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RESEARCH ARTICLE

A novel one pot three component synthesis of some isochromenes via vinylogous aldol reaction

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Abstract

Multicomponent reactions play a vital role in synthesizing heterocyclic compounds. Here we developed one pot three component synthesis of isochromenes via vinylogous aldol reaction. A comparative study of catalyst and screening of solvents were also carried out. Synthezised copmpounds were well characterized by using various spectroscopic techniques.

INTRODUCTION

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials. They are economically and environmentally advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic, and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increased use in the discovery process for new drugs and agrochemicals[1]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles[2]. In the past decade, research in academia and industry has increasingly emphasized the use of MCRs for a broad range of products.[3]

2-Aminochromenes are widely employed as pigments, cosmetics, agrochemicals and represent an important class of chemical entities being the major constituents of several natural products.[4] Fused chromenes exhibit a wide spectrum of biological applications as antimicrobial, antiviral, [5] mutagenicity, antiproliferative, sex pheromone, antitumor, [6] and central nervous system agents. Due to the unique pharmacological properties of 2-aminochromenes, the development of synthetic methods enabling facile access to this heterocycle, is desirable

As part of our ongoing research in the synthesis of 2-amino chromenes via three-component reaction of salicylaldehyde and malononitrile with various reagents such as indole, Hantzsch dihydropyridine,[7] indium,[8] and triethyl phosphite,[9] here we wish to report our investigation of a three component reaction involving malononitrile, cyclic ketone and Aldehydes with various solvents and catalysts.

2. Material and Methods

2.1 Chemicals and reagents.

All chemicals were purchased from Sigma-Aldrich U.S.A. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany.)

2.2 Equipments and analytical instruments

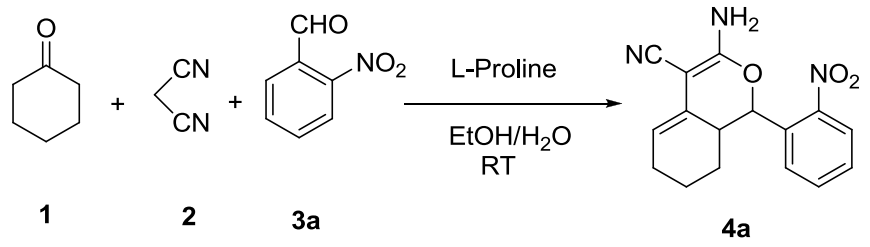
IR spectra were recorded on a Perkin–Elmer FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-D_6 using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz respectively. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA1112 CHN analyzer.

2.3 General procedure for the synthesis of isochromenes 4a-m

To a stirred mixture of cyclohexanone (1 mmol) and malononitrile (1 mmol) in EtOH-H_2O mixture, 2-nitro benzaldehyde **3a** (1 mmol), and L-Proline (0.5 mmol) were added. The reaction mixture was stirred at room temperature for the appropriate time (**Table1)**. After complete conversion as indicated by TLC, the solid product was filtered and washed with ethanol to obtain isochromene **4a**.

3. Result and Discussion

In continuation of our interest in the vinylogous aldol reaction[10] and multi component reactions, here we developed a method for the synthesis of isochromene derivatives. The strategy we have developed begins with multi component reaction of cyclohexanone **1**, malononitrile **2** and 2-nitro benzaldehyde **3a** in ethanol –water mixture at room temperature in the presence of L-Proline. The reaction undergoes smoothly within 15 min yielding 85% of the product (**Scheme1**). The solid product was filter and washed with ethanol to afford pure product. However, the product was further purified by recrystallization from ethyl acetate.



Scheme.1

Table.1
Synthesis of isochromene derivatives via scheme 2.

Entry	Aldehyde **3** (R)	Time (min)	Product **4**[a]	Yield[b] (%)
1	2-nitro	15	4a	85
2	4-methyl	10	4b	95
3	2,4-dichloro	12	4c	87
4	4-nitro	15	4d	85
5	4-methoxy	10	4e	96
6	4-chloro	15	4f	89
7	3,4-dimethoxy	10	4g	92
8	3,4,5-trimethoxy	12	4h	90
9	3-nitro	15	4i	86
10	2-chloro-6-fluoro	15	4j	82
11	2-fluoro	15	4k	85
12	2-methyl	10	4l	92
13	4-bromo	15	4m	86

[a]All products were characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectroscopy
[b]Isolated yield.

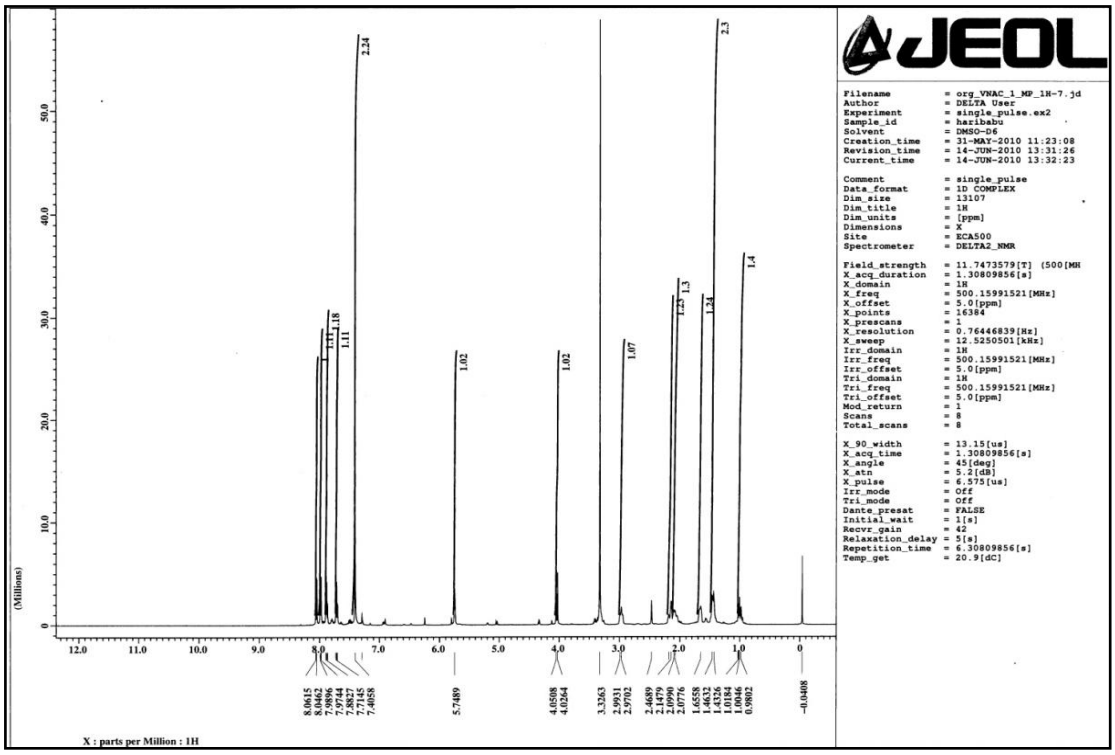


Figure.1 ^{1}HNMR spectrum of compound 4a

In the ^{1}HNMR spectra, the olefinic proton $\mathbf{H_b}$ appears at 5.74 ppm, NH_2 proton resonated at δ = 7.40 ppm as a singlet. The double at 4.04 ppm (J = 12.2 Hz) and triplet at 2.98 ppm (J =11.45 Hz) were assigned to $\mathbf{H_a}$ and $\mathbf{H_c}$ respectively. The peaks at 7.71-8.05 ppm were attributed to aromatic protons (**fig 1, 2 and 3**). In the ^{13}CNMR spectra, the peaks at 42.5 ppm, 125.9 ppm and the range between 128-134 ppm were assigned to tertiary, olefinic and aromatic carbons respectively (**fig 4**).The IR stretching frequency at 3356 cm^{-1} corresponds to NH_2 group. The band at 2928 cm^{-1} , 2208 cm^{-1}, 1623 cm^{-1} and 1526 cm^{-1} might be correspond to C-H (aromatic), CN , C=C and N-O stretching vibrations of NO_2 group respectively (**fig 5**). The mass spectrum revealed the molecular ion peak $(M+H)^+$ at m/z 298. The formation of the product was further conformed by elemental analysis.

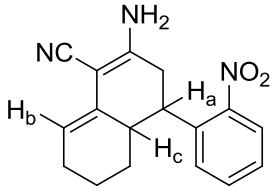


Figure.2 Structural diagram of compound 4a

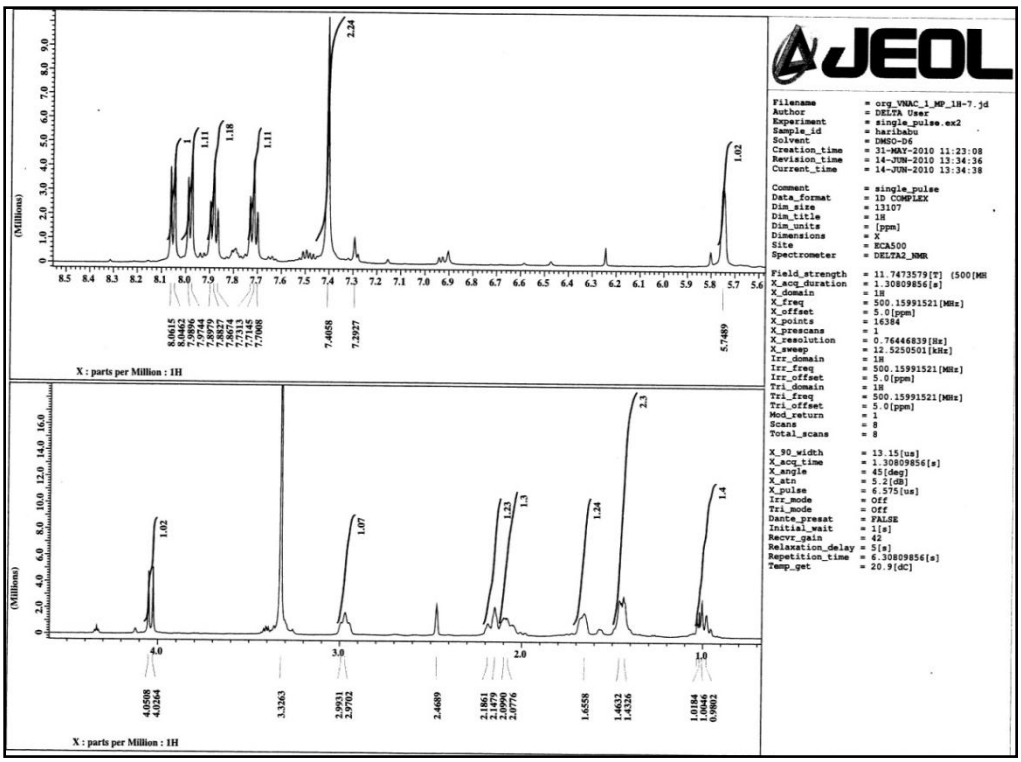


Figure.3 ^{1}HNMR spectrum (expanded) of compound 4a

With the demonstration of the utility of this protocol in general, we attempted a series of reactions with a variety of aldehydes (**Scheme 2, Table 1**), catalysts (**Table 2**) and solvents (**Table3**). It is noteworthy that irrespective of the presence of electron withdrawing or releasing substituent in the ortho, para or meta position in the aldehyde, the reaction proceeded fairly well and afforded the desired products in good to excellent yields (**Table 1**).However the reaction with aliphatic aldehydes was unsuccessful.

The same reaction was carried out with various catalysts including L-proline, sodium carbonate and KF-alumina, the L-Proline was found to be an efficient catalyst for the synthesis of isochromene derivatives and results are summarized in table 2.

Table.2

Comparative study of Na_2CO_3, L-Proline and KF-alumina catalysts for the synthesis of 4 in ethanol-water mixture.

Product	Time (min)	Yield[a] (%)		
		L-Proline	Na_2CO_3	KF-Alumina
4a	15	85	62	70
4b	10	95	65	70
4c	12	87	60	69
4e	10	96	72	79
4g	10	92	69	72
4h	12	90	74	80
4j	15	82	60	68
4k	15	85	65	70

[b]Isolated yield

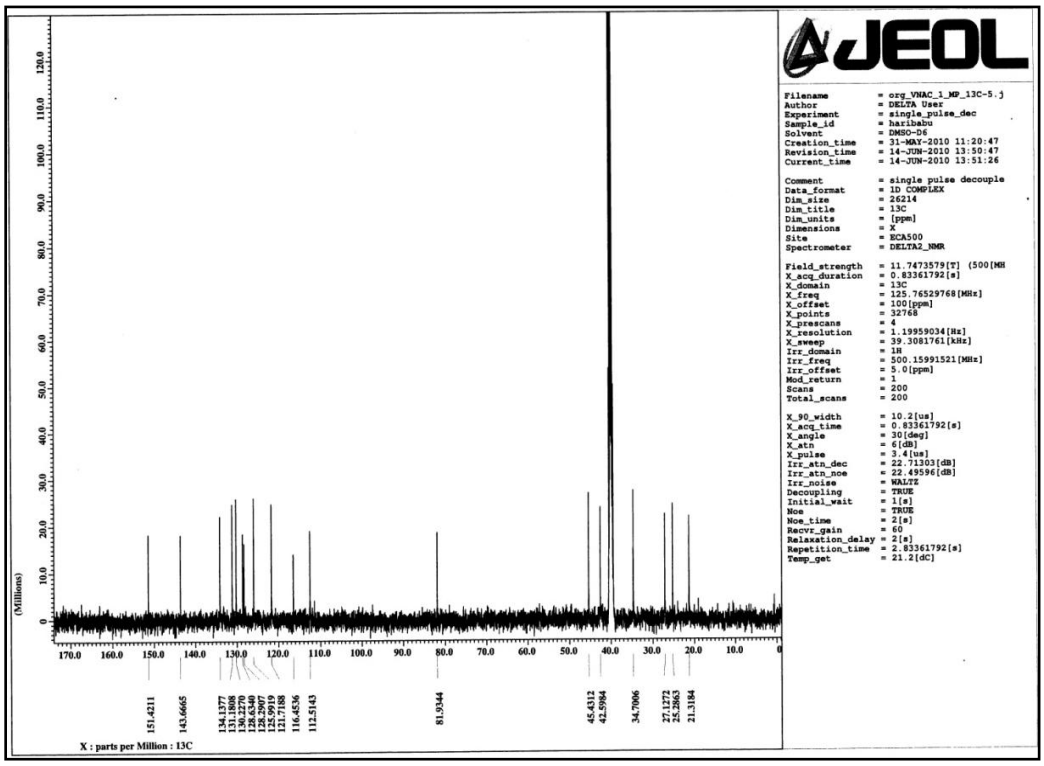
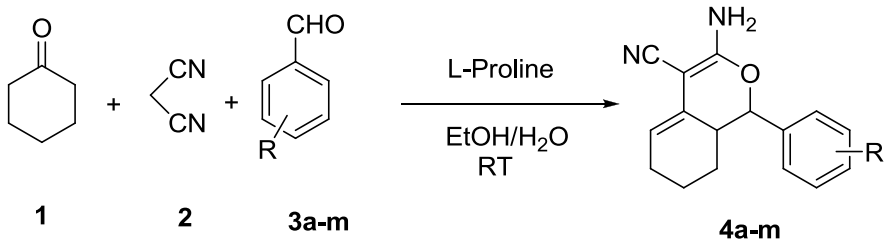


Figure.4 ^{13}CNMR spectrum of compound 4a

Table.3
Screening of solvents

Product	Time (min)	Yield[a] (%)		
		Ethanol	Water	Ethanol-Water mixture
4a	15	82	45	85
4b	10	92	48	95
4c	12	89	42	87
4e	10	95	51	96
4g	10	95	45	92
4h	12	87	42	90
4j	15	92	40	82
4k	15	88	43	85

[b]Isolated yield



Scheme.2

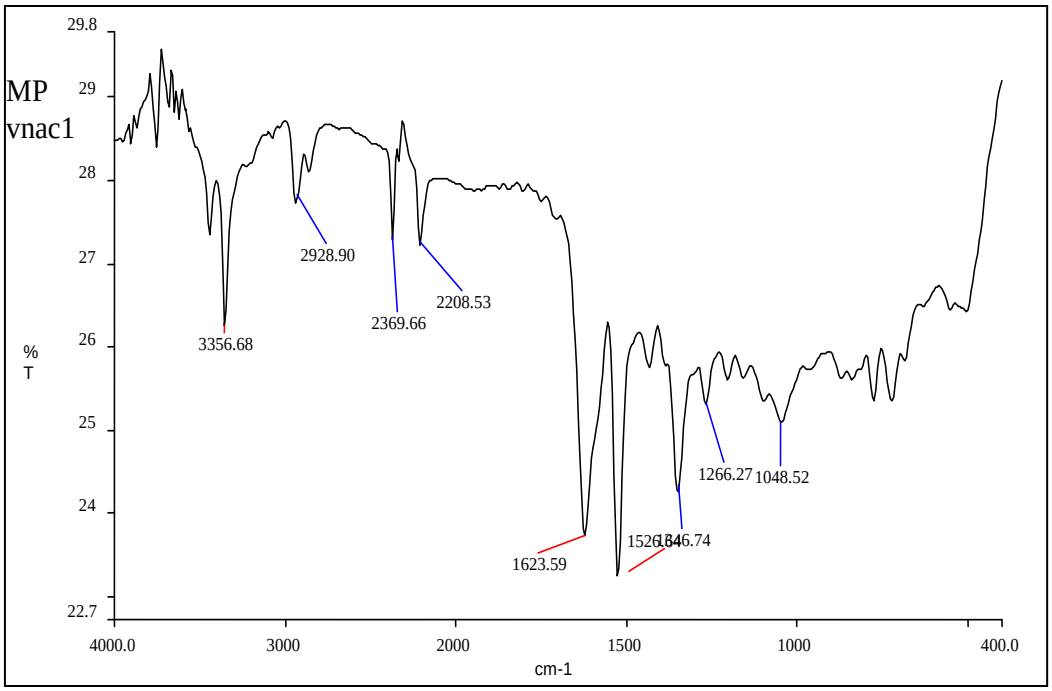


Figure.5 IR spectrum of compound 4a

In another attempt, when the reaction was carried out with water and ethanol solvents separately, the products were obtained in good to excellent yield in ethanol and ethanol-water mixture, poor yield in water in presence of L-Proline as catalyst. The results are summarized in table 3.

Characterization of compounds 4a-m

Compound **4a**: 3-amino-6,7,8,8a-tetrahydro-1-(2-nitrophenyl)-1H-isochromene-4-carbonitrile, Yellow solid; R_f ; 0.16.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 1.0 (q, 1H, *J*=6.90Hz), 1.45(d, 2H, *J*=15.3Hz), 1.65(m, 1H), 2.12(m, 2H), 2.98(t, 1H, *J*=11.45Hz), 4.04(d, 1H, *J*=12.20Hz), 5.74(S, 1H), 7.40(S, 2H), 7.71(t, 1H, *J*=8.4Hz), 7.88(t, 1H, *J*=7.60Hz), 7.98(d, 1H, *J*=7.60Hz), 8.05(d, 1H, *J*=7.65Hz) ; ^{13}CNMR: 125MHz, DMSO-D_6: δ 21.3, 25.2, 27.1, 34.7, 42.5, 45.4, 81.9, 112.5, 116.4, 121.7, 125.9, 128.2, 130.2, 134.1, 143.7, 151.4; (IR (ν_{max}cm^{-1}KBr): 3356, 2928, 2369, 2208, 1623, 1526, 1346, 1266, 1048; MS m/z 298 $(M+H)^+$; Anal. Calcd for $C_{16}H_{15}N_3O_3$ C, 64.64; H, 5.09; N, 14.13; O, 16.14; Found C, 64.32; H, 5.84; N, 14.91; O, 16.27.

Compound **4b**: 3-amino-6,7,8,8a-tetrahydro-1-(4-methylphenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.30.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.83(q, 1H, *J*=11.45Hz), 1.4(m,1H), 1.49(m, 1H), 1.64(m,1H), 2.04(m, 1H), 2.14(m, 1H), 2.30(S, 3H), 2,69(t, 1H, J=11.45Hz), 3.22(d, 1H, *J*=12.25Hz), 5.70(S, 1H), 7.13(S, 2H), 7.21(m, 3H), 7.39(m, 1H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.3, 21.6, 25.4, 27.5, 34.6, 43.4, 51.5, 82.5, 112.8, 116.5, 121.0, 127.1, 129.5, 131.8, 132.6, 138.8, 143.8; (IR (ν_{max}cm^{-1}KBr): 3424, 3336, 3249, 2949, 2870, 2365, 1650, 1516, 1457, 1340; MS m/z 267$(M+H)^+$; Anal. Calcd for $C_{17}H_{18}N_2O$ C, 76.66; H, 6.81; N, 10.52; O, 6.01; Found C, 76.21; H, 6.36; N, 10.84; O, 6.75.

Compound **4c**: 3-amino-6,7,8,8a-tetrahydro-1-(2,4-dichlorophenyl)-1H-isochromene-4-carbonitrile, Pale yellow solid; R_f ; 0.32.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.82(q, 1H, J=10.75Hz), 1.46(m, 2H), 1.71(m, 1H), 2.20(m, 1H), 2.87(t, 1H, J=11.45Hz), 3.87(d, 1H, J=12.25Hz), 5.76(s, 1H), 7.45(s, 2H), 7.66(m, 2H), 7.83(m, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.5, 24.3, 26.6, 34.3, 41.4, 46.2, 78.3, 81.5, 112,1, 115.9, 121,0, 128.2, 130.9, 136.2, 143.2, 165.3; IR (ν_{max}cm^{-1}KBr): 3456, 3358, 3239, 2943, 2835, 2360, 1627, 1573, 1435; MS m/z 321$(M+H)^+$; Anal. Calcd for $C_{16}H_{14}Cl_2N_2O$ C, 59.83; H, 4.39; Cl, 22.08; N, 8.72; O, 4.98; Found C, 59.28; H, 4.68; Cl, 22.39; N, 8.18; O, 4.56.

Compound **4d**: 3-amino-6,7,8,8a-tetrahydro-1-(4-nitrophenyl)-1H-isochromene-4-carbonitrile, Yellow solid; R_f ; 0.29.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 1.08(m, 2H), 1.39(m, 1H), 1.72(d, 1H, *J*=12.25Hz), 2.11(s, 2H), 2.51(d, 1H, *J*=20.6Hz), 4.88(d, 1H, *J*=11.45Hz), 5.27(s, 1H), 6.85(s, 2H), 7.71(d, 2H, *J*=8.4Hz), 8.27(d, 2H, *J*=8.4Hz); ^{13}C NMR: 125MHz, DMSO-D_6: δ 26.8, 29.2, 29.6, 65.6, 83.8, 84.1, 87.6, 115.6, 124.1, 128.7, 133.7, 134.1, 146.5, 149.9, 152.9, 168.8; IR (ν_{max}cm^{-1}KBr): 3426, 3330, 3235, 3198, 2940, 2861, 2191, 1933, 1640, 1583, 1523, 1439, 1419, 1348, 1317, 1292, 1102; MS m/z 298 (M+H) $^+$; Anal. Calcd for $C_{16}H_{15}N_3O_3$ C, 64.64; H, 5.09; N, 14.13; O, 16.14; Found C, 64.52; H, 5.80; N, 14.52; O, 16.42.

Compound **4e**: 3-amino-6,7,8,8a-tetrahydro-1-(4-methoxyphenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.43.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.82(q, 1H, *J*=10.70Hz), 1.39(m, 1H), 1.50(m, 1H), 1.65(m, 1H), 2.04(m, 1H), 2.13(m, 1H), 2.65(t, 1H, *J*=11.45Hz), 3.16(d, 1H, *J*=12.25Hz), 3.74(S, 3H), 5.7(S, 1H), 6.86(d, 1H, *J*=7.65Hz), 6.95(d, 1H, *J*=7.60Hz), 7.06(S, 2H), 7.22(d, 1H, *J*=8.40Hz), 7.41(d, 1H, *J*=8.40Hz) ; ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.6, 25.4, 27.5, 34.7, 43.5, 51.3, 55.4, 82.6, 112.8, 114.8, 116.5, 121.2, 126.5, 128.3, 133.8, 143.8, 160.0; (IR (ν_{max}cm^{-1} KBr): 3421, 3341, 3251, 3013,2947, 2867, 2835, 2361,2213, 1896, 1647, 1602, 1514, 1390; MS m/z 283 (M+H) $^+$; Anal. Calcd for $C_{17}H_{18}N_2O_2$ C, 72.32; H, 6.43; N, 9.92; O, 11.33; Found C, 72.52; H, 6.80; N, 9.54; O, 11.85.

Compound **4f**: 3-amino-6,7,8,8a-tetrahydro-1-(4-chlorophenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.48.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.82(q, 1H, *J*=11.45Hz), 1.41(d, 2H, *J*=12.2Hz), 1.63(m, 1H), 2.05(m, 1H), 2.16(m, 1H), 2.75(t, 1H, *J*=11.50Hz), 3.61(d, 1H, *J*=12.25Hz), 5.69(S,1H), 7.36(S, 2H), 7.47(m, 2H), 7.57(m, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.5, 25.4, 27.5, 34.2, 43.2, 50.2, 82.0, 112.9, 116.7, 120.9, 129.3, 129.5, 134.2, 134.3, 134.7, 143.8; (IR (ν_{max}cm^{-1}KBr): 3442, 3342, 3252, 3226, 2947, 2866, 2833, 2360, 1646, 1602, 1493, 1277,838; MS m/z 283 (M+H) $^+$; Anal. Calcd for $C_{16}H_{15}ClN_2O$ C, 67.02; H, 5.27; Cl, 12.36; N, 9.77; O, 5.58; Found C, 67.52; H, 5.48; Cl, 12.54; N, 9.45; O, 5.06.

Compound **4g**: 3-amino-6,7,8,8a-tetrahydro-1-(3,4-dimethoxyphenyl)-1H-isochromene-4-carbonitrile, Pale yellow solid; R_f ; 0.29.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.87(m, 1H), 1.53(m, 2H), 1.67(s, 1H), 1.23(d, 1H, *J*=16.0Hz), 1.06(d, 1H, *J*=19.1Hz), 2.76(m, 1H), 3.45(m, 1H), 3.78(s, 6H), 5.72(s, 1H), 6.96(s, 1H), 7.13(m, 2H), 7.38(s, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.5, 25.4, 27.5, 34.4, 37.7, 51.2, 55.8, 56.2, 81.9, 112.3, 116.7, 119.7, 120.7, 125.2, 127.3, 129.5, 144.2, 149.; IR (ν_{max}cm^{-1}KBr): 3433, 3335, 3253, 3229, 2938, 2834, 2212, 1649, 1600, 1518, 1468, 1443, 1422, 1391, 1264, 1206, 1170; MS m/z 313 (M+H) $^+$; Anal. Calcd for $C_{18}H_{20}N_2O_3$ C, 69.21; H, 6.45; N, 8.97; O, 15.37; Found C, 69.31; H, 6.80; N, 8.26; O, 15.72.

Compound **4h**: 3-amino-6,7,8,8a-tetrahydro-1-(3,4,5-trimethoxyphenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.38.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.86(q, 1H, *J*=13.00Hz), 1.45(m,1H), 1.52(m, 1H), 1.65(m, 1H), 2.03(m, 1H), 2.15(m,1H), 2.78(t, 1H, *J*=11.45Hz), 3.41(d, 1H, *J*=13.00Hz), 3.66(S, 3H), 3.71(S, 3H), 3.76(S, 3H), 5.68(S, 1H), 6.79(S, 1H), 6.83(S, 1H), 7.34(S, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.5, 25.4, 27.4, 34.5, 43.4, 51.6, 56.5, 60.6, 81.9, 104.6, 110.6, 112.9, 113.4, 116.7, 120.8, 129.4, 138.2, 144.1, 153.6; IR (ν_{max}cm^{-1}KBr): 3446, 3358, 3253, 3220, 3004, 2940, 2837, 2202, 1640, 1593, 1510, 1465, 1428, 1334, 1248, 1128, 1007, 846; MS m/z 343(M+H) $^+$; Anal. Calcd for $C_{19}H_{22}N_2O_4$ C, 66.65; H, 6.48; N, 8.18; O, 18.69; Found C, 66.31; H, 6.82; N, 8.36; O, 18.23.

Compound **4i**: 3-amino-6,7,8,8a-tetrahydro-1-(3-nitrophenyl)-1H-isochromene-4-carbonitrile, Yellow solid; R_f ; 0.35.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 1.03(m, 2H), 1.36(m, 1H), 1.65(d, 1H, *J*=11.45Hz), 2.05(S,2H), 2.50(m, 1H), 4.91(d, 1H, *J*=10.70Hz), 5.19(S, 1H), 6.90(S, 2H), 7.70(t, 1H, *J*=7.65Hz), 7.89(d, 1H, *J*=7.60Hz), 8.23(d, 1H, *J*=6.90Hz), 8.28(S, 1H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.9, 24.4, 24.8, 39.1, 60.7, 82.6, 110.7, 119.5, 122.9, 124.3, 129.3, 130.7, 134.8, 140.2, 148.4, 164.2; IR (ν_{max}cm^{-1}KBr): 3464, 3312, 3224, 3185, 2951, 2196, 1637, 1579, 1526, 1479, 1431; MS m/z 298 (M+H) $^+$; Anal. Calcd for $C_{16}H_{15}N_3O_3$ C, 64.64; H, 5.09; N, 14.13; O, 16.14; Found C, 64.84; H, 5.32; N, 14.82; O, 16.32.

Compound **4j**: 3-amino-6,7,8,8a-tetrahydro-1-(2-chloro-6-fluorophenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.29.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.89(q, 1H, *J*=13.00Hz), 1.42(m,2H), 1.70(m, 1H), 2.16(m, 2H), 2.99(t, 1H, *J*=), 3.89(d, 1H, *J*=12.25Hz), 5.71(S, 1H), 7.40(m, 1H), 7.48(S, 2H), 7.54(m, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: 21.5, 25.2, 27.7, 34.0, 40.9, 48.2, 81.9, 112.3, 116.6, 119.7, 121.1, 127.3, 133.1, 137.0,

144.1, 161.1; IR (ν_{max}cm^{-1}KBr): 3450, 3325, 3254, 2940, 2223, 1655, 1612, 1500, 1454, 1385; MS m/z 305 $(M+H)^+$; Anal. Calcd for $C_{16}H_{14}ClFN_2O$ C, 63.06; H, 4.63; Cl, 11.63; F, 6.23; N, 9.19; O, 5.25; Found C, 63.24; H, 4.22; Cl, 11.34; F, 6.26; N, 9.28; O, 5.40.

Compound **4k**: 3-amino-6,7,8,8a-tetrahydro-1-(2-fluorophenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.46.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.82(q, 1H, *J*=13.00Hz), 1.42(m, 2H), 1.62(m, 1H), 2.08(m, 1H), 2.16(m, 1H), 2.81(t, 1H, *J*=), 3.67(d, 1H, *J*=13.00Hz), 5.71(S, 1H), 7.30(m, 1H), 7.35(m, 1H), 7.37(S, 2H), 7.48(m, 1H), 7.66(t, 1H, *J*=7.65Hz); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.3, 25.3, 27.3, 34.1, 42.6, 43.2, 82.1, 112.5, 112.7, 116.3, 116.6, 121.4, 125.4, 128.8, 129.7, 141.7; IR (ν_{max}cm^{-1}KBr): 3422, 3336, 3245, 2933, 2211, 1648, 1600, 1492, 1451, 1393; MS m/z 271 $(M+H)^+$; Anal. Calcd for $C_{16}H_{15}FN_2O$ C, 71.10; H5.59; F, 7.03; N, 10.36; O, 5.92; Found C, 71.41; H, 5.43; F, 7.21; N, 10.43; O, 5.94.

Compound **4l**: 3-amino-6,7,8,8a-tetrahydro-1-(2-methylphenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.16.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.85(q, 1H, J=11.45Hz), 1.44(m, 2H), 1.65(m, 1H), 2.18(m, 2H), 2.38(s, 3H), 2.77(m, 1H), 3.67(d, 1H, J=12.20Hz), 5.74(s, 1H), 7.59(m, 6H, NH proton merged with aromatic proton); ^{13}C NMR: 125MHz, DMSO-D_6: δ 19.7, 21.0, 24.8, 26.6, 35.0, 45.5, 81.6, 112.7, 116.2, 120.2, 126.4, 128.5, 129.0, 131.1, 133.0, 138.3, 143.9; IR (ν_{max}cm^{-1}KBr): 3489, 3423, 3358, 3320, 3239, 2943, 2921, 2859, 2835, 2360, 2342, 2215, 21188; MS m/z 267 $(M+H)^+$; Anal. Calcd for $C_{17}H_{18}N_2O$ C, 76.66; H, 6.81; N, 10.52; O, 6.01; Found C, 76.52; H, 6.38; N, 10.48; O, 6.26.

Compound **4m**: 3-amino-6,7,8,8a-tetrahydro-1-(4-bromophenyl)-1H-isochromene-4-carbonitrile, White solid; R_f ; 0.59.(25%EAPE) ^{1}H NMR: 500 MHz, DMSO-D_6: δ 0.86(q, 1H, *J*=11.62Hz), 1.38(d, 2H, *J*=12.4Hz), 1.72(m, 1H), 1.85(m, 1H), 2.38(m, 1H), 2.65(t, 1H, *J*=11.52Hz), 3.58(d, 1H, *J*=12.45Hz), 5.68(S,1H), 7.38(S, 2H), 7.49(m, 2H), 7.68(m, 2H); ^{13}C NMR: 125MHz, DMSO-D_6: δ 21.5, 25.7, 28.5, 35.4, 44.2, 51.4, 83.2, 113.0, 116.8, 120.0, 124.8, 128.0, 135.5, 144.0, 148.6, 154.2; (IR (ν_{max}cm^{-1}KBr): 3442, 3342, 3252, 2947, 2866, 2360, 1646, 1493, 1277; MS m/z 331 $(M+H)^+$; Anal. Calcd for $C_{16}H_{15}BrN_2O$ C, 58.02; H, 4.56; Br,24.13; N, 8.46; O, 4.83; Found C, 58.21; H, 4.42; Br,24.34; N, 8.58; O, 4.64.

4. Conclusions

In summary, we have demonstrated a new, one-pot, three component reaction that offers a simple method for the synthesis of isochromene derivatives from aromatic aldehydes, malononitrile, and cyclic ketone using various solvents and catalyst. Regarding solvents, ethanol-water mixture was found to be good one. In the screening of catalyst, we found that L-proline achieved a better yield. This method offers several advantages like milder reaction conditions, shorter reaction time, high yield, ecofrindly and simple experimental and isolation procedures making it an efficient route to the synthesis of isochromenes.

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