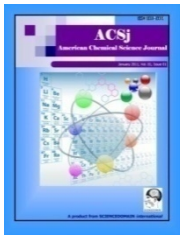

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Silica Ammonium Acetate as an Efficient and Recyclable Heterogeneous Catalyst for Synthesis of 4*H*-pyran Derivatives under Ultrasound Irradiation at Ambient Conditions

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Authors' contributions

This work was carried out in collaboration between all authors. Author GMN designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author AMAAK managed the analyses of the study. Author HAO managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

A simple, versatile and efficient method has been developed for the synthesis of 4*H*-pyran derivatives 4a-k via a three-component cyclocondensation of aldehydes, malononitrile and ethyl acetoacetate under heterogeneous conditions using silica supported ammonium acetate as the recyclable catalyst, promoted by ultrasound irradiation. The present method offers several advantages such as the products are obtained in excellent yields and are in a state of high purity, non hazardous reaction conditions as well as short reaction times.

Keywords: Ultrasound; heterogeneous; recyclable; multicomponent reaction; 4H-pyrans.

1. INTRODUCTION

Multicomponent reactions (MCRs) have greatly contributed to the convergent synthesis of complex and structurally interesting organic molecules from simple and readily available

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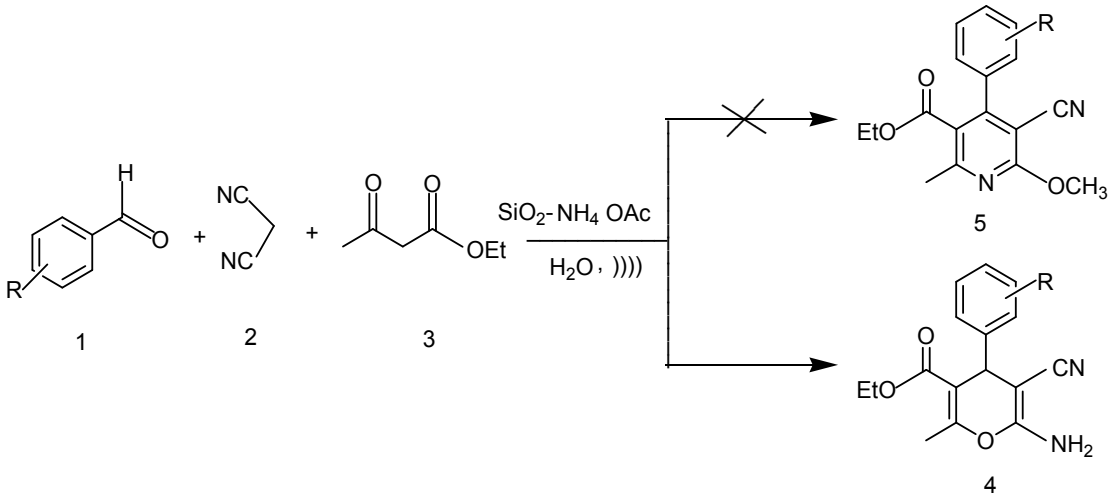
starting materials and have emerged as a powerful tool for drug discovery [1]. The MCRs strategy offers significant advantages over conventional multi step synthesis due to its flexible, convergent and atom economical nature [2]. In a true sense, MCRs represent environmentally benign processes by reducing the number of steps, energy consumption and waste production [3]. These features make MCRs well-suited for the construction of diversified arrays of valuable heterocyclic scaffolds. Therefore, great efforts have been done and still are being made to find and develop new multi component reactions. Usually, to drive the conversion of MCR, one or two components are excessive and this always leads to the trouble of separating and purifying the target products. 4*H*-pyrans 4a-k are an important class of heterocycles because the core fragment is constituted by a great variety of natural products and biologically active compounds. On the other hand polyfunctionalized 4*H*-pyran derivatives have attracted great attention recently in synthetic organic Chemistry due to their wide range of biological activity and pharmacological property such as anti-coagulant, anti-cancer, spasmolytic, diuretic, and anti-ancaphylactin [4]. The pharmacological activities exhibited by these compounds are mainly due to the presence of different heterocyclic ring systems. These compounds can be used for the treatment of neuro-degenerative diseases, including Alzheimer's disease as well as for the treatment of schizophrenia and myoclonus. Furthermore, a number of 2-amino-4*H*-pyran derivatives are useful as photoactive materials [5]. 4*H*-pyrans are also useful intermediates for the synthesis of various compounds such as pyranopyridine derivatives [6], polyazanaphthalenes, pyrano [2,3-*d*] pyrazoles [7], pyrano pyrimidines and pyridin-2-ones [8] with various other biological activities. Thus, in view of their wide utility, researchers have synthesized the 4*H*-pyran unit using different methods including radioactive and non-radioactive techniques such as microwave irradiation [9]. Generally, 2-amino-4-aryl-3-cyano-4*H*-pyrans were synthesized by the cyclization of arylidenemalononitriles and active methylene compounds in the presence of organic bases such as piperidine [10], pyridine [11], triethylamine [12,13]. In addition, the one-pot synthesis of 4*H*-pyrans has been reported using tetrabutylammonium bromide [14], (S)-proline, rare earth perfluorooctanoates, and hexadecyltrimethylammonium bromide [15]. Moreover, the cyclization arylidenemalononitriles and ethyl acetoacetate in the presence of triethylbenzylammonium chloride, as phase-transfer catalysts, in an aqueous medium has been reported [16]. Recently, one-pot synthesis of these compounds has been reported using Mg/La mixed oxide [15], MgO [17,18] and tetramethylguanidine [19] as basic catalyst. But most of the reported reagents are associated with certain disadvantages such as tedious work-up, expensive nature of the reagent, toxic nature etc. In order to cumbersome these problems, emphasis has been laid on the use of supported reagents. The major advantage of supported reagent is the reusability of the catalyst which makes the process inexpensive. Moreover, it also contributes towards the area of "Green Chemistry".

The demand for increasing clean and efficient chemical synthesis is continuously becoming more urgent from both an economic and an environmental standpoint. Organic synthesis in the absence of solvent or the water of solvent has been received much attention because of several advantages in preparative procedures, such as environmental compatibility, easy work-up, enhanced selectivity, reduction of by-products and much improved reaction rates [20,21]. These would be especially important during industrial production.

In keeping with our interest in the application of ultrasound irradiation in organic synthesis, we herein disclose a simple and efficient synthesis of 4*H*-pyran derivatives via a three-component cyclocondensation reaction of aldehydes, malononitrile, and ethyl acetoacetate using silica supported ammonium acetate as an efficient and recyclable heterogeneous catalyst under ultrasound irradiation.

Silica Supported ammonium acetate [22] can be regarded as the acyclic ester and have been used as in many organic reactions owing to their stability, low cost, poisonlessness and easy availability. Herein, we report a safe, facile and one-pot synthesis of 2-amino-3-cyano-4*H*-pyran derivatives 4a-k by three-component reaction catalyzed by ammonium acetate under water as a solvent shown as Scheme 1.



Scheme 1. Synthesis of 4*H*-pyran derivatives
R= H, Cl, NO_2, OMe

2. EXPERIMENTAL DETAILS

2.1 Materials and Reagents

All reagents were purchased from Merck and Loba and used without further purification. All melting points were measured in open capillaries and are uncorrected. Silica gel used for TLC was 200-300 mesh with binder. IR spectra were recorded on a SHIMADZU instrument. ^{1}H NMR and ^{13}C NMR were recorded on BrukerMSL-300 MHz and BrukerMSL-200 MHz instruments All spectra were recorded in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) down field from tetra methyl silane (TMS) as the internal standard. Elemental analyses were determined by an elemental analyzer (CHNS-O, EA 1108-elemental analyzer, Carlo Erba instruments). For ultrasound assisted organic reactions, ultrasonicator was used. The technical specifications are as follows:

Electric supply: 230 v A.C. 50 Hz, 1phase.
Ultrasonic frequency: 36 ±3 KHz.
Ultrasonic power: 100 watts.

2.2 General Experiment

2.2.1 Preparation of catalyst

The catalyst was prepared by grinding silica (1 g, K 100) with ammonium acetate (0.5 g) in a pestle and mortor at room temperature. The catalyst was stored in desiccators [23].

2.2.2 General procedure for the preparation of 4H- pyrans (4a-4k)

To a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and ethyl acetoacetate (1 mmol) the Silica supported ammonium acetate catalyst (10 mole %) was added in 5 ml water and the resulting mixture was irradiated in an ultrasound at 100 W for the appropriate time (Table 4). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured onto crushed ice and stirred for 2-5 min. The crude product was collected by filtration under suction, washed with ice cold water and recrystallized from hot ethanol to afford pure benzopyranopyrimidines derivatives.

3. RESULTS AND DISCUSSION

4*H*-pyran derivatives were obtained in excellent yields and in shorter reaction time through the one-pot condensation of aromatic aldehydes (1 mmol), malononitrile (1 mmol) and dicarbonyl compounds (1 mmol) using silica supported ammonium acetate as the recyclable catalyst (10 mol %) in water as a solvent under ultrasound irradiations (100 W). To optimize the reaction conditions, benzaldehyde, malononitrile and ethyl acetoacetate were selected as the model substrates to examine the effects of different solvents (toluene, CH_3CN, ethanol, water and methanol) and molar ratios of the catalyst at room temperature. The reactions were monitored by TLC and all the yields reported in Table 1 are isolated. The effect of different solvents on the course of reaction was studied (Table1). From the results given in Table 1, it was found that among various solvents tried, water was found to give optimum results in term of reaction time and yield. Thus, the optimum conditions for the reaction are: benzladehyde (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol) and 0.2 g of silica supported ammonium acetate. Room temperature was found to be the optimum, reaction time was shorter. The results are summarized in Table 1.

Table 1. Condensation between benzaldehyde, malononitrile and ethyl acetoacetate in different solvents under ultrasound irradiation

Entry	Solvent	Reaction time (min)	Isolated Yield (%)
1	Toluene	20	60
2	CH_3CN	10	75
3	Ethanol	10	80
4	Water	5	95
5	Methanol	15	85

To investigate the reaction in detail a model reaction was carried out by condensing aromatic aldehydes malonitrile and ethyl acetoacetate in various solvents and catalyst (10 mol %) such as K_2CO_3, TBABr, TBABr + K_2CO_3, KH_2PO_4, CH_3COONa, $(NH_4)_3PO_4$, L-Proline and NH_4OAC (Table 2). The results showed that when ammonium acetate was used as a catalyst

its reaction was more effective than L-Proline, K_2CO_3. The results of the reactions are depicted in Table 2.

Table 2. A model reaction by condensing Aromatic aldehydes, Malonitrile and Ethyl acetoacetate in various catalysts (10 mol%) under ultrasound irradiation at 100 W

Entry	Catalyst	Time (min)	Yield %
1	K_2CO_3	30	30
2	TBABr	30	trace
3	TBABr+K_2CO_3	25	50
4	KH_2PO_4	30	10
5	CH_3COONa	20	80
6	NH_2PO_4	30	trace
7	L-Proline	15	40
8	NH_4 OAC	5	95

We have also studied the effect of concentration of catalyst (ammonium acetate) under ultrasound irradiation at 100 W in water as a solvent. It was observed that 10 mol% of the catalyst was the optimum quantity to get the desired product in excellent yield. The results are depicted in Table 3.

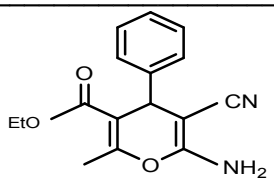
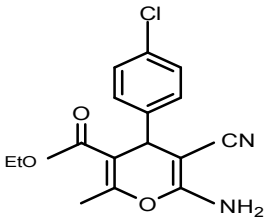
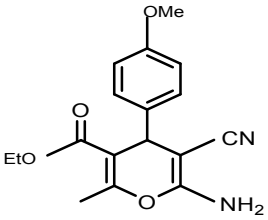
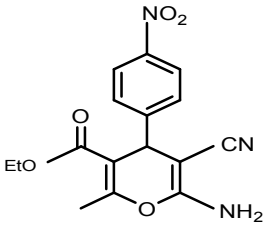
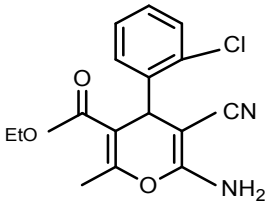
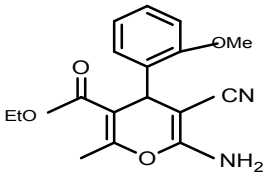
Table 3. Effect of the Concentration of the catalyst in methanol under ultrasound irradiation at 100 W

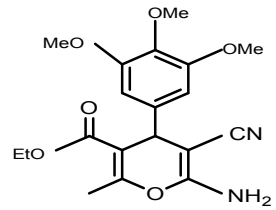
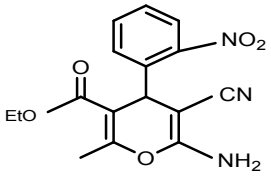
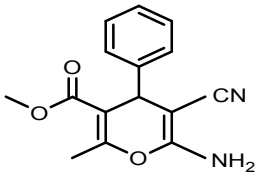
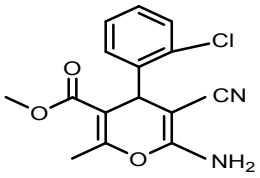
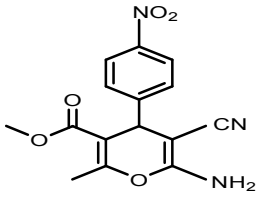
Entry	Ammonium acetate in mol %	Yield %
1	5	70
2	7	75
3	8	80
4	10	95
5	12	85

Different aldehydes containing electron-withdrawing, electron releasing substituents and β-diketoesters were used for universal applicability of the method for the synthesis of pyrans. It was found that in all cases, the yields were excellent.

Using the optimized conditions, the reactions of various aromatic substituted aldehydes, ethyl acetoacetate and malononitrile were investigated (Scheme 1). It was found that all the reactions proceeded smoothly to afford the corresponding products in high yield. The reaction of various aromatic aldehydes containing electron- withdrawing groups (entries 4b, 4d, 4e, 4h, 4j, 4k) and electron-releasing groups (4c, 4f and 4g) were examined. They all gave the products in goods yields (Table 4).

Table 4. Condensation of aldehydes and active methylene compounds using silica supported ammonium acetate as a reusable catalyst under ultrasound irradiation

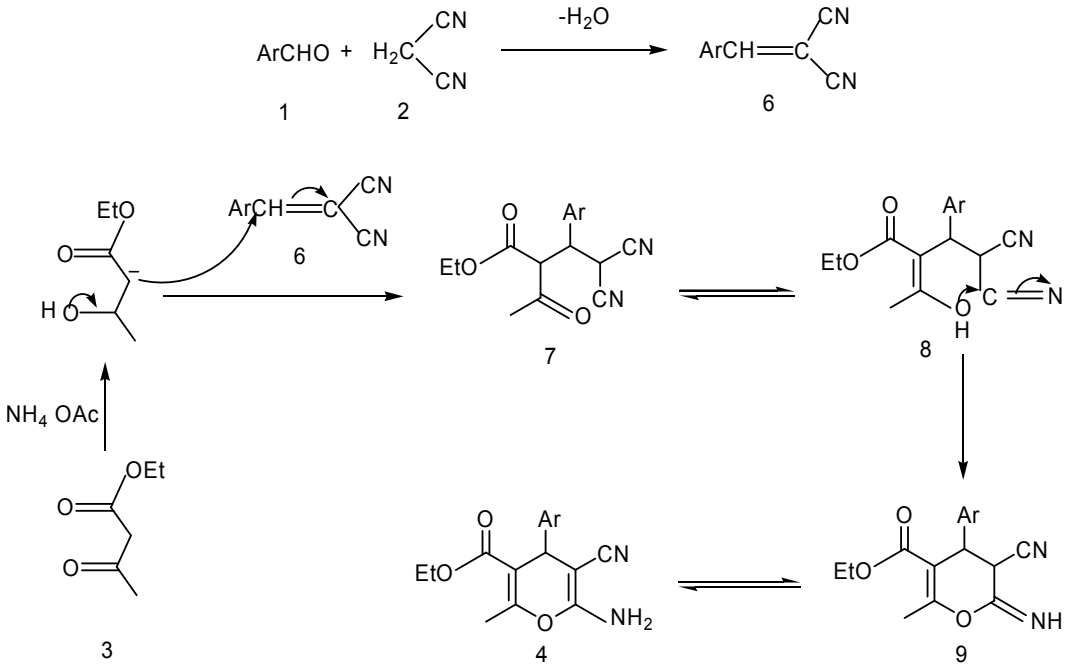
Entry	Product	Time (min)	Yield (%)	M. Pt / Lit. M. Pt (ºC)
4a		5	95	192-194 (195-196) 17
4b		10	93	169-171 (170-172) 15
4c		15	85	133-135 (136-137) 15
4d		5	95	175-177 (176-178) 15
4e		10	92	179-181 (180-181) 15
4f		10	88	198 200 (196-197) 17

4g		15	91	182 184 (-)
4h		5	98	177 179 (177.5-178.5) 17
4i		5	85	150 152 (154.5-155.5) 17
4j		10	90	158 160 (143.5-144) 17
4k		5	95	182-184 (180-181) 17

The aldehydes containing electron withdrawing groups gave the products in shorter time as compared to the aldehydes containing electron-donating groups. When using heterogeneous catalyst, the important issue is the recyclability. To test this, a series of three consecutive runs of the reactions of benzaldehyde, malononitrile and ethyl acetoacetate with the catalyst were carried out (I^{st} use: 95% isolated yield after 5 mins; 2^{nd} use: 90% isolated yield after 10 mins; 3^{rd} use: 80% isolated yield after 20 mins). These results demonstrate that there is decrease in the activity of the catalyst after every use. This may be due to either the deactivation of active centers resulting from complexation with both starting materials and products or by microscopic changes in the structure of the catalyst.

We proposed the possible mechanism to account for the reaction. First, the aromatic aldehyde 1 is condensed with malononitrile 2 to afford the α-cyanocinnamonitrile derivative 6. The step (1+2→6) can be regarded as a rapid Knoevenagel reaction. Since, in a model reaction, the Knoevenagel reaction of malononitrile and aromatic aldehydes can be carried out in water without any catalyst, we conjecture that the second step requires the presence of ammonium acetate. The active methylene of 3 reacts with the electrophilic C=C double bond in 6 giving the intermediate 7, which tautomerizes into 8. The latter is then cyclized by

nucleophilic attack of the OH group on the cyano (CN) moiety, giving intermediate 9. Finally, the expected product 4 is afforded by tautomerization (9→4), (Scheme 2).



Scheme 2. Plausible mechanisms for the synthesis of Pyrans 4.

3.1 Charecterization Data

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate, 4a:

White solid; M.P.: 192-194ºC

IR:(KBr)υ_{max}: 3360,2927,2727,2189,1674,1608,1500,1457,1377,1169,1060,965,722cm^{-1}
^{1}H-NMR:1.1(t,J=7.2Hz,3H,CH_3),2.4(s,3H,CH_3),4.1(q,J=7.2Hz,2H,CH_2),4.3 (s,1H,CH),4.4(brs, 2H, NH_2),7.1-7.3(m,5H,Ar-H).

Elemental analysis (%): $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67;N, 9.85; Found:C, 67.64;H, 5.75; N, 9.82.

Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate, 4b:

White solid; M.P.: 169-171ºC

IR: (KBr)υ_{max}: 3405, 3019, 2193,1670,1083,1383, 1216, 1065,925,770, 669 cm^{-1}

^{1}H-NMR: 1.1(t, J=6.9Hz,3H, CH_3),2.2(s, 3H, CH_3), 4.0(q,J=6.9Hz, 2H,CH_2),4.4 (s,1H,CH),4.5(brs,2H,NH_2),7.1(d, J=8.1Hz, 2H,Ar-H), 7.3(d, J=8.1Hz, 2H,Ar-H).

Elemental analysis (%): $C_{16}H_{15}Cl\ N_2O_3$:C, 60.29;H,4.74; N,8.79; Found:C, 60.29;H, 4.79;N, 8.83.

Ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate, 4c:

White solid; M.P.: 133-135ºC

IR: (KBr)υ_{max}: 3280, 2929,2727,2210,1683,1456,1377,1303,1154,1076, 964,722 cm^{-1}

^{1}H-NMR:1.14(t,J=7.2Hz,3H,CH_3),2.3(s,3H,CH_3),3.7(s,3H,OCH_3), 4.0(q,J=7.2 Hz, 2H,CH_2),4.39(s,1H,CH),4.47(brs, 2H, NH_2), 6.8(d, J=7.0Hz, 2H,Ar-H), 7.1(d, J=7.0Hz, 2H,Ar-H)

Elemental analysis (%): $C_{17}H_{18}N_2O_4$: C,64.96;H,5.77;N,8.91; Found: C,64.92;H,5.81;N,8.95.

Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate, 4d :

Yellow solid; M.P.: 175-177ºC

IR: (KBr)υ_{max}: 3342,3020,2197,1682, 1521,1348, 1268, 1215,1062, 760,669 cm-1

^{1}H-NMR: 1.1(t, J=7.2Hz, 3H, CH_3), 2.1(s, 3H, CH_3), 4.1(q, J=7.2Hz, 2H, CH_2),4.6(s, 1H, CH),4.7(brs, 2H, NH_2),7.4(d, J=7.0 Hz, 2H, Ar-H), 8.2(d, J=7.0Hz, 2H,Ar-H).
Elemental analysis (%): $C_{16}H_{15}N_3O_5$:C,58.36; H, 4.59;N,12.76; Found:C, 58.32; H,4.61;N, 12.79.

Ethyl6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate, 4e:

White solid; M.P.: 179-181ºC

IR: (KBr)υ_{max}: 3405,3019,2193,1677,1590,1215,1068,757,669 cm-1

^{1}H-NMR:1.0(t,J=7.2Hz,3H,CH_3),2.2(s,3H,CH_3),4.0(q,J=7.2Hz, 2H, CH_2),4.4(brs, 2H, NH_2),5.0(s, 1H, CH),7.1-7.2 (m, 4H, Ar-H).
Elemental analysis (%):$C_{16}H_{15}ClN_2O_3$:C,60.29; H, 4.74;N, 8.79; Found:C, 60.30;H,4.77; N, 8.84.

Ethyl 6-amino-5-cyano-4-(2-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate, 4f:

White solid; M.P.: 198 200ºC

IR (KBr)υ_{max}: 3309, 2900, 2728, 2192,1688, 1601, 1457,1377, 1156, 1061,772,448cm^{-1}

^{1}H-NMR:1.1(t,J=7.2Hz,3H,CH_3),2.4(s,3H,CH_3),3.8(s,3H,OCH_3), 4.0(q, J=7.2Hz, 2H,CH_2),4.4(s,1H,CH),4.5(brs,2H,NH_2),6.8-7.3(m,4H,Ar-H),

^{13}C-NMR : 13.85, 18.36, 38.63, 55.12, 60.61, 61.87, 107.72, 112.07, 113.50, 119.85, 129.48, 145.40, 156.81, 157.55, 159.64, 165.82

Elemental analysis (%): $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91;Found:C, 64.95; H, 5.79; N, 8.92.

Ethyl6-amino-5-cyano-4-(3,4,5-trimethoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate,4g:

White solid; M.P.: 182 184ºC

IR (KBr)υ_{max}: 3341,2980, 2195,1702, 1593,1505,1461,1327,1258, 1055 cm-1

^{1}H-NMR: 1.12(t, J=7.2Hz, 3H, CH_3), 2.35(s, 3H, CH_3), 3.80(s,3H, OCH_3),3.86(s,6H,OCH_3), 4.0(q,J=7.2Hz, 2H,CH_2), 4.39 (s, 1H, CH), 4.49(brs, 2H, NH_2), 6.4(s, 2H, Ar-H).

^{13}C-NMR :13.98, 18.38, 38.96, 56.08, 60.71, 62.26, 104.47, 107.86, 137.07, 139.40, 153.23, 156.0, 157.37, 165.88.

Elemental analysis (%):$C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N,7.48; Found:C, 60.98; H,5.95; N, 7.50.

Ethyl 6-amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4*H*-pyran-3-carboxylate, 4h:

Yellow Solid; M.P.: 177 179ºC

IR(KBr)υ_{max}:
3369,2924,2727,2208,1717,1682,1600,1460,1377,1304,1154,1065,965,722,446cm-1

^{1}H-NMR: 1.1(t, J=7.2Hz, 3H, CH_3), 2.4(s, 3H, CH_3), 4.0(q, J=7.2Hz, 2H, CH_2), 4.6(s, 1H, CH), 5.3(brs, 2H, NH_2), 7.3-7.8 (m, 4H, Ar-H).

^{13}CNMR: 13.63,18.43,32.89,60.91,107.24,118.21,124.0,127.87,130.58,133.23,139.09, 149.03,158.06,165.02

Elemental analysis (%): $C_{16}H_{15}N_3O_5$:C, 58.36; H,4.59;N,12.76; Found:C,58.32;H,4.65; N, 12.79.

Methyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate, 4i:

White solid; M.P.: 150 152ºC

IR (KBr)υ_{max}: 3431,3223,2947,2195,1689,1604,1409,1342, 1261, 1120, 1061,951,744, 583 cm-1

^{1}H-NMR: 2.37(s, 3H, CH_3), 3.58(s, 3H, OCH_3), 4.44(s, 1H, CH), 4.48(brs, 2H, NH_2), 7.18-7.32(m, 5H, Ar-H),

^{13}C-NMR: 18.45,38.60,51.64,62.08,107.81,118.92,127.33,128.59, 143.65, 157.00, 157.57, 166.36

Elemental analysis (%): $C_{15}H_{14}N_2O_3$:C, 66.66; H, 5.22; N,10.36;Found:C,66.71; H,5.30; N, 10.45.

Methyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate, 4j:

White solid; M.P.: 158 160ºC

IR (KBr)u_{max}: 3431, 2923, 2727, 2195,1675,1455, 1377, 1157, 1063, 722 cm-1

^{1}H-NMR: 2.4(s, 3H, CH_3), 3.6 (s, 3H, OCH_3), 4.6(brs, 2H, NH_2), 5.0(s, 1H, CH), 7.1-7.4(m, 4H, Ar-H),

^{13}C-NMR: 18.40, 35.44, 51.67, 61.02, 106.76, 118.49, 127.28, 128.35, 129.85, 133.01, 140.88, 157.69, 166.11;

Elemental analysis (%): $C_{15}H_{13}ClN_2O_3$:C,59.12; H,4.30; N,9.19;Found:C, 59.21;H, 4.37; N, 9.15.

Methyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate , 4k:

Yellow solid; M.P.: 182-184ºC

IR (KBr)u_{max}: 3402, 3330, 3202, 2955, 2201,1689,1605,1520,1345, 1065,865,731 cm-1

^{1}H-NMR: 2.39(s, 3H, CH_3), 3.58(s, 3H, OCH_3), 4.54(s, 1H, CH), 4.69(brs, 2H, NH_2), 7.36(d,J=8.0Hz, 2H,Ar H), 8.16(d, J=8.0Hz, 2H,Ar-H).

^{13}C-NMR: 18.69, 38.69, 51.88, 60.72, 106.65, 118.27, 124.03, 128.30, 147.04, 150.95, 157.74, 157.75, 165.77.

Elemental analysis (%): $C_{15}H_{13}N_3O_5$:C,57.14;H, 4.16; N,13.33;Found: C, 57.20; H, 4.10; N, 13.45

4. CONCLUSION

In conclusion, we have developed an efficient method for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives under ultrasound irradiation in water at ambient temperature using silica supported ammonium acetate catalyst which simultaneously catalyzes the reaction and helps in solublization of the reactants in water. The presented protocol possess fruitful features like high yields, shorter reaction times, efficiency, generality, recyclability of the catalyst, scalability of the method, the use of small amount of the catalyst, simplicity in operation, low cost and the use of water as solvent. To put it differently, the method significantly contributes to the practice of green chemistry.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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