** was prepared via condensation of 2-cyano-*N*-(2-hydroxyethyl)-acetamide (**3**) with, cyclo hexenone derivative **75** in dimethylsulfate in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (**76**) (Scheme 28) [32].



Scheme 28

3. Conclusion

The objective of the present study was to shows a systematic and comprehensive survey of the method of preparation and the chemical reactivity of 2-cyano-*N*-(2-hydroxyethyl)acetamide. The target compounds are important intermediate for the synthesis of a variety of synthetically useful and novel heterocyclic systems.

Acknowledgement

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