ONE POT MULTICOMPONENT SYNTHESIS OF FUNCTIONALIZED PYRIDINES USING MORPHOLINE ORGANOBASE AT AMBIENT TEMPERATURE

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An atom efficient synthesis of polysubstituted dihydropyridine derivatives was accomplished by the one-pot four-component condensation of aldehydes, amines, dialkyl acetylene dicarboxylates and active methylene group-containing compounds such as malononitrile or ethyl cyanoacetate using morpholine as a catalyst at ambient temperature. Broad substrate scope, non-chromatographic purification, good yields of the products makes it be a useful and valuable methodology for employing the 1,4-dipolar intermediates in synthetic organic chemistry. Use of organobase as a single catalyst, room temperature conditions renders the method protocol as a significant addition to the existing methods for the synthesis of multifunctionalized dihydropyridines.

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INTRODUCTION

Multi-component reactions (MCRs) contribute significantly to the sustainable and diversity-oriented synthesis of various heterocyclic compounds in combinatorial and medicinal chemistry.[1] Reduced number of steps, high atom economy, energy efficient, time-saving and cost-effective nature of the MCRs make them highly desirable tools in synthetic organic chemistry. These reactions constitute important green tools for the synthesis of highly functionalized molecules in organic chemistry.

Cascade reactions, also known as domino reactions or tandem reactions, are chemical processes involving at least two consecutive reactions occurring, such that each subsequent reaction occurs due to the entity formed in the previous step, without the need to isolate the intermediate. These reactions thus assist in reducing the number of steps involved in the synthesis of biologically potent heterocyclic compounds[2]. Cost effective synthesis of highly functionalized and diverse heterocyclic compounds from readily available precursors is an enduring task for synthetic organic chemists. The formation of C-C, C-N and C-S bonds is also one of the significant challenges to the researcher community[3].

Dihydropyridines (DHPs) are abundant in various natural products as well as pharmaceutically important heterocyclic compounds; constituting the skeleton of drugs such as amlodipine, clevidipine, aranidipine and nifedipine (Figure 1). DHP is also a core component of calcium channel blockers used in the treatment of cardiovascular diseases, including hypertension and spastic smooth muscle diseases.[4-5] DHP derivatives exhibit a broad spectrum of biological activities and well-studied for applications in the treatment of Alzheimer's disease, cardiovascular diseases and hypertension.[6] Furthermore DHPs are also well known for antimicrobial,[7] anticancer,[8] antioxidant,[9] anti-inflammatory,[10] antidiabetic,[11] antitubercular[12] and analgesic[13] activities. These derivatives showed therapeutic properties including platelet antiaggregatory activities,[14] HIV protease inhibition[15] and neuroprotection.[16]

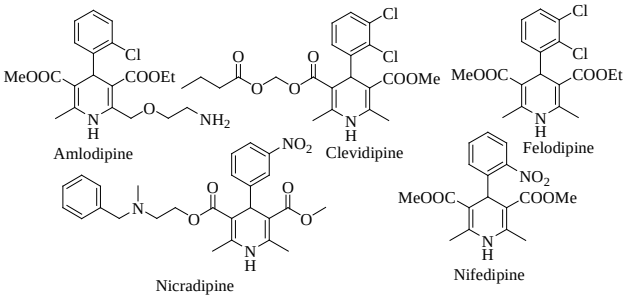
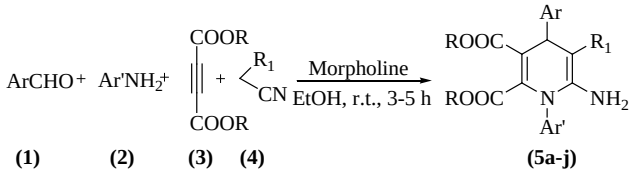


Figure 1. Some biologically active dihydropyridines

Thus, considering the therapeutic and pharmacological activities of DHP derivatives, considerable attention has been focused on designing efficient methodologies for the synthesis of these heterocyclic compounds. The classical, most simple and straightforward synthesis of these heterocycles is the Hantzsch's reaction of an aldehyde, β-ketoester and ammonia. However, only a few reports are available for the synthesis of highly functionalized 1,4-DHPs involving the use of Meglumine,[17] grinding technique,[18] triethylamine,[19] sodium hydroxide,[20] PEG-400,[21] ammonium hydrogen phosphate $(NH_4)_2HPO_4$,[22] yttrium triflate,[23] p-toluenesulfonic acid (p-TSA)[24] and L-proline.[25] However, many of these methods require prolonged reaction time, use of costly reagents and high reaction temperature.

Morpholine is a colorless, water-soluble organobase possessing both amine and ether functionalities. The presence of etheral oxygen withdraws electron density from the nitrogen, rendering morpholine less nucleophilic and less basic than piperidine. It is documented for the catalytic applications for the synthesis of various heterocyclic compounds such as α, β-unsaturated nitroalkenes[26], chromene core structured heterocyclic compounds[27]and

Hantzsch's polyhydroquinoline derivatives[28]. Thus, in continuation of our successful efforts in the development of new strategies for the synthesis of bioactive heterocyclic compounds[29]; herein we report the atom efficient synthesis of polysubstituted dihydropyridine derivatives by the one-pot four component condensation of aldehyde (**1**), amine (**2**), dialkyl acetylene dicarboxylate (**3**) and active methylene compound such as malononitrile or ethyl cyanoacetate (**4**) using morpholine as an organobase at room temperature in short reaction time to afford the corresponding products in high yields (**Scheme 1**).



Scheme 1. One pot synthesis of DHPs using morpholine organobase

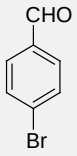
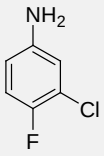
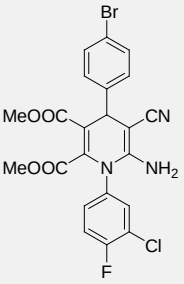
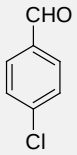
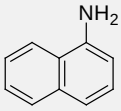
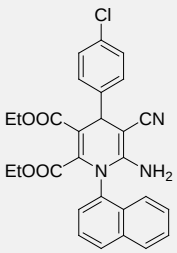
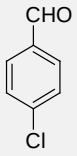
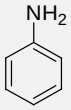
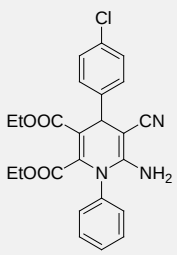
EXPERIMENTAL

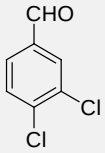
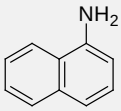
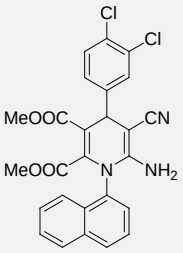
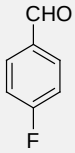
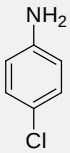
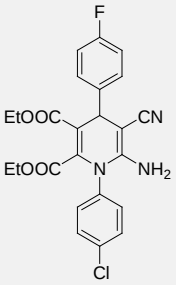
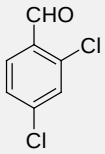
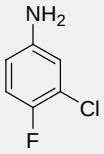
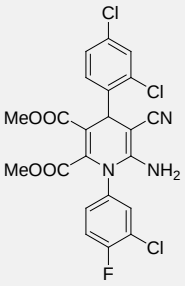
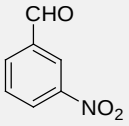
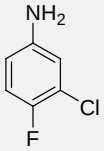
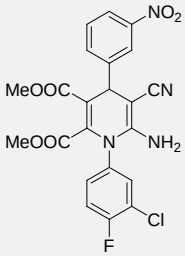
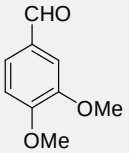
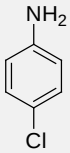
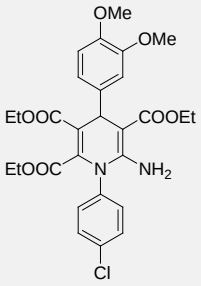
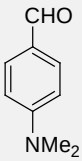
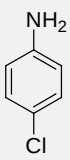
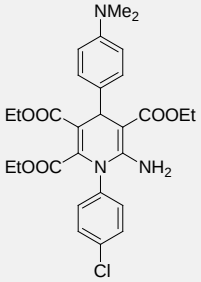
Chemicals used were SD fine or Sigma Aldrich made and used without further purification. The progress of the reaction was monitored on silica-gel coated aluminum TLC plates (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF 200 spectrophotometer and chemical shifts were expressed in δ ppm in $CDCl_3$ with reference to TMS as the standard. IR spectra were recorded on Shimadzu FTIR (Prestige 21) spectrophotometer, mass spectra on a Shimadzu MS-Q spectrometer and melting points of the products were recorded on a digital melting point apparatus (Optics technology) using capillaries open at one end and were uncorrected.

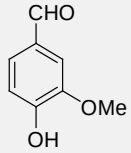
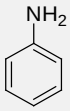
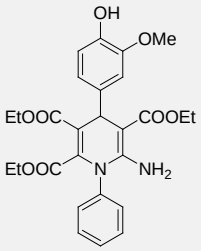
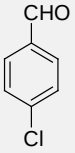
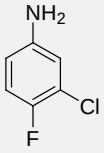
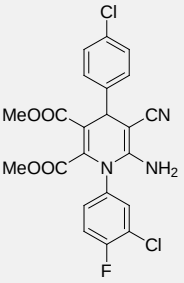
General procedure for the one pot four component synthesis of highly functionalized DHPs

A mixture of aldehyde (2 mmol), malononitrile (3 mmol) and morpholine (20 mol%) in ethanol (3 mL) was stirred at room temperature for 10 minutes; followed by dropwise addition of arylamine (2 mmol) and then dialkyl acetylene dicarboxylate (2 mmol). The contents were stirred at room temperature for an appropriate time as specified in Table 1. The progress of the reaction was monitored by thin layer chromatography (40 % ethyl acetate:n-hexane). After completion of the reaction, the reaction mass was concentrated, poured into ice-cold water and filtered off residue as the crude multifunctionalized dihydropyridine which was further purified by crystallization in ethanol.

Table 1. Yields, reaction time and physical constants of DHPs using morpholine organobase

Entry	Aldehyde	Amine	R	R_1	Product	Time, h	Yield (%)*	M. P. (°C)
1			Me	CN		4.0	78	108-109
2			Et	CN		4.5	85	137-138
3			Et	CN		3.0	89	176-177

4			Me	CN		4.5	80	101-102
5			Et	CN		3.5	82	183-184
6			Me	CN		4.0	76	117-118
7			Me	CN		3.0	86	120-121
8			Et	COOEt		4.0	80	142-143
9			Et	COOEt		5.0	78	115-116

10			Et	COOEt		5.0	77	109-110
11			Me	CN		4.0	84	112-113

(*For aldehyde: 2 mmol, active methylene compound: 3 mmol, DMAD or DEAD: 2 mmol, amine: 2 mmol, in ethanol in the presence of 20 mol % morpholine)

The spectral data of the synthesized compounds is mentioned below:

Dimethyl-6-amino-4-(4-bromophenyl)-1-(3-chloro-4-fluorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (Table 1, Entry 1):

Off white solid; M.P.=108-109 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.1 (s, 3H), 3.18 (s, 3H), 3.89 (s, 2H), 4.7 (s, 1 H), 7.48 (d, 4H), 8.02 (d, 3H); IR (neat) cm^{-1} 3332, 2959, 2172, 1741, 1696, 1641, 1562, 1372, 1210, 1032; Mass: 520.1$(M+1)^{+}$.

Diethyl-6-amino-4-(4-chlorophenyl)-5-cyano-1,4-dihydro-1-(naphthalen-1-yl)pyridine-2,3-dicarboxylate (Table 1, Entry 2):

Off white solid; M.P.=137-138 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.9 (t, 3H), 1.12 (t, 3H), 4.0 (s, 2H), 4.2 (q, 4 H), 4.8 (s, 1H), 7.3 (m, 7H), 7.5 (d, 4H); IR (neat) cm^{-1} 3461,3336, 2966, 2177, 1746, 1695, 1646, 1566, 1371, 1239, 1032; Mass: 502 (M+1)+.

Diethyl-6-amino-4-(4-chlorophenyl)-5-cyano-1,4-dihydro-1-phenylpyridine-2,3-dicarboxylate (Table 1, Entry 3):

Yellow solid; M.P.=176-177 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.9 (t, 3H), 1.1 (q, 3H), 3.9 (m, 2H), 4.1 (q, 4H), 4.7 (s, 1H), 7.39 (m, 6H), 7.5 (d, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ ppm 13.42, 13.91, 38.27, 60.96, 62.19, 104.94, 120.44, 128.61, 128.88, 129.94, 130.48, 130.62, 132.85, 135.09, 141.76, 143.59, 149.81, 162.81, 162.88, 164.98; IR (neat) cm^{-1} 3382.9 (-NH_2), 2972.2 (C-H in -CH_3), 2187.9 (-CN), 1722.58 (-C=O), 1649.22; Mass: 452 $(M+1)^{+}$.

Dimethyl-6-amino-4-(3,4-dichlorophenyl)-5-cyano-1,4-dihydro-1-(naphthalen-1-yl)pyridine-2,3-dicarboxylate (Table 1, Entry 4):

Yellow solid; M.P.=101-102^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.12 (s, 3H), 3.22 (s, 3H), 4.01 (s, 2H), 4.88 (s, 1H), 7.49 (d, 3H), 7.22 (m, 7 H); IR (neat) cm^{-1} 3336, 2964, 2172, 1746, 1695, 1644, 1566, 1372, 1217, 1032; Mass: 508. $(M+1)^{+}$.

Diethyl-6-amino-1-(4-chlorophenyl)-5-cyano-4-(4-fluorophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (Table 1, Entry 5)

Yellow solid; M.P.=183-184 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 1.05 (t, 3H), 1.1 (t, 3H), 3.9 (m, 2H), 4.05 (q, 4H), 4.7 (s, 1H), 7.1 (d, 2H), 7.3 (m, 4H), 7.5 (d, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ ppm 13.04, 13.57, 39.38, 60.27, 61.36, 104.61, 115.15, 120.54, 128.58, 129.37, 132.04, 133.88, 135.14, 141.35, 141.38, 150.34, 159.93, 162.36, 164.29; IR (neat) cm^{-1} 3338.7 (-NH_2), 2982.3 (C-H str. -CH_3), 2184.8 (-CN), 1744.41 (-C=O); Mass: 470 $(M+1)^{+}$.

Dimethyl-6-amino-1-(3-chloro-4-fluorophenyl)-4-(2,4-dichlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (Table 1, Entry 6):

White solid; M.P.=117-118^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.1 (s, 3H), 3.15 (s, 3H), 4.01 (s, 2H), 4.78 (s, 1H), 7.4 (d, 4H), 7.62 (d, 2H); IR (neat) cm^{-1} 3334, 2970, 2179, 1749, 1698, 1631, 1572, 1370, 1203, 1044; Mass: 510.72 $(M+1)^{+}$.

Dimethyl 6-amino-1-(3-chloro-4-fluorophenyl)-5-cyano-1,4-dihydro-4-(3-nitrophenyl)pyridine-2,3-dicarboxylate (Table 1, Entry 7):

Off white solid; M.P.=120-121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 3.21 (s, 3H), 3.28 (s, 3H), 4.12 (s, 2H), 4.73 (s, 1H), 7.81 (d, 3H), 8.07 (d, 4H); IR (neat) cm^{-1} 3340, 2969, 2273, 1749, 1648, 1568, 1372, 1219, 1033; Mass: 486.91 $(M+1)^+$.

Triethyl-6-amino-1-(4-chlorophenyl)-1,4-dihydro-4-(3,4-dimethoxyphenyl)pyridine-2,3,5-tricarboxylate (Table 1, Entry 8):

White solid; M.P.=142-143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.9 (t, 3H), 1.03 (t, 3H), 1.12 (t, 3H), 3.02 (s, 3H), 3.08 (s, 3H), 3.96 (s, 2H), 4.12 (q, 4H), 4.19 (q, 2H), 4.7 (s, 1H), 7.53 (d, 3H), 7.90 (d, 4H); IR (neat) cm^{-1} 3335, 2957, 2176, 1744, 1694, 1638, 1560, 1372, 1215, 1033; Mass: 559.03 $(M+1)^+$.

Triethyl-6-amino-1-(4-chlorophenyl)-4-(4-(dimethylamino)-phenyl)-1,4-dihydropyridine-2,3,5-tricarboxylate (Table 1, Entry 9):

Yellow solid; M.P.=115-116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.89 (d, 3H), 1.1 (t, 3H), 1.21 (t, 3H), 2.56 (s, 6H), 3.93 (s, 2H), 4.02 (q, 4H), 4.13 (q, 2H), 4.82 (s, 1H), 7.8 (d, 4H), 8.05 (d, 4H); IR (neat) cm^{-1} 3338, 2970, 2181, 1747, 1696, 1652, 1570, 1381, 1313, 1132; Mass: 541.9 $(M+1)^+$.

Triethyl-6-amino-1,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-1-phenylpyridine-2,3,5-tricarboxylate (Table 1, Entry 10):

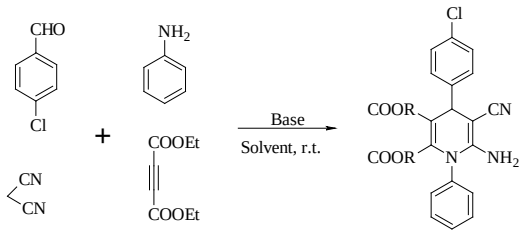
Faint solid; M.P.=109-110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 0.99 (t, 3H), 1.1 (t, 3H), 1.2 (t, 3H), 3.2 (s, 3H), 3.92 (s, 2H), 4.03 (q, 2H), 4.14 (q, 2H), 4.19 (q, 2H), 4.78 (s, 1H), 5.9 (s, 1H, -OH), 7.27 (m, 5H), 7.43 (d, 3H); IR (neat) cm^{-1} 3328, 2803, 2184, 1748, 1690, 1643, 1562, 1370, 1213, 1032; Mass: 510.38 $(M+1)^+$.

Dimethyl-6-amino-1-(3-chloro-4-fluorophenyl)-4-(4-chlorophenyl)-5-cyano-1,4-dihydropyridine-2,3-dicarboxylate (Table 1, Entry 11):

Faint yellow solid; M.P.=112-113 °C; 1H NMR ($CDCl_3$, 400 MHz) δ ppm 3.28 (s, 3H), 3.41 (s, 3H), 4.02 (s, 2H), 4.67 (s, 1H), 7.82 (d, 4H), 7.95 (d, 3H); IR (neat) cm^{-1} 3336, 2956, 2183, 1846, 1695, 1640, 1558, 1372, 1213, 1029; Mass: 476.01 $(M+1)^+$.

RESULTS AND DISCUSSION

Initially to optimize reaction conditions, the reaction of 4-chlorobenzaldehyde (1 mmol), malononitrile (1.5 mmol), diethyl acetylene dicarboxylate (1 mmol) and aniline (1 mmol) mixture was probed as a model condensation reaction using various bases and solvents at room temperature for the synthesis of diethyl-6-amino-4-(4-chlorophenyl)-5-cyano-1,4-dihydro-1-phenylpyridine-2,3-dicarboxylate (DHP-3) (Scheme 2, Table 2).



Scheme 2. Model reaction for optimization of reaction conditions

Table 2. Optimization of reaction conditions for the model reaction

No.	Conditions	Time,h	Yield,%@
1	N,N-DIPEA (10 mol %), EtOH, r.t.	5	36
2	Pyrrolidine (10 mol %), EtOH, r.t.	5	70
3	Imidazole (10 mol %), EtOH, r.t.	5	45
4	Cs_2CO_3 (10 mol %), EtOH: H_2O, r.t.	8	64
5	DABCO (10 mol %), EtOH, r.t.	8	53
6	Morpholine (10 mol %), EtOH, r.t.	3	84
7	Morpholine (20 mol %), r.t., EtOH	3	89
8	Morpholine (20 mol %), r.t., MeOH	3	81

@Reactions carried on 4-chlorobenzaldehyde (1 mmol), malononitrile (1.5 mmol), diethyl acetylenedicarboxylate (1 mmol) and aniline (1 mmol).

From Table 2, bases like N,N-diisopropyl(ethyl)amine (N,N-DIPEA), pyrrolidine, imidazole, DABCO or cesium carbonate (Cs_2CO_3) were not suitable to catalyze the transformation at room temperature after 5-8 h of reaction time. Among the several bases tried for the probe model reaction; use of morpholine (20 mol %) was found to be sufficient enough to carry out the transformation via one-pot synthesis of highly substituted 1,4-DHPs at ambient temperature. If no base was added, the reaction did not yield the desired product even after stirring for overnight (12 h). Morpholine was required in higher concentration (20 mol %) which could be most probably due to its decreased basicity and presence of an electron withdrawing oxygen atom in the ring. The reactions were found to be better in ethanol rather than methanol in terms of the yield of desired products.

Encouraged with these results, scope and generality of the catalytic efficiency of morpholine were extended by using diversely substituted aldehydes and amines (Table 1).

Furthermore, the use of dimethyl acetylene dicarboxylate instead of diethyl acetylene dicarboxylate and ethyl cyanoacetate in place of malononitrile also accomplished satisfactory results. Diethyl acetylenedicarboxylate showed slightly high reactivity as compared to dimethyl acetylene dicarboxylate. Aldehydes possessing electron donating as well as electron withdrawing substituents afforded the desired products without significant variation in yields. Thus, the domino one-pot reaction was successful with different active methylene compounds, dialkyl acetylene-dicarboxylate, aromatic aldehydes and amines (Table 1) revealing that the reaction works well and tolerates both electron-withdrawing and electron-donating substituents in

aromatic ring generating the target molecules in high yields with negligible variations in the product. It indicates that the present protocol has a broad substrate scope. After completion of the reaction as monitored by TLC, the reaction mass was concentrated on a rotary evaporator, poured onto crushed ice, stirred for 10 minutes and filtered off the resulting precipitated solid as a crude product which was further purified by crystallization with ethanol. Thus the work-up procedure for the morpholine catalyzed synthesis of DHPs was found to be convenient and straightforward. The products were confirmed by comparison of their physical constants with the literature values and analysis of spectroscopic data viz ^{1}H, ^{13}C NMR, IR and MS spectra.

A plausible mechanism for morpholine base catalyzed the synthesis of 1, 4-DHPs is outlined in Figure 2:

Step-1: The base abstracts proton from the acidic compound - malononitrile or ethyl cyanoacetate affording benzylidene intermediate (**I**) involving the Knoevenagel condensation.

Step-2: Treatment of DMAD or DEAD with the ethanolic solution of aromatic amine generates the 1,3-dipole intermediate (**II**).

Step-3: Michael addition of intermediate (**I**) with the dipolar intermediate (**II**), followed by migration of hydrogen, cyclization and tautomerization of the imino group (C=NH) to the amino (-C-NH_2) group results in the formation of the desired product.

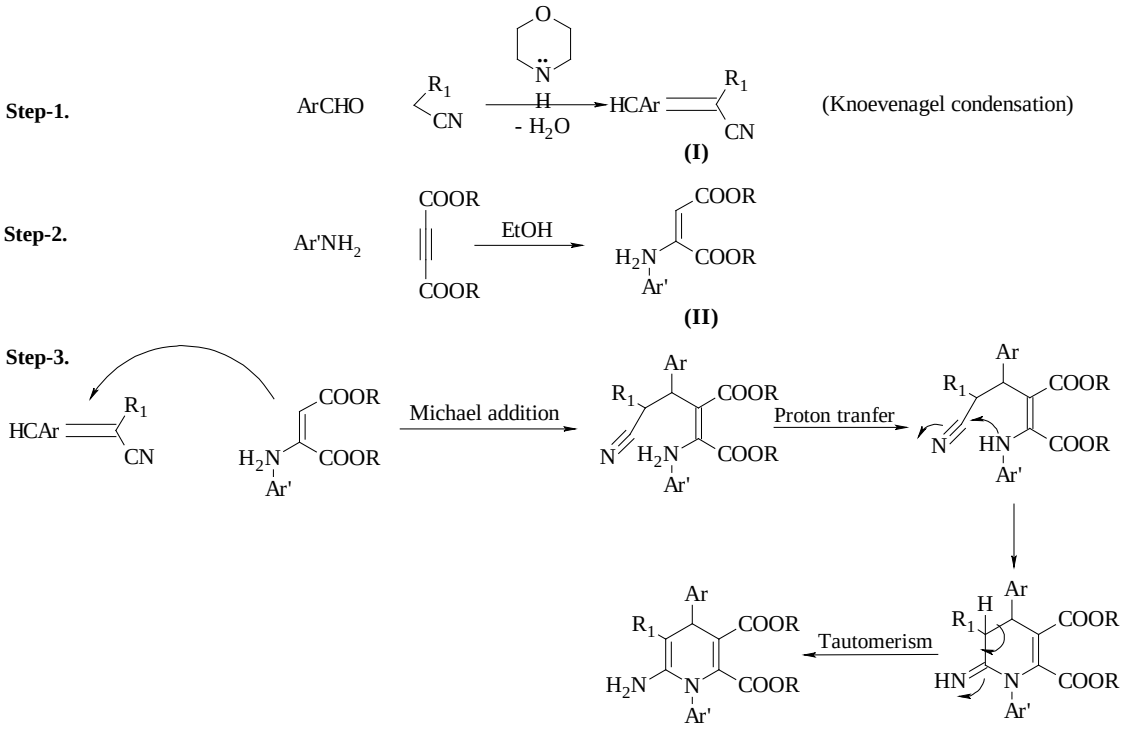


Figure 2. A plausible mechanism for the morpholine base catalyzed the synthesis of polysubstituted pyridines

CONCLUSION

In summary, an atom efficient, practical strategy and easy access to highly functionalized 1,4-DHP derivatives using morpholine as an organobase has been developed by one-pot four-component reaction of an aldehyde, acidic active methylene compound, DEAD or DMAD and various amines via tandem Knoevenagel, Michael and intramolecular nucleophilic additions at ambient temperature. Ease of work up, room temperature conditions, broad substrate scope, no need of column chromatographic purification and good yields make the present protocol attractive for the construction of DHPs.

It also provides a practical methodology for employing the 1,4-dipolar intermediate to design new multicomponent reactions in synthetic organic chemistry.

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