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Cesium Fluoride catalysed tandem Knowvengel-Michael reaction for the synthesis of 6-amino-1,4-dihydro-3-methyl-1,4-phenyl pyrano [2,3-c] pyrazoles

Vijay N. Bhosale*[1], Gopinath S. Khansole[2], Jaman J. Angulwar[3] and Sunil S. Choudhare[4]

[1]Department of Chemistry P G Research Centre Yeshwant Mahavidyalaya, Nanded
[2]Department of Chemistry D.A.B.N.Arts & Science College, Chikhali, Sangli
[3]Department of Chemistry Dayanand Science College, Latur
[4]Department of Chemistry S.D. College, Soegaon, Aurangabad

ABSTRACT

An environmentally benign tandem Knowvengel-Michael reaction of ethylacetoacetae, hydrazine hydrate,malononitrile and substituted aromatic aldehyde for the synthesis of 6-amino -1,4-dihydro -3- methyl -1,4-phenyl Pyrano [2,3-c] Pyrazoles .

Keywords: Knowvengel-Michael reaction, Malononitrile. Pyrano pyrazole, Aromatic Aldehyde, Hydrazin hydrate, etc.

INTRODUCTION

Now a days it is very tough task to synthesize the fused heterocycles by maintaining green synthetic approach. Because synthesis of organic molecules produce large amount of waste product, which harm the environmental and also consume excess of solvent. To overcome these problem multicomponent reactions (MCR) is the best method to synthesize fused heterocycles. Multicomponent Reactions (MCR'S) are very useful in the synthesis of variety of organic molecule[1-3]. These MCR strategy has more advantages over traditional approaches because of multicomponent reactions in single step gives higher yield without any isolation of intermediate. MCR'S closely related with the principals of green chemistry in terms of saving time, energy, cost, side product and environmental friendly.[4]By using this type of multicomponent stratergy we have synthesized the different derivatives of pyrano pyrazolo compounds. A Pyranopyrazole derivative has unique position in the class of organic compounds because of their broad range of pharmacological activities[5]. Some alkyl and aryl pyrazole has sedative action on CNS[6]. Pyranopyrazole moities of the drug with wide medicinal application such as Analgesic[8], anticancer, antimicrobial , antifungal, inhibitor of human Chk1 Kinase[7-10]Pyrazole and its synthetic derivatives has been found to exhibit industrial, agricultural and some biological applications[11-15] . Khurana et al reported Synthesis of Pyrano pyrazole derivatives from four components by using 1-butyl-3-methylimidazolium tetrafluroborate as an ionic liquid[16]. Jin et al reported three component synthesis by using *p*-dodecylbezenesulfonic acid(DBSA)[17]

Chemist reported various methods for the synthesis of Pyrano pyrazole derivatives.Various method of Four component synthesis by using heteropoly acids[18] ZnO nanoparticle[19] , $NaHSO_3$ using ultrasound mediated[20] and

molecular iodine nonrecovrable[21] also have been reported. Overall, all these reported method are effective but which require long time, expensive catalyst like ionic liquid. So in oder to overcome problem, keeping green approach in mind, in this present investigation we have reported synthesis of the pyranopyrazole derivatives by simple, efficient and ecofriendly methods. We have synthesized pyranopyrazoles derivatives by using Cesium Fluoride as a catalyst. Now a days, the catalytic activity of Cesium fluoride is useful as an efficient,reusable for sulfonylation and desulfonylation of heteroatoms, acid imparting high regio and chemoselectivity in chemical reaction, it is active for the transesterification of diethylcarbonate by different alcohols and diols with an activity nearly independent of the structure of the substrate.

MATERIALS AND METHODS

Melting points were determined on electro-thermal melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on various spectrometers at 400MHz and 100MHz respectively using TMS as a internal standard.

General procedure for the synthesis of substituted 6-amino -1,4-dihydro -3- methyl -1.4- phenyl Pyrano [2,3-c] pyrazoles (5a-5m):
A mixture of ethylacetoacetate (EAA) (3mmol), hydrazine hydrate (3 mmol), malononitrile (3mmol) was refluxed independently with substituted aromatic aldehydes (3mmol) for one to five hours in presence of Cesium fluoride in ethanol.The reaction mixture was kept over night, filtered and recyrstallized from ethanol. The formed product of different substituted 6-amino -1,4-dihydro -3- methyl -1.4- phenyl Pyrano [2,3-c] (5a-5m) pyrazoles is obtained.

Spectral Analysis:
6-amino-1,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (5a)
M.P.242-244^{0}C; **IR (KBr**): 3415, 3360, 3160, 2992, 1646, 1590, 1394, 1270, 875 cm^{-1}; **^{1}H-NMR:** (400MHz, DMSO-d$_6$) δppm 12.08(s,1H), 7.08-7.42(,m,5H), 6.82(s,br,2H), 1.73(s,3H); **ES-MS :***m/z:* 253 (M+1)

6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5b):
M.P. 210-212^{0}C; **IR** (KBr): 3463 3255, 3109, 2190, 1624, 1596.1492, 1392. 1257, 871 cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d$_6$) δppm 12.00(s,1H),7.08-6.88 (,m,H),6.82(s,br,2H),1.99(s,3H); **Mass** : **ES-MS :***m/z:* 283 (M+1); **^{13}C-NMR:** (400MHz,DMSO-d$_6$) δppm 9.73,35.422,54.98,57.59,97.861,113.74, 128.46,135.51, 136.46, 154.74, 157.941, 160.659

6-amino-1,4-dihydro-3-methyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile(5c):
M.P. 206-208^{0}C; **IR** (KBr): 3409 3317, 3190, 2923, 2190, 1647, 1600.1508, 1488. 1157,871 cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d$_6$) δppm 12.00(s,1H),7.12-7.82 (,m,H),7.08(s,2H) 6.82(s,br,2H), 4.54 (s,1H) 2.26 (s,3H) 1.79(s,3H); **Mass** : **ES-MS :***m/z* 267 (M+1)

6-amino-4-(4-bromophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5d)
M.P. 178-180^{0}C; **IR** (KBr): 3409 3317, 3190, 2923, 2190, 1593, 1519.1419,1157,829 cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d$_6$) δppm 12.4 (s,1H), 7.52–6.93 (,m,H),7.08(s,2H) 6.82(s,br,2H), 4.62 (s,1H) 2.26 (s,3H) 1.79(s,3H); **Mass** : **ES-MS :***m/z* m/e 330(M+), 332 (M+2)

6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5e)
M.P. 332-336^{0}C; **IR** (KBr): 3409 3305, 3174, 2187, 1647.1600,1488,1184,875cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d$_6$) δppm 12.14 (s,1H), δ7.39–6.93 (m,4H), 6.82(s,br,2H), 4.63 (s,1H) 2.26 (s,3H) 1.79(s,3H)
Mass : **ES-MS :***m/z* 287(M+1)

6-amino-1,4-dihydro-4-(3,4-dimethoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-carbonitrile(5f)
M.P. 310-312^{0}C; **IR** (KBr): 3412,3308, 3174, 2187, 1647.1600,1488,1184,875cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d$_6$) δppm 12.50 (s,1H), δ6.54–6.51,6.64 (,m,3H), 4.63 (s,1H) 2.79 (s,3H) 1.79(s,3H); **Mass** : **ES-MS :***m/z* 287(M+1

6-amino-1,4-dihydro-4-(3-hydroxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5g)
M.P. 209-211^{0}C; **IR** (KBr): 3408,3316, 3179, 2150, 1640,1609,1560 ,1498,1184,870cm$^{-1;}$ **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.80 (s,1H), δ7.54–6.51,6.64 (,m,4H),5.00 (s,1H) 2.79 (s,2 H) 1.79(s,3H); **Mass** : **ES-MS :***m/z* 269(M+1)

6-amino-1,4-dihydro-4-(4-hydroxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5h)
M.P. 221-223^{0}C; **IR** (KBr): 3415,3354, 3056, 2926,2140, 1645,1618,1541 ,1478,1267,865cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.30 (s,1H), δ7.54–7.01(m,4H), 6.83 (s,br,2H), 5.60 (s,1H) 2.79 (s,2 H) 1.62 (s,3H); **Mass** : **ES-MS :***m/z* 298(M+1)

6-amino-1,4-dihydro-3-methyl-4-(3-nitrophenyl) pyrano[2,3-c]pyrazole-5-carbonitrile(5i)
M.P. 193-195^{0}C; **IR** (KBr): 3480,3354, 3180, 2150, 1640,1636,1538 ,1480,1175,872cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.89(s,1H), δ7.98–7.45 (,m,4H), 6.91 (s,br,2H), 1.79 (s,3H); **Mass** : **ES-MS :***m/z* 298(M+1)

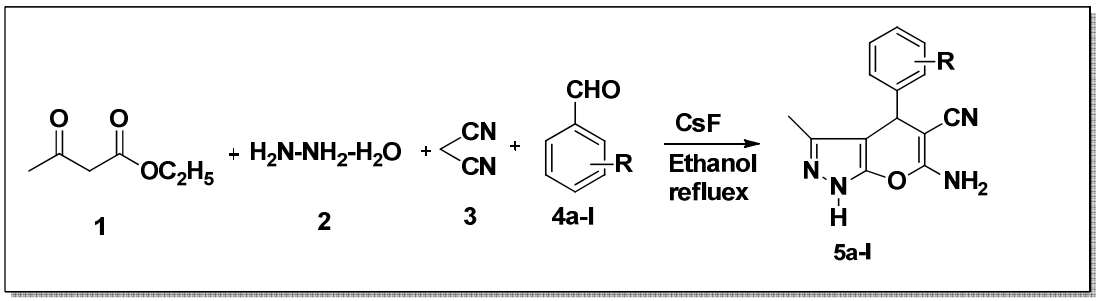
6-amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile(5j)
M.P. 249-252^{0}C; **IR** (KBr): 3476,3365, 3158, 2146, 1678,1647,1575 ,1465,1184,880cm$^{-1;}$ **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.89(s,1H), δ7.98–7.80,7.45 (,m,4H), 2.72(s,2 H) 2.80 (s,3H); **Mass** : **ES-MS :***m/z* 298(M+1)

6-amino-1,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5k)
M.P. 243-245^{0}C; **IR** (KBr): 3480,3371, 3163, 2150, 1660,1652,1580 ,1470,1174,875cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.80 (s,1H), δ7.10–6.51,6.64 (m,3H),5.00 (s,1H) , 3.37 (s,3H), 2.79 (s,2 H) 1.62 (s,3H); **Mass** : **ES-MS :***m/z* 299(M+1)

6-amino-4-(4-fluorophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5l)
M.P. 161-163^{0}C; **IR** (KBr): 3454,3360, 3140, 2152, 1645,1658,1590 ,1486,1198, 882cm^{-1} ; **^{1}H- NMR: :**(400MHz,DMSO-d_6) δppm 12.80 (s,1H), δ7.04–710,6.85 (m,4H), 2.79 (s,2 H) 1.62 (s,3H); **Mass** : **ES-MS :***m/z* 271(M+1)

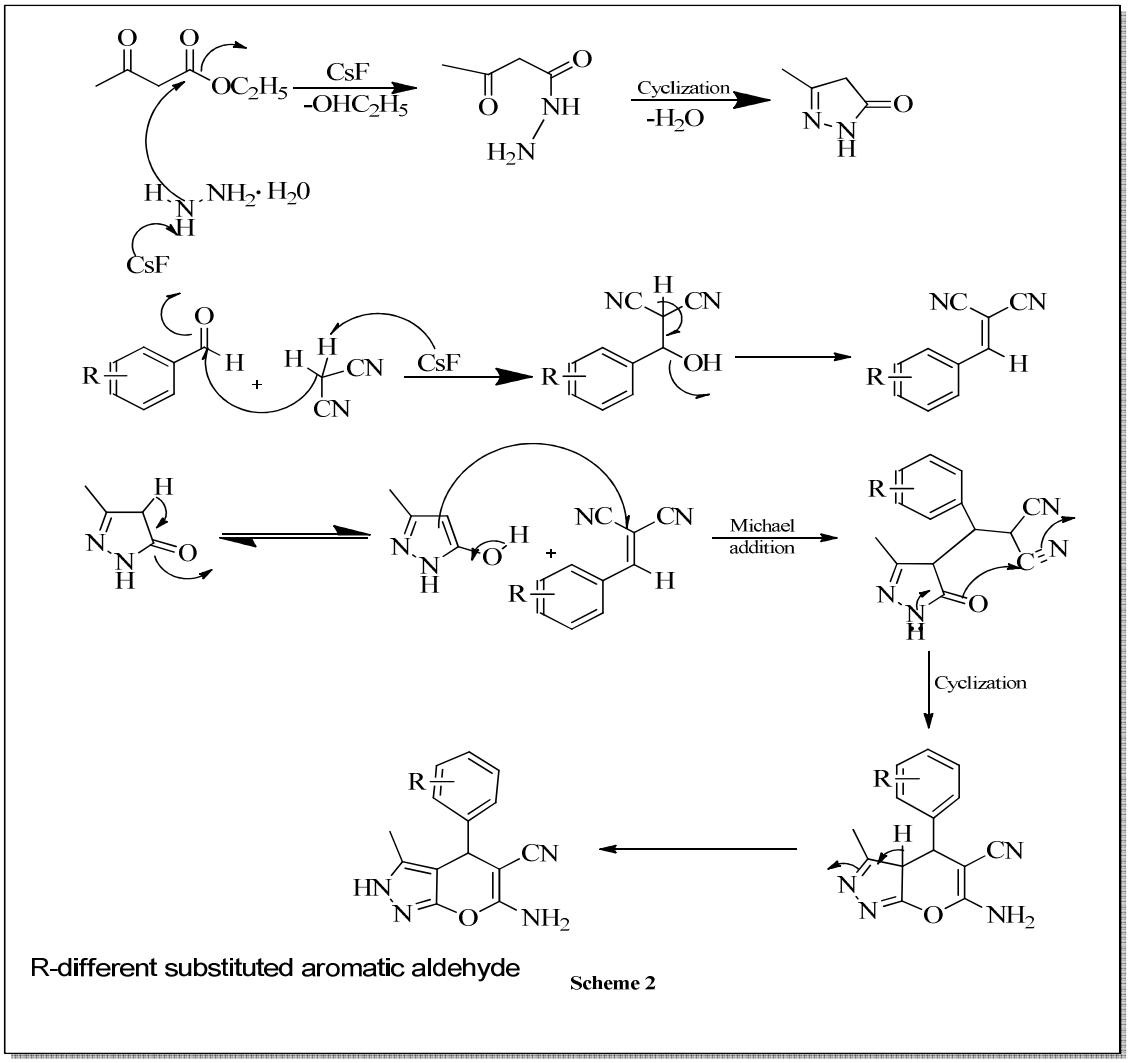
RESULTS AND DISCUSSION

In a typical reaction procedure,a mixture of benzaldehyde (3 mmol), malononitrile (3 mmol), hydrazine hydrate (80%) (3 mmol) and ethylacetoacetate (3 mmol) was refluxed for one hours at 50^{0}C in the presence of cesium fluoride as the catalyst in ether as solvent to form 6-amino -1,4-dihydro -3- methyl -1.4- phenyl Pyrano [2,3-c] pyrazoles. The progress of the reaction is monitored by using TLC. After completation of reaction solid product is obtained. The reaction mixture was kept overnight then it is filtered and recrystalised from ethanol. The obtained yield of product is 85%. The optimum yield of the product was obtained when 5 mol% of cesium fluoride was employed.



Four component condensation (MCR) are extended using a range of substituted aromatic aldehyde and results are summarized in table no.1. The 4-methoxy, 4-methyl, 4-bromo,4-chloro subsitituted aromatic aldehyde give excellent yield. Other substituted aldehyde which having electron donating and electron withdrawing group gives good yield.

The structures of these compounds were assigned on the basis of elemental analysis and spectral data. All synthesized compounds exhibits sharp bands at 3483-3255cm^{-1} due to NH_2 & 2190 cm^{-1} due to CN stretching. The ^{1}H-NMR spectrum exhibits a characteristic peaks at δ7.53 ppm for aromatic proton and broad singlet peak at δ4.53 ppm due to the NH_2 groups.



Scheme 2

Table No. 1

Entry	Aldehyde (Ar)	Time (Hrs)	Yield%	M.P.^{0}C	Reference M.P.^{0}C
5a	-C_6H_5	1	68%	242-244	243-245
5b	4-OCH_3 C_6H_4	1	82%	210-212	209-211
5c	4-CH_3 C_6H_4	1	81%	206-208	205-207
5d	4-Br C_6H_4	3.5	80%	178-180	177-179
5e	4-Cl C_6H_4	1	79%	332-334	331-333
5f	3,4-OCH_3 C_6H_4	4.15	64%	310-312	311-313
5g	3-OH C_6H_4	4.45	67%	209-211	210-2012
5h	4-OH C_6H_4	4.45	68%	221-223	220-222
5i	3-NO_2 C_6H_4	3.15	58%	193-195	194-196
5j	4-NO_2 C_6H_5	3.15	60%	249-252	250-252
5k	3,OCH_3, 4-OH C_6H_3	1.15	65%	243-245	244-246
5l	4-F C_6H_4	2	62%	161-163	162-164

A tentative reaction mechanism for the four component synthesis of 6-amino -1,4-dihydro -3- methyl -1.4- phenyl Pyrano [2,3-c] pyrazoles is shown in scheme 2.The aromatic aldehyde can react with malononitrile to from the dicyano-olfin through knoevenagel condensation.ethyl acetoacetate react with hydrazine hydrate with cyclization to form 3-methyl-1H-pyrazol-5(4H)-one. Further it reacts with dicyano-olfin via a Michal–type's addition to followed cyclization to form final product.

CONCLUSION

In conclusion we have demonstrated an environmentally benign cesium fluoride catalysed tandem Knoevengal-Michael reaction in ethanol for the synthesis of different substituted 6-amino -1,4-dihydro -3- methyl -1.4- phenyl Pyrano [2,3-c] pyrazoles. The method eliminates the use of hazardous organic solvents and toxic catalysts and thus provides a better and practical alternative to exisisting procedures.

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