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One Pot Synthesis Of Tetrahydropyrimidine-5-Carbonitrile Analogous Promoted By Transition Metal Halide

PAILAKODANDA VENKATA SAIRAM[1], Dr. N, KRISHNARAO [1*]

1*.Department of organic chemistry, PRISM PG&DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016

ABSTRACT:

A simple and highly versatile an efficient three-component cyclocondensation of substituted aryl aldehyde, malononitrile and guanidine hydrochloride as an ammonia source promoted by Transition metal halide catalyst such as $ZrOCl_2$ in ethanol at 75^0C scaffold corresponding 1, 4, 5, 6-Tetrahydropyrimidine-5-carbonitrile. Hence, the practicality approach was investigated for the one pot synthesis desired compounds generate good to excellent yields. The derivatives of titled product was evaluated by advanced spectroscopic data viz; IR, ^{1}HNMR, ^{13}CNMR and LCMS and also determined by elemental analysis. The condensed reaction preceded a milder conditions, simple work-up, non-chromatographic purification of the desired products, without experiencing a discernible decrease in efficiency, the catalysts can be extracted and repurposed for further processes. This method is additive-free and incorporates nanotechnology for the synthesis of desired product and also has well to excellent exceptional yields, a wide range of substrate compatibility, and an instantaneous reaction time.

KEYWORDS:

Aromatic aldehyde, malononitrile, $ZrOCl_2$, 2, 4-diamino-6-phenyl-1, 4, 5, 6-tetrhydropyrimidine

1. INTRODUCTION:

One of the most important useful, powerful and an efficient process for synthesis of organic molecule in a modern synthetic organic synthesis field is known multi component reactions(MCR) and have been proven to be a most elegant and continuous path way to access complex structures in a single synthetic procedure from simple construction blocks. The formation of carbon-carbon and carbon-heteroatom bonds in a single one pot allows three component reactions to reveal high atom-economy, high selectivity, and procedurally simplicity. It has been performed to be a very elegant and quick method route to way complex molecule structures from simple building blocks [31, 32,33]. Now days, this type three component a one-pot reaction are good yields to excellent. It differs from multi stage reactions are followed by several fundamental ways [2], and it allows for fast access to combinatorial libraries of organic molecules for effective lead structure identification and optimization in drug discovery [3, 4]. Furthermore, it is extremely compatible with the objectives of sustainable and green chemistry to accomplish multiple transformations in a single manipulation.

Pyrimidines and its derivatives having nitrogen containing six membered heterocyclic moieties is exclusively special interest. They constitute an important class of natural, non-natural products and several compounds exhibit useful biological activities. Pyrimidines, being an integral part of DNA and RNA impart diverse pharmacological activities. The synthetic and biological significance pyrimidine plays an important role of this scaffold at a prestigious position in medicinal chemistry and its analogues are heterocyclic six member heterocyclic ring contains two heteroatom such as nitrogen atoms position at “1” and “3”. The titled moieties are present a major class of molecules which have been received more attention because of their wide range of pharmacological activity. Now days, the preparation of tetrahydropyrimidine and their analogous are highly recognised in synthetic organic chemistry as well as medicinal chemistry. The parts of pyrimidine moieties is containing in several useful biologically active compounds that have been represented to use in medical practice. Hence, presently much more showing an attention has been maintained to derivatives of pyrimidine which is formed by combination their hydrogenation. This class of compounds were elaborated broad ranges of biological and pharmacological properties which show a very resemblance pharmacological profile to classical dihydropyridine calcium channel modulators and their various condensed derivatives were reported to contain calciumntagonist anti-inflammatory (10), Antibacterial Agents (11), antibacterial, Antifungal Activities (12, 19), Antimicrobial activity(13), Antibacterial Agents (14), antimicrobial activity(15),m1 Agonists(16), Anticancer Agents(17), Antioxidant Activity(18).The tetrahydropyrimidine moieties are an important for biology activity, so it's important to investigate their physicochemical characteristics, such conductance, density, and refractive index, in order to learn more about how these compounds are used in the biological sector. In present work, some new derivatives of Tetrahydropyrimidine promoted by NanoTiO_2which have been synthesized and characterization of these derivatives is done by IR, NMR and mass spectral.

The previous reported survey announcement majority on work has been done majority on work tetrahydropyrimidine. The plenty of researchers have been prepared tetrahydropyrimidine and its derivatives

promoted by several synthetic process. The tetrahydropyrimidine and its analogous are of important heterocyclic molecules that have been subjected to a major number and variety of designed structural modifications in order to prepare useful derivatives with different biological properties. The numbers of scholar and researchers day to day have been worked on QSAR study of tetrahydropyrimidine. The titled derivatives can be reported various catalyst Nano catalyst and non-catalyst are either protic acids or Lews acids presented $CuO@SiO_2$ (20), $Fe_3O_4@GA@Isinglass$ (21), ZrO_2/La_2O_3 (22), $Fe\text{-}MOF@Fe_3O_4$ (23), ZnO (24), $Co\text{-}MOF@Ag_2O$ (25), Zinc Nanomagnetic(26), $Fe_3O_4@SiO_2@APTES@MPIB\text{-}Mn(II)$ (27), SiO_2/DBN(28), Nano catalyst(29).

We reported the present work highly an efficient versatile and appropriate process. It is used for synthesis of tetrahydropyrimidine-5-carbonitrile analogous with help of Transition metal Nano catalyst.. Our research perfectly and progressively the catalytic properties of magnetically separable $ZrOCl_2$ numerous organic transformations has scaffold us to the identification that the effectiveness of $ZrOCl_2$ catalysts for the synthesis of Tited analogous has not been previously reported. Hence, our aimed to focus been done to investigate the impact of ZrOCl2 catalyst in the one-pot synthesis of titled via cyclocondensation of aromatic carbaldehyde, malononitrile and as ammonia sources is guanidine hydrochloride.

2. Methods and Materials:

2.1. Experimental Procedure:

The synthetic grade reagent and chemicals were all purchased commercially from Merck Chemicals PVL and Fine Chemicals, and they provided the solvent purity without the need for additional purification. The melting temperatures of recently synthesized compounds were measured in open capillaries using an Aggarwal thermometer; the results are uncorrected. Using $CDCl_3$ solutions, ^1H NMR and ^{13}CNMR spectra were acquired on a Brucker 400MHz spectrometer. Chemical shifts are presented as singlet(s), doublet (d), triplet (t) and multiplicative (m). The measurement of chemical shifts is expressed in parts per million (ppm) references to TMS and using an LCMS instrument, the molecular weight of the desired product molecules was determined. The freshly synthesized derivatives underwent elemental analysis using a Carlo ErbaEA 1108 elemental analyser. Mixture for reaction was examined and observed using Merck aluminium thin-layer chromatography (TLC).

2.2.General procedure of derivatives 2,4-diamino-6-phenyl-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4a):

In a 100mL RB flask, substituted aryl aldehyde (1.125 mmol), malanonitrile (1.5 mmol), and freshly made catalytic $ZrOCl_2$ were combined with ethanol. After the solution turned clear, the addition of ammonia sources such as 1.525 (mmole) of guanidine hydrochloride into the above reactants and continued reaction at 75^0C for two hours. After the reactants were consumed during the appropriate time of reaction until the reaction was identified by TLC (5:5, ethyl acetate: n-hexane). Crushed ice was filled with the reaction mixture. Ethyl acetate was used to extract the product from the solution after it had been neutralized with an aqueous solution of diluted HCl and brine solution was then used to wash the mixed organic layer. In order

to obtain the solid product, the organic layer was dried on anhydrous Na_2SO_4 and the solvent was extracted using a vacuum pump at a lower pressure. All of the synthetic chemicals were recrystallized from ethanol.

2.2.1.2,4-diamino-6-phenyl-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4a):

Yield: 85%, pale-yellow solid; m.p (ºC): 220-222 ; ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm :8.973(s,1H,N-H,pyrimidinering),7.384-7.174(m,5H,Ar-H),6.533(s,2H,NH2),6.294 (s,2H,NH_2), 740(d,j=8.8Hz,1H-CH-),3.297(t,j=7.6Hz,2H,-CH-),2.335(s,1H,-CH-);^{13}CNMR(100MHz,CDCl3):δppm:161.94, 135.72,129.15,127.68,125.81,117.06,56.44,42.62,40.76.LC-MS(m/z):215.47. Molecularformule: $C_{11}H_{13}N_5$. Elemental Analysis: calculated: C- 63.39, H-6.09.N-32.54.Obtained: C-61.35,H-6.08 ,N-32.59.

2.2.2.2,4-diamino-6(4-hydroxyphenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4b):

Yield:89%,paleyellowsolid;mp(ºC):212-214;^{1}HNMR(400MHz,$CDCl_3$)δppm:9.315(s,1H,-OH), 8.708 (s,1H, N-H, pyrimidine ring),7.135 (d,J = 7.6Hz, 1H,Ar-H),7.056 (d, J = 7.6Hz, 1H,Ar-H),6.674 (s,2H,NH2), 6.612 (d, J = 8.8Hz, 1H,Ar-H), 6.433 (d, J = 8.4Hz, 1H,Ar-H),6.378 (s,2H,NH2), 3.790 (d, J=8.4Hz,1H, CH),3.130 (t j=8.0Hz,2H,-CH-),2.524(s,1H,-CH-);13CNMR(100MHz,CDCl3)δppm:164.78,152.17,130.60,128.88,123.36,118.88,57.45, 43.47,40.78;LC-MS(m/z):231.62(M+H).Molecularformule:$C_{11}H_{13}N_5O$.ElementalAnalysis: Calculated:C-53.24,H-5.36.N-8.28,Obtained:C-53.20,H-5.34,N-8.34.

2.2.3.2,4-diamino-6-(3-ethoxy-4-hydroxyphenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4c):

Yield: 90%, pale yellow solid; m.p (ºC): 234-236;1H NMR (400 MHz, CDCl3): δ, ppm = 9.587(s,1H,-OH), 8.459 (s,1H, N-H, pyrimidine ring),7.224 (s,1H,Ar-H), 7.074 (d, J = 8.0Hz, 1H,Ar-H),6.872(d,J=9.2Hz,1H,Ar-H),6.453(s,2H,NH2),6.045(s,2H,NH2),3.677(s,1H,-CH-),3.342-3.309(m,1Hz,-CH-H),2.511(s,1H,-CH-);^{13}CNMR(100MHz,CDCl3)δppm:164.78, 154.17,132.62,128.45,123.56,119.48,58.45,43.27,40.33,17.20;LCMS(m/z):229.62(M-H). Molecularformule:$C_{11}H_{13}N_5O$;ElementalAnalysis:calculated:C-53.24,H-5.36.N-8.28,Obtained:C-53.20,H-5.34,N-8.34.

2.2.4.2,4-diamino-6(4-hydroxy-3-methoxyphenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4d):

Yield: 89%, pale-yellow solid; m.p (ºC): 215-217; 1H NMR (400 MHz, $CDCl_3$):δ ppm: 9.931(s,1H,-OH),8.848(1H,1H,N-H),6.863-6.695(m,3H,Ar-H),6.721(2H,s,NH_2),6.252(2H,s, NH_2),3.916(d,J=7.2,1H,-CH-),3.721(s,3H,OCH_3),3.388(s,1H,-CH-);^{13}CNMR(100MHz, $CDCl_3$)δppm:162.17,146.26,143.48,132.17,125.26,122.35,120.11,117.08,55.25,42.92,40.35.LCMS:(m/z)261.48.Molecularformule:$C_{12}H_{15}N_5O_2$;ElementalAnalysis:calculated:C-55.16,H-5.79.N-26.80,Obtained:C-55.10,H-5.77,N-26.88.

2.2.5.2,4-diamino-6(3,4,5-trimethoxyphenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4e):

Yield: 95%, pale yellow compound ; m.p (ºC): 245-247; ^{1}H NMR (400 MHz, $CDCl_3$)δ ppm :9.259 (1H, s, NH),8.568 (1H, s, NH), 7.656 (2H, d, J = 9.2, Ar-H), 7.318 (2H, d, J = 8.0, Ar-H), 5.117 (1H, d, J = 6.8,

CH), 3.615 (3H, s, OCH_3), 3.127 (3H, s, CH_3), 2.224 (3H, s,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:172.58,165.45,162.76,144.15,137.06,135.44,127.42,119.27,107.24, 54.79,50.05,22.85,17.01;LC-MS:(m/z):261.38.Molecularformule: $C_{15}H_{17}N_2O_2$.ElementalAnalysis:calculated:C-56.41,H-5.37.N-13.16,Found:C-56.35,H-5.36,N-13.22.-

2.2.6..2,4-diamino-6(4-fluorophenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4f):

Yield-89%,^{1}HNMR(400MHz,$CDCl_3$)δppm:8.935(s,1H,N-H,pyrimidinering),8.525(s,2H, NH_2),7.310-7.153(m,4H,Ar-H),6.348(s,2H,NH2),4.125(d,J=9.2Hz,-CH-),3.386(d,J=8.8Hz, 1H,-CH-),2.690(d,J=7.6Hz,-CH_2-).^{13}CNMR(100MHzCDCl3)δppm:162.15,155.46,137.02. 129.05, 125.34, 119.75, 57.94, 43.15, 40.66. LCMS (m/z) =233.28; Molecularformule: $C_{11}H_{12}FN_5$. Elemental Analysis: calculated: C-56.64, H-5.19, N-30.03. Obtained: C-56.60, H-5.18, N-30.09.

2.2.7.2,4-diamino-6(4-Chlorophenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4g):

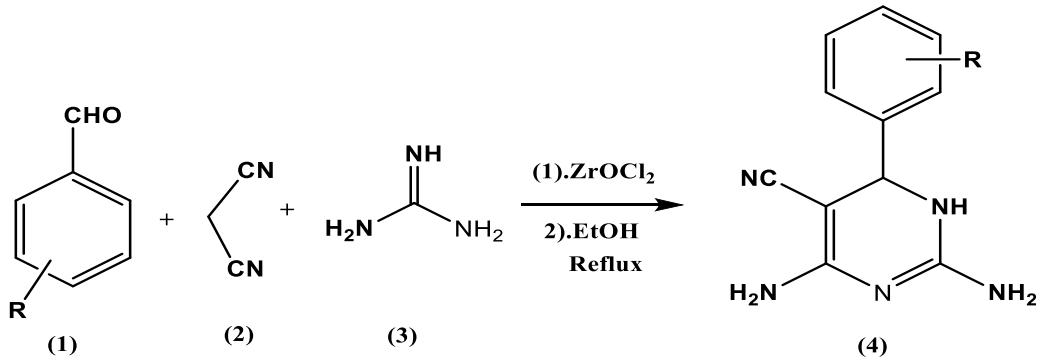
Yield-88%.1HNMR(400MHz,CDCl3)δppm:8.867(s,1H,N-H,pyrimidinering),8.092(s,2H, NH_2),7.478-7.311(m,4H,Ar-H),6.321(s,2H,NH_2),3.607(d,J=7.61H,-CH-),3.222(d ,j=8.4Hz,-CH-),2.513(s,1H,-CH-).13CNMR(100MHz,CDCl3)δppm:163.17,137.04,130.62,128.71, 128.09,119.01,54.82,43.08,40.39.LCMS(m/z)=251.19(M+2).Molecularformule:$C_{12}H_{15}ClN_5$.ElementalAnalysis:calculated:C-52.91,H-4.84,N-28.05.Obtained: C-52.87,H-4.83,N-28.12.

2.2.8.2,4-diamino-6(4-nitrophenyl)-1,4,5,6-Tetrahydropyrimidine-5-carbonitrile(4h):

Yield:85%,pale-yellowsolid;mp(ºC):212-214;1HNMR(400MHz,$CDCl_3$):δppm:8.953(s,1H, N-H,pyrimidinering),8.228(d,J=9.2Hz,1H,Ar-H),8.178(d,J=8.4Hz,1H,Ar-H),7.531-7.361 (m,2H,Ar-H),6.645(s,2H,NH2,NH2),6.625(s,2H,NH2),4.146(d,J=8.8Hz,1H,-CH-),3.525(t, j=8.4Hz,2H,-CH-),2.841(d,j=7.6Hz,-CH-);13CNMR(100MHz,$CDCl_3$)δppm:163.65,145. 74,144.81,125.91,123.04,119.01,56.65,43.34,41.79;LCMS(m/z)=260.51.Molecularformule:$C_{11}H_{12}N_6O_2$;ElementalAnalysis:calculated:C-50.77,H-4.65.N-32.29,Obtained:C-50.73,H-4.64,N-32.35

3.RESULTS AND DISCUSSION:

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents and catalyst



(1) (2) (3) (4)

R = (4a) H, (4b) 4-OH, (4c) 3-OC_2H_5-4-OH, (4d) 3-OCH_3-4-OCH_3, (4e) 3,4,5-$(OCH_3)_3$, (4f) 4-F, (4g) 4-Cl, (4h) 4-NO_2

(Scheme-1)

In a model reaction, the reaction substituted aryl aldehyde reacted with malanonitrile and guanidine chloride in the presence of $ZrOCl_2$ catalysts to give the corresponding titled derivatives in good to excellent yields. The nature of the substituent on the arylaldehyde has not significant effect on yield of reaction, effect of the catalyst amount was investigated (Table -1). To minimize the formation of by products and to achieve excellent yield of the desired product, the reaction is optimized by varying the amount of catalyst (5, 10, and 15). The percentage of the desired product was obtained using $ZrOCl_2$ as the catalyst and it was found to maximum is 94. The same reaction when pe-formed without catalyst for 3 h gave no product. When the catalyst content was increased to 15 mg and the product formation decreased to 85%. Therefore, it was identified that the use of 10 mg of the catalyst was sufficient to promote the reaction, and greater amounts of the catalyst did not develop the yield. In this reaction, different catalyst was applied at 70^0C and observed the effect of catalyst, reaction time, the percentage of the desired product and work up performers of catalyst. The effect and reusability of catalyst is $ZrOCl_2$ compared with SnO_2 and ZnO. The height percentage of the desired product was obtained by using $ZrOCl_2$ than the rest of the two catalysts.

Table-1: Amount and catalyst of the synthesized derivatives:

S.NO	Catalyst	Amount (mmol)	Time (min)	Yield (%)[a]
1	SnO_2	05	120	55
2		10	180	60
3		15	210	45
4	$ZrOCl_2$	05	60	88
5		10	90	95
6		15	120	85
7	ZnO	05	150	47
8		10	200	58
9		15	240	50
10	Absence of catalyst	-	240	

[a] Isolate yields. Followed by reaction condition is substituted aromatic aldehyde (mmol), malononitrile (mmol), guanidine hydrochloride in the ethanol as the solvent

A reaction medium that is effective in both time and yield was discovered. It is important to note that, even after 120 minutes, no product was discovered in the absence of catalyst. These findings suggest that there is significant catalytic activity in the catalyst throughout this transition.

The reaction of malenonitrile, guanidine chloride and aromatic substited aldehyde was maintained by time of reaction and also applying various polar solvents, non-polar solvents and polar aprotic solvents, such as CH_3CN, MeOH, EtOH, DCM, and toluene, in order to optimize the reaction conditions, including solvents and different temperature (Table -2, entries 1–5). Low product yields were obtained even after 240 minutes for the reaction in toluene and 300 minutes for the reaction in dichloromethane (DCM) solvent (Table 2, entries 4 and 5). Even so, the yields for acetonitrile and methanol under reflux conditions were only moderate (Table 2, entries 3 and 4). In this reaction, constant temperature followed by the various solvents applied and performed during reaction generated different percentage of products.

Table -2: Effect of the solvent of synthesized derivatives (4e):

Entry	**solvent**	**Temperature(^{0}C)**	**Time(min)**	**Yield (%)**
1	CH_3CN	75	210	65
2	Methanol	75	180	72
3	Ethanol	75	120	95
4	DCM	75	240	41
5	Toluene	75	300	49

Arylaldehyde (mmol), malanonitrile (mmol), and guanidine hydrochloride (mmol) with help of Nano catalyst (25mmol) under at 75^{0}C condition in various solvents.

The reaction conducted in ethanol at reflux for 120 minutes with a catalyst present produced the best results (Table-2, entry-3). Ethanol was therefore chosen as the reaction's solvent. We observed in reaction time that a utilizing aqueous medium in this reaction produced moderate yields of products under reflux conditions after lengthy reaction times, despite the fact that aqueous medium is a desired solvent for chemical reactions due to causes of low cost, highly safety and do not effected on environmental issues.

The ability to reuse the catalyst through straightforward filtration without losing its activity and is one of the most significant benefits of transition metal ZrOCl2 catalysis over Lews acid catalyst, protic acid catalyst and non-transition metal catalyst it's with equivalent. The catalyst's recovery and reusability were examined in the section under "Derivatives Formation" Once the reaction was finished. The catalyst was filtered out, then repeatedly cleaned with 50 mL acetone, twice with doubly distilled water, and finally dried at 100°C. Next, the next run made use of the recovered catalyst. The catalyst can be reused multiple times without experiencing a significant loss of activity, according to the results of three consecutive runs.

In the presence of ZrOCl2 catalysts, a number of substituted aryl aldehydes interacted with malononitrile and guanidine chloride to obtain the corresponding titled analogous in good to outstanding yields. The aryl aldehyde's substituent type has no appreciable impact on the reaction's yield. But catalysts' characteristics are important. Table 1 shows that the best outcomes from the Nano catalyst. The results showed that the range of isolated yields was 85–95%, respectively.

Finally, the obtained results of synthesis of desired titled from malononitrile and guanidine chloride and various substituted aromatic aldehyde. Again, it can be identified that the aldehyde reactants bearing electron releasing groups and electron attracting groups showed some difference during the reaction and obtained notable yields. Moreover the wide range of isolated yields was found 85–95% respectively.

The spectroscopic methods are submitted in the supplementary material for this article. The ^{1}HNMR spectra exhibited a peak at 9.931-8.674 δppm shown the presence of N-H proton, a peak between 8.174-7.124 δppm showed aromatic proton, a peak exhibited between 3.754-3.615 δppm represents methoxy protons, a peak shown between 9.931-9.587 δppm indicates hydroxyl proton(-OH) and a peak exhibited between 3.338 δppm represents –CH-protons. The methyl protons appears at1.115ppm appear at the ^{13}CNMR spectra recorded a peak maximum at 170.12 δppm is belongs to the carbonyl group in nitro substituted group. The LCMS spectra recorded the molecular weight of halogen substituted such as 4i,4J and 4K showed (M+2) peak .The derivatives "4b" exhibited (M^{+}+H) peaks. Whereas the derivatives "4c " showed at (M-H) peaks.

4. CONCLUSION:

In this study, we have successfully devised a green, environmentally friendly synthesis of Tetrahydropyrimidine. The synthesized Tetrahydropyrimidine derivatives were evaluated by infrared spectroscopy to check for the presence of the necessary functional group. Furthermore, the structure of the molecules was revealed by the suitable chemical shift values obtained from an NMR spectroscopy result. It was discovered that the experimental results and the published literatures agreed rather well. This approach offers several noteworthy benefits, including solvent reaction conditions, high efficiency, quick reaction durations, and high product yields. Due to its simplicity, it is a desirable substitute for the clean synthesis of tetrahydropyrimidine, which are materials with biological and medicinal significance. We have developed the simple and highly efficient three components such as benzil, aromatic aldehydes and ammonium acetate promoted by $ZrOCl_2$ in presence ethanol as solvent.

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