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Research Article

ECO-FRIENDLY ONE-POT SYNTHESIS AND CHARACTERIZATION OF 1, 4–DIHYDRO PYRIDINE DERIVATIVES

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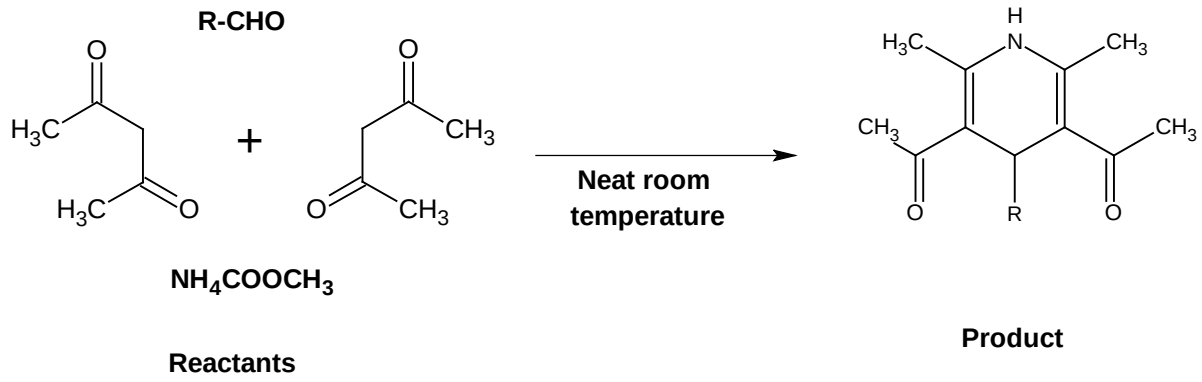
ABSTRACT

A simple,eco-friendly and efficient method has been described for the synthesis of 1,4- dihydro pyridine derivatives employing a one-pot, three component reaction of aryl aldehydes, two molecules of acetyl acetone and ammonium acetate under solvent-free conditions by Knoevenagel's condensation (Hantzsch synthesis), the aldehyde reacts with one molecule of acetyl acetone to give 2, 4- diketone; a second intermediate is an keto enamine which is produced by condensation of the second equivalent of the acetyl acetone and ammonium acetate under solvent free conditions; the two resulting units are then joined by a Michael- type addition followed by ring closure to give 1,4 -dihydro pyridine in excellent yields within a short reaction period.

Keywords: Hantzsch condensation, One-pot Synthesis, 1,4- dihydropyridine, Acetyl acetone, Ammonium acetate.

INTRODUCTION

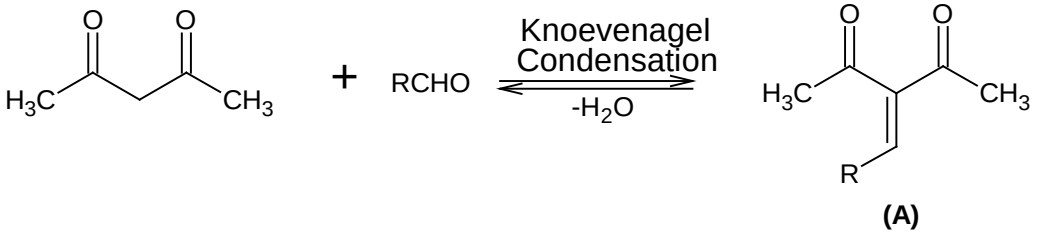
Pyridine and its derivatives are known as an important class of heterocyclic compounds. They are used in the treatment of congestive heart failure, since they act as a dual cardio selective agonist (GPLA) / smooth muscle selective calcium channel antagonist (GPILSM). Furthermore ,4- phenyl substituted 3,5-diacetyl,1,4- dihydro-pyridines show cytotoxic activity against human-oral squamous carcinoma (HSC-2)cells[1,2].One –pot three component condensation[3-5] of aldehydes, acetyl acetone, and cyclic 1, 3-dicarbonyl compound is the most convenient method for the preparation of these compounds. In this context some methods and catalysts have been reported. Furthermore, 1,4- dihydro pyridines and its analogues can be prepared by reaction of acetyl acetone with aldehydes in the presence of a catalyst. Though many classical methods are available for the synthesis of 1,4- dihydro pyridines, these methods require high temperature, prolonged reaction time and drastic reaction conditions and the yields are unsatisfactory due to the occurrence of several side reactions. This work reports, a simple efficient, eco-friendly solvent free synthesis[6] of 1, 4- dihydro pyridines without using any catalyst at room temperature (RT).Systematic studies directed towards the development of practically safe, and eco -friendly procedures has led to an efficient method, for the synthesis of 1,4- dihydropyridine through three –component reactions of aldehydes, ammonium acetate and acetyl acetone under solvent -free conditions. (Scheme 1&2).



Scheme 1

Mechanism

Step 1



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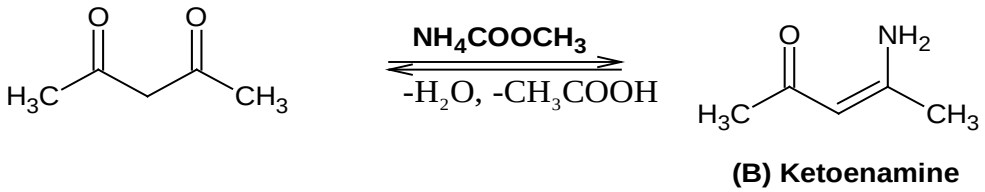
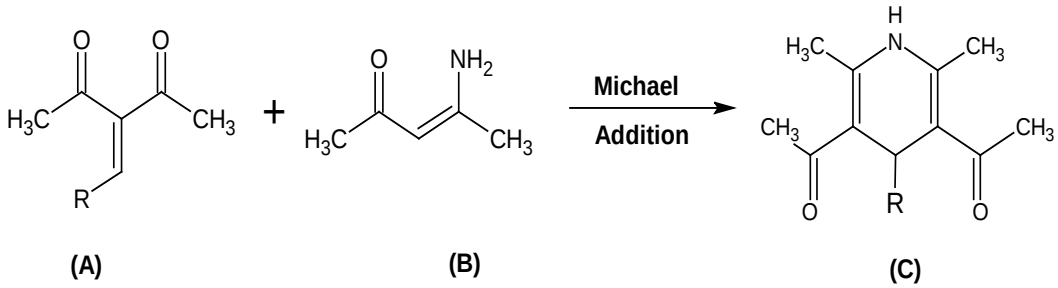
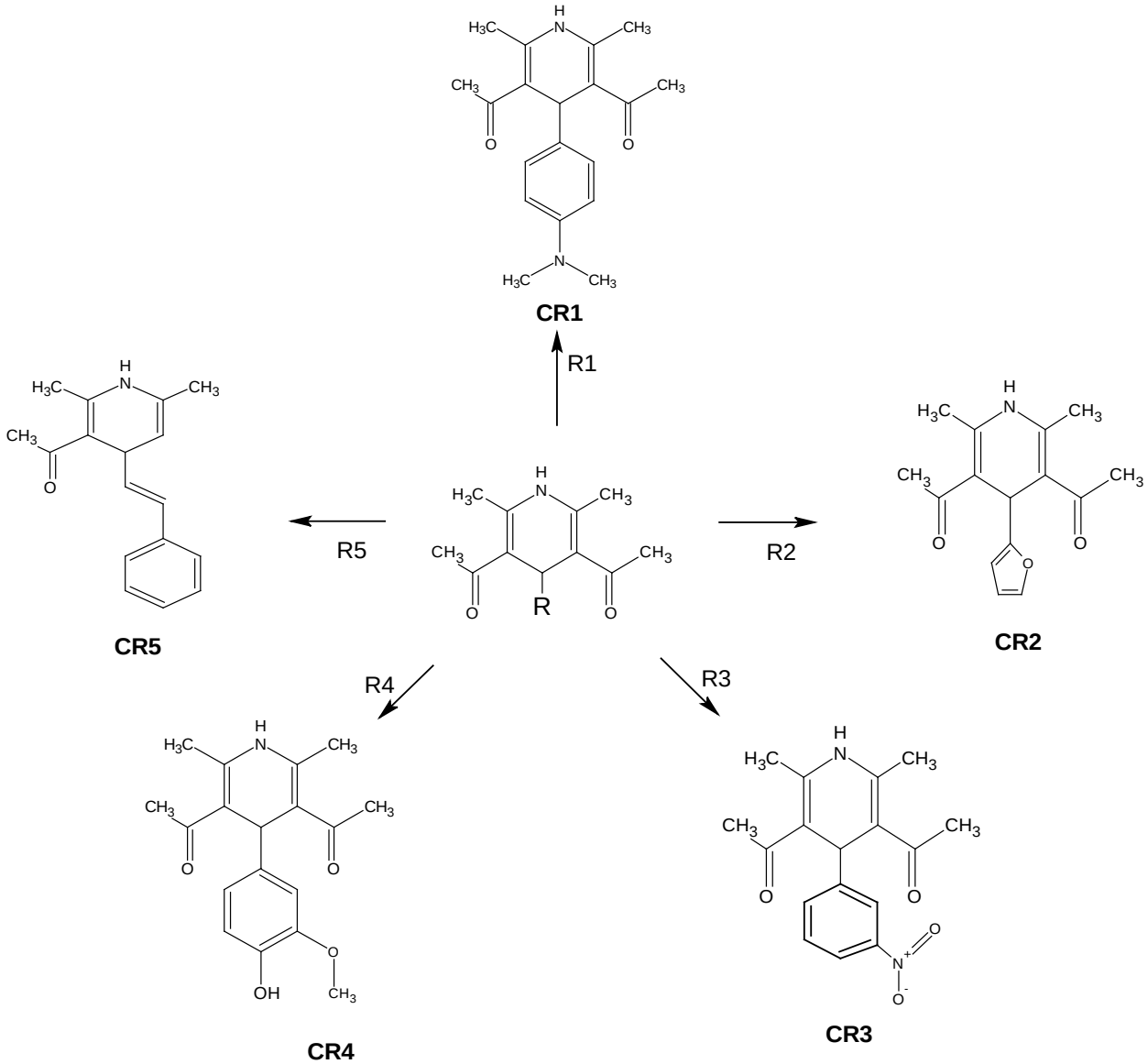


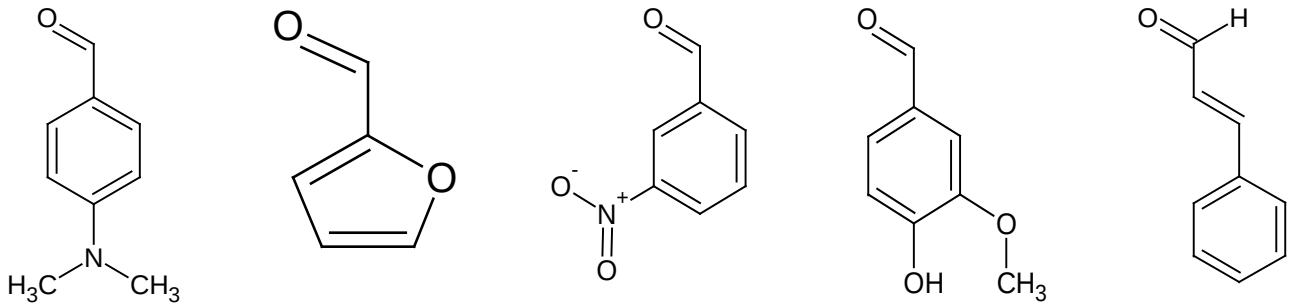
Step 3



Synthetic Scheme II



R1 **R2** **R3** **R4** **R5**



MATERIALS AND METHODS

Melting points were determined by open capillary method and are presented uncorrected. Purity of the compounds were checked by TLC using n-hexane and ethyl acetate as mobile phase. The visualization of spot was carried out by examining under UV light / iodine vapours in a tightly closed chamber.

All the isolated compounds were characterized by IR, ^{1}H NMR, and Mass Spectroscopy. The IR spectra were recorded using of ^{1}FT-IR spectrophotometer (ABB MB 3000) in the range of 4000-400 cm^{-1} by KBr pellet technique.

The ^{1}H NMR **s**pectra were recorded in (Bruker AV III, 500 MHz NMR spectrometer) instrument using deuterated chloroform as solvent and TMS as internal standard, coupling constants (J) were in measured in Hz:

The mass spectra were recorded using (JEOL GC MateII Mass spectrometer) by electron ionization technique.

General procedure for the synthesis of 1, 4 -dihydro pyridine derivatives[7, 8]

To a stirred mixture of aromatic aldehyde (0.318 g, 3mmole), and acetyl acetone (0.696 g, 6mmol), ammonium acetate (0.231g, 3mmol) was added; the reaction mixture was homogenized by stirring to a viscous liquid. The progress of the reaction was monitored by TLC.The mobile phase for CR1&CR2 is methanol/chloroform (1:4) and for CR3,CR4& CR5 ethyl acetate/n-hexane (6vol:4vol).After completion of the reaction, a small amount of ethanol was added to the viscous liquid and stirred for 5 min. Ice-cold water was added to the mixture, the solid thus obtained was filtered. The crude product was purified by recrystallisation from ethanol: water (95:5) mixture.

Table 1: Synthesis of 1, 4- dihydro pyridine derivatives

S. No.	R	Product	Time (minutes)	% Yield	M.P °C
1.	Para dimethyl amino benzaldehyde	CR1	30	90	85
2.	Furfuraldehyde	CR2	25	95	150
3.	3-Nitrobenzaldehyde	CR3	40	75	140
4.	Vanillin	CR4	30	60	84
5.	Cinnamaldehyde	CR5	40	80	170

Characterization of synthesized compounds[9-12]

1,1'-{4-[4-(dimethylamino)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5- diyl} diethanone(CR1)

Light yellow colored crystalline powder, mp: 85-88˚C, Yield 90%.

Molecular formula: $C_{19}H_{24}N_2O_2$, molecular weight- 312.40606.

IR (KBr) cm^{-1}: 3456 (-NH str), 2993(aromatic C-H str), 2847 (aliphatic C-H)1636(C=O, COCH3) , 1196(-C-N), 1574 (aromatic C=C), 741(-C-C),

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 6H, CH_3), 3.08(s, 6H, COCH3), 4.36(s, 6H, N $(CH_3)_2$,

4.90(s, 1H, CH), 6.69-6.70(d, *J=7Hz*, 2H, aromatic CH), 7.73-7.74

(d, *J=7Hz*, 2H, aromatic C-H), 9.74(s, 1H, NH).

MS: m/z value: 312.5739 (M) + ion peak.

1, 1'-[4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl]diethanone(CR2)

Greenish yellow coloured powder, mp: 150-153˚C, yield 95 %.

Molecular formula: $C_{15}H_{17}NO_3$, molecular weight: 259.30038.

IR (KBr) cm^{-1}: 3325 (-NH str), 3086(aromatic C-Hstr), 2939(aliphatic C-H str), 1690 (-C=O),

1582(-C=C), 1095 (-C-N), 748(-C-C) 1281(-C-O),

^{1}H NMR ($CDCl_3$): δ 2.31(s,3H,CH_3),2.35(s,3H,CH_3),2.38(s,3H,$COCH_3$), 2.44(s,3H,$COCH_3$),

5.15(s, 1H, CH), 6.20-6.79(m, 3H, Hetero aromatic CH), 10.02(s, 1H, NH)

MS: m/z value-259.1402 (M) +ion peak.

1,1'-[2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-diyl]diethanone - methane (1:1)(CR3)

Brick red crystalline powder, mp140-143˚C. Yield 75%,

Molecular formula: $C_{17}H_{18}N_2O_4$, molecular weight: 314.33582.

IR (KBr) cm^{-1}: 3333(-NHstr), 3078(aromatic C-H), 2924(aliphatic C-Hstr),1697(C=O),

1582(C=C),C-C (771), 1088(C-N), 1342(NO_2 gp),

^{1}H NMR($CDCl_3$): δ 2.01(s,3H,CH_3),2.10(s,3H,CH_3),2.24(s,3H,$COCH_3$), 2.44(s,3H,$COCH_3$),

4.81(s,1H,CH),7.19-8.83(m,7.19-8.83(m,4H,aromaticCH), 10.15(s,1H, NH)

MS: m/z value-314.4289. (M)+ion peak.

1,1'-[4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4- **dihydropyridine-3,5-diyl]diethanone*(CR4)***

Cream crystalline powder, mp: 84-87˚C, yield 60%.

Molecular formula: $C_{18}H_{21}NO_4$, molecular weight 315.36364.

IR (KBr) cm^{-1}: 3433(-NH str), 2993(aromatic-CH str),2962(aliphatic C-H),1628

(C=O,COCH3), 1134(C-N), 1574(C=C), 795 (C-C), 3580 (OH str),

^1H NMR($CDCl_3$): δ 1.92 (s,3H,CH_3),1.98 (s,3H,CH_3),2.73(s,3H,$COCH_3$),2.79(s,3H,$COCH_3$),

3.97(s,3H,OCH_3),4.62(s,1H,CH),6.39(s,1H,OH), 7.04-7.44(m,3H, Ar-CH),

9.83 (s, 1H, NH).

MS: m/z value-315.8742(M +1) ion peak.

1, 1'-{2, 6-dimethyl-4-[(E)-2-phenylethenyl]-1,4-dihydropyridine-3,5-diyl}diethanone (CR5)

Yellowish brown powder, mp-170-173˚C, yield 80%.

Molecular formula: $C_{19}H_{21}NO_2$, molecular weight 295.37554.

IR (KBr) cm^{-1}: 3433(-NH str), 2970(aromaticC-Hstr), 2924(aliphatic C-H), 1643(-C=O),

1582(aromatic C=C), 1149(-C-N), 756(C-C), 1612(alkenes C=C)

^1H NMR($CDCl_3$) : δ 2.19(s,6H,CH_3),2.30(s,6H,$COCH_3$),2.42-2.43(d,1H,CH),4.42-4.43

(d,J=6HZ,2H,vinylCH),7.10-7.52(m,5H,Aromtic CH),9.93(s,1H,NH).

MS: m/z value-295.0011 (M)+ion peak.

RESULTS AND DISCUSSION

It has been observed that the process of eco-friendly synthesis technique shortened the reaction time and minimized the byproducts formation there by giving a pure product with a better yield. The maximum reaction time for synthesis of compounds (CR1-CR5) was about 30 minutes. The title compounds showed vibration frequency ranges 2962-2924 (aliphatic-CH str), 3086-2970(aromatic CH str), 3456-3325(NH str), 1149-1049(C-N), 1690-1628(C=O), 1582-1574(C=C) respectively. The ^1H NMR spectral data of all the synthesized compounds were in conformity with the structure assigned. In the molecular ion peaks (M^+) of mass spectra confirmed the molecular weights of the synthesized compound.

The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxyl and olefines under reaction conditions. The reaction condition for the synthesis of 1,4-dihydro pyridine derivatives, using paradimethyl amino benzaldehyde, acetyl acetone and ammonium acetate was optimized.The reactions proceeded smoothly with different aldehydes substituted with electron donating /electron withdrawing groups giving excellent yields. In general, aldehydes with electron-donating substituents required longer times to complete the reaction than the aldehydes containing electron with-drawing substituents.

CONCLUSION

To conclude, the method adopted for the one –pot synthesis of newer 1, 4- dihydropyridine derivatives following the green chemistry[13] approach.The synthetic procedure is efficient cost-effective, safe less time consuming and could be performed at room temperature.The other advantages of the method include simple experimental procedure, solvent free condition, relatively high yield with lesser impurities and easy separation of products.

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