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ONE- STEP MULTI COMPONENT SYNTHESIS OF HIGHLY SUBSTITUTED PYRIDINE DERIVATIVES USING BARIUM OXIDE NANOPARTICLES AS CATALYST

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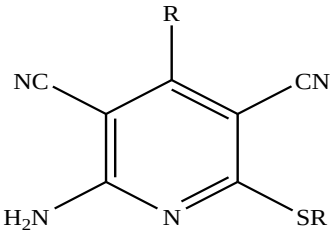
ABSTRACT: In one pot multicomponent synthesis of 2-amino,3,5-dicyno,4-aryl-6-sulfanylpyridine is 'Privileged medicinal Scaffold', this reaction has been indicated via multicomponent reaction of aromatic aldehyde, malononitrile as active methylene group and thiourea using Barium oxide nanoparticles as catalyst. The BaO NPs as a catalyst is a very effective Heterogeneous base catalyst in small amounts. We get excellent yield in a short time.

KEYWORD: Multicomponent reaction, Malanonitrile, Heterogeneous base catalyst, Pyridine, Substituted Pyridine.

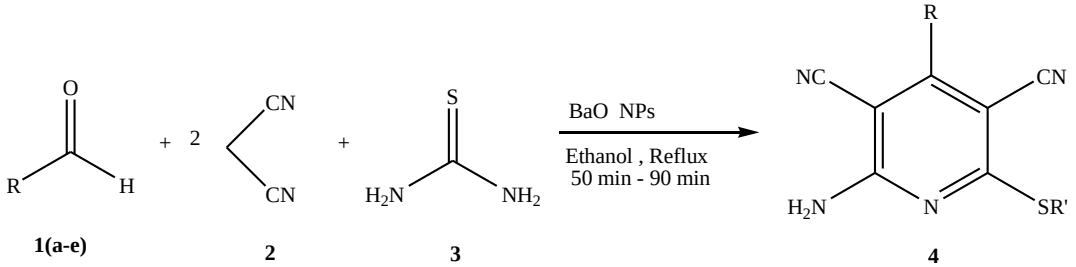
INTRODUCTION: The synthesis of 'Privileged medicinal Scaffold' or highly substituted pyridine is most important as this compound act as ligands for the number of functionally and structurally various biotic receptors so distributed as plan of action for beginning pharmaceutical agents for various implementation.[1] Highly substituted Pyridine is indicated via multicomponent reactions .In this reaction three or more subtract react to give a final product in one pot operation readably for multi-step synthetic tract a number of reaction and distillation steps are the most important standard for the regulation and potentiality of the process and should be cheap as able to be done. MCR reaction are the dominant device in novel drug synthesis this process is approve fast for creation of various organic compound. In this reaction carbon forms the bond with various elements like N, S & O it gives countless compound with pharmaceutical, biological and material properties.[2]



Substituted Pyridine

2-amino,3,5-dicyno,4-aryl-6-sulfanylpyridine substitution is useful to inhibit various protein like mitogen activated protein kinase (MARK), activated protein kinase-2 (PK-2) and also for target for tumor necrosis factor.[3] This Pyridine fraction has been found in both naturally & organic functionalized compound, this is active organic molecule for living organisms having remarkable various remedial benefits. Which shows anti-bacterial, anti-biofilm and anti-infective properties.[4] Salicylaldehyde react with ZrP_2O_7 catalyst forms Benzopyranopyridine. Which shows activity against anti-proliferative, anti-myosis, anti-rheumatic, anti-asthmatic [5] pyridine skeleton is the most important due to broad Spectrum biological activities as anti-miotic, anti-inflammatory. which is also important for the agrochemicals, organic intermediates, supermolecules ,nanoparticles and polymers [6] also pyrrolidone system is substituted with hydrophobic pyridine ring system because pyridine is acts as convulsant[7] N-heterocycle is the important in natural organic chemistry the synthesis of substituted pyridine which is particularly attractive because such component limited or complete structure of many synthesis compound in drug chemistry.[8] Central part of the pyridine has been found to be factors of few influential inhibitors of phosphodiesterase-4 (PDE4) that are favorable for the probable treatment of asthma & chronic obstructive pulmonary disease (COPD).[9]

The highly substituted pyridine has been developed using different method such as mannich reaction of aldehyde and iminium salt, passerini reaction of aldehyde and active methylene group with thiourea.[10] highly substituted pyridine which is form with heterogeneous base catalyst like MgO, Si, Mg-Al as catalyst gives green approach with using green solvent like water and ethanol.[11-13] also using Nanoparticles for the synthesis of pyridine ring which is a highly effective and also the required clement condition to produce high yield of product in short time.[14-16] In continuous of our attempts to succeed a systematic catalytic entity for numerous multicomponent reactions.[17-22] Here in report we synthesis of highly substituted pyridine derivatives 'privileged medicinal scaffold' 2-amino,3,5-dicyno,4-aryl.6-sulfanylpyridine using aromatic aldehydes, Malononitriles and Thiourea in the presence of Barium oxide nanoparticles as heterogeneous solid base catalyst in aqueous ethanol media in (1:1) ratio. Barium oxide nanoparticles as an effective, non-explosive, non-volatile, eco-friendly and easy to handle catalyst can be used in catalysis organic modification.



1(a-e) **2** **3** **4**

Scheme 1

Synthesis of highly substituted pyridines derivatives catalyzed by BaO nanoparticle

EXPERIMENTAL: All materials are the commercial reagent grade and were used without any purification. Barium Oxide Nanoparticles were prepared in accordance with procedure reported by A.Zeenath Bazeera & M.Irfana Amrin[10]. Progress of Reaction monitored by Thin layer chromatography (TLC) pure the product by Recrystallization technique using particular solvent. All melting points are determined in open capillary tubes in paraffin oil bath.

Preparations of Barium Oxide (BaO) Nanoparticles

By thermochemical method to synthesis of Barium oxide nanoparticles 20 mL pure ammonia was added to $Bacl_2$ vigorous stirring on magnetic stirrer at 580 – 690 rpm solution contain Ba^{2+} Exothermic reaction Barium chloride with ammonia should be added to precursor the solution temperature is 35,50 & 65 degree Celsius and PH was set in 10 at basic condition. and distilled water was added to maintain PH while vigorous stirring of solution continue till white precipitate is formed. the precipitate wash with distilled water and dried on hot plate at 100 ^{0}C for 1 hours .to produce BaO nanoparticles dried precipitate at 450 ^{0}C for 100 min.

Typical procedure for the synthesis of 2 -amino,4-aryl-3,5-dicyano-6-sulfanyl pyridine (4a -4e)

Method A

The reaction ratio is 1:1:1. To a mixture of aldehyde (1 mmol), malononitrile (2 mmol), in 2.5 mL ethanol and 2.5 mL of water, was added BaO nanoparticles (0.01g,0.1 mmol), and the reaction mixture stirred for 10 min at 45 ^{0}C. Then thiourea (1 mmol) was added and the solution was refluxed and stirred for 50 to 90 min.

Progress of the reaction was continuously monitored by TLC. When the reaction was complete, the mixture was cooled at room temperature and extracted with 3 mL ethyl acetate then 4 mLwater is added remove the water layer catalyst is remove with aqueous layer as catalyst is soluble in water. The organic layer is dried by adding sodium sulphate. the dried material is recrystallized with Ethanol. Light yellow crystal is obtained. Melting point (210-212 ^{o}C)

Method B

A mixture of appropriate aldehyde (1 mole), malononitrile (2 mole), thiourea (1 mole) and catalyst barium oxide is added (1 mole), further to this mixture (1:1) ratio of ethanol and water is added as a solvent. The reaction mixture is stirred on reflux condition for 50 min. At 50 ^{o}C temperature the progress of reaction is monitored by TLC. The product confirmed, it is cooled to room temperature. The precipitate is filtered and washed with water. Catalyst is removed with water, dried and crude product is recrystallized with ethanol. Light yellow Crystals are obtained. Melting point (212-214 ^{o}C)

RESULT AND DISCUSSION:

We improve the reaction condition on the basis of catalyst, solvent and reactant and also time and temperature. In the first instance we prepared barium oxide nanoparticle using thermal chemical method. To test the capability of the catalytic activity, we select to concern our basic research on the multicomponent reactions of aldehyde, malononitrile and thiols in the presence of various heterogeneous base catalyst and nanoparticles.

We decide to use nanoparticles as a catalyst because in several reports be revealed the remarkable level of the nanoparticles as catalyst in the term of discrimination, reactivity and enhanced yield of the product. We found that BaO NPs is effective catalyst in comparison of other catalyst in this multicomponent reaction and this catalyst is also water soluble.

During the optimization of reaction condition, we run the model reaction using para-chlorobenzaldeyde as aldehyde, malononitriles and thiourea in the presence of barium oxide nanoparticles as catalyst and water and ethanol is green solvents in 1:1 proportion that is the

most effective solvents for this multicomponent reaction. This model reaction was carried out minimum time in the presence of small amount of loading catalyst give the excellent yield of the product obtained is 2-amino-3,5-dicyano,4-chlorobenzene- 6-sulfanylpyiridine (4a) in short reaction time. We performed the reaction using various aldehyde such results are summarized in table.1

After completion of the reaction process, the Barium oxide nanoparticles were separated by centrifuge the mixture was cooled at room temperature and extracted with 3 mL ethyl acetate and then 4 mL water is added to remove the water layer catalyst. The organic layer is dried by adding sodium sulphate under the IR lamp. the dried material is recrystallized with Ethanol.

The structure of the isolated product (**4a**) confirmed on the basis of LCMS and ^{1}H NMR further more in ^{1}H NMR shows 7 proton signals obtained in spectral analysis (7. 9δ) d signal obtained proton attached to the benzene ring (6. 9 δ) d & (7. 0 δ) signal proton attached to same benzene ring (8.3 δ) d very high delta value because both sides having cyanide group (3. 55 δ) signal show singlet which attached to nitrogen. (2. 5 δ 3H) show singlet is directly attached to the nitrogen.

A sharp broad peak obtained at retention time is 0. 92 at this retention time 340. 37 Mass obtained at base peak and the reported mass of the product is 335. 803

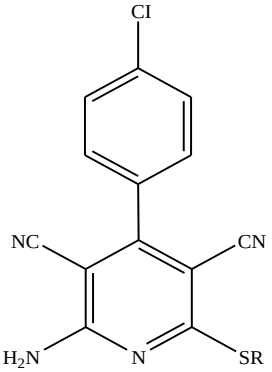
Table1 Synthesis of Highly substituted Pyridine using by BaO nanoparticles.

Entry	**R**	**R`SH**	**Product**	**Time (min)**	**Yield (%) [a]**	**M.P (^{0}C) [(2)]**
1	C_7H_5ClO	CH_4N_2S	4a	60 min	80%	210-212
2	C_7H_6O	CH_4N_2S	4b	75 min	85%	208-210
3	$C_7H_6O_2$	CH_4N_2S	4c	50 min	90%	218-220
4	C_7H_5ClO	CH_4N_2S	4d	65 min	90%	214-216
5	$C_8H_8O_3$	CH_4N_2S	4e	85 min	75%	209-211

[a]Isolated Yields.

SPECTRAL ANALYSIS:

All known compounds were identical in all physical and spectroscopic properties with which the structure of isolated product on the basis of their elemental analysis and spectral data.



2-amino-3,5-dicyano,4-chlorobenzene- 6-sulfanylpyiridine (4a)

Light yellow solid M.P-210-212 ^{0}C
^{1}H NMR (DMSO -d_6 400 MHz, δ ppm) : 3.3 (S, 2H, NH_2), 2.5 (S,3H,SR), 7.9 (d, 1H, H-Ar), 7.9 (d ,1H ,H-Ar), 7.0 (d, 1H , H-Ar), 6.9 (d ,1H , H-Ar), 8.3 (S, 1H, H-Ar)
LCMS : m/z 340.37 (m+2)

CONCLUSION:

In summary, an efficient and economical method for preparation of highly substituted pyridine derivatives been developed using BaO NPs heterogeneous base catalyst in green media. The product are obtained in good yield and reaction time is significantly low and remarkable method is three - components in one pot of aldehyde, malononitriles and thiourea in order to synthesize 2-amino-3,5-dicyano,4-aryl6-sulfanylpyiridine derivatives.

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