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One Pot Multi Component Synthesis of Novel Dihydropyridine Derivatives

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ABSTRACT

The one pot synthesis of dihydropyridine derivatives (1a-e) were synthesized in good yields by the Hantzsch reaction of different aryl hetero cyclic aldehydes (2a-e) with acetoacetic ester 3 and ammonium acetate 4 in presence of organocatalysts, guanidine hydrochloride. The present work describes the synthesis and characterization of novel dihydropyridine derivatives (1a-e) first time with spectral data (^{1}H-NMR, ^{13}C-NMR, IR and MS).

Key words: Guanidine hydrochloride, Ammonium acetate, Aldehyde, Ethyl acetoacetate: A four component coupling reaction

INTRODUCTION

Heterocyclic chemistry is an important branch of organic chemistry which has been drawing attention for more than a century. N-containing heterocyclics are especially the most predominantly studied ones because they constitute many biologically active compounds and natural products. Dihydropyridine derivatives are an important class of N-containing heterocyclics that comprise some of the most important components of the biologically significant compounds. These compounds form key units in many pharmacological compounds that are expected to exhibit anti-bacterial, anti-fungal, anti-inflammatory, and anti-hypertensive properties.

There are several methods reported [1-15] for the synthesis of dihydropyridine derivatives so far. These synthetic methods include the reaction of alkyl [16] and aryl [17] aldehydes with ammonia acetate and β-keto ester in the presence of guanidine hydrochloride [18]. Here, the author synthesized 1,4-dihydropyridine derivatives using heterocyclic aldehydes because of the great biological importance of heterocyclic aldehydes in both medicinally and industrially. Heterocyclic compounds have received considerable attention due to their broad range of biological activities and many of the pharmaceuticals and agrochemicals are heterocyclics.

Majority of these methods experience drawbacks like extended reaction time, corrosive and toxic solvent, pricey reagent, requirement of higher amounts of catalyst, and extreme reaction conditions like strongly acidic medium and elevated reaction temperature. Owing to the wide range of practical limitations that affect the quantitative yield of the product, there has been quite a significant amount of research going on in the synthesis of these biologically significant heterocyclics. An important advancement in this area is the application of organocatalysts for the synthesis of dihydropyridine derivatives. Urea and thiourea derivatives are used in the design of organocatalysts [19]. The use of organo catalyst improves the yield and rate of the reaction. Effect of catalyst on different dihydropyrimidines preparations are shown in Table 1.

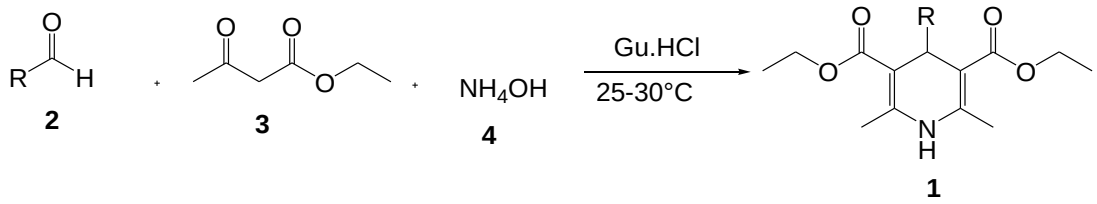
Table 1: **Effect of catalyst on the preparation of dihydropyridine derivatives**

entry	product	without catalyst		with catalyst	
		Time	Yield	Time	Yield
1	1a	10 h	50%	3 h	92%
2	2a	8 h	55%	2 h	90%
3	3a	10 h	53%	3 h	82%
4	4a	7 h	60%	2.5 h	85%
5	5a	8 h	50%	2 h	80%

Guanidine hydrochloride is one such organocatalysts that are proved catalyze the synthesis of dihydropyridine derivatives by Hantzsch reaction [20]. Guanidine hydrochloride has the following advantages compared to the other catalytic systems: cheaply available, high reactive and environmentally-friendly [21,22]. Guanidine hydrochloride can prove to be an effective catalyst for the synthesis of dihydropyridine derivatives by Hantzsch reaction [23], especially when one pot reaction is carried out.

MATERIALS AND METHODS

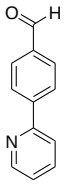
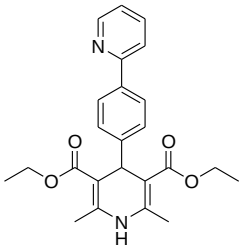
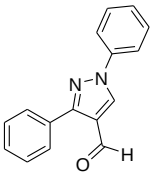
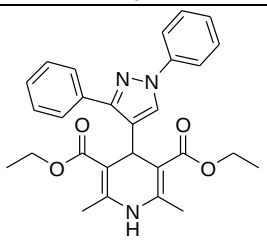
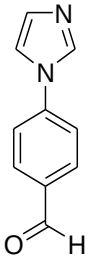
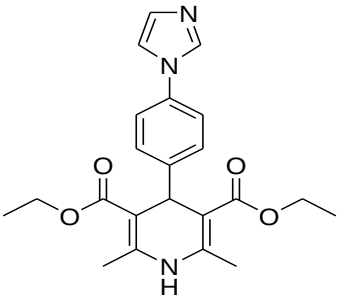
The development of efficient and versatile catalytic systems for Hantzsch reaction is an active on-going research area and thus, there is a scope for further improvement toward milder reaction conditions, variations of substituents and better biological activities. Therefore, we have utilized various heterocyclic aldehydes as efficient substituents for the Hantzsch four-component one-pot synthesis in our laboratory. In an initial experiment, using traditional conditions, Benzaldehyde: Ethyl acetoacetate: Ammonium acetate in a 1:2:1 ratios were stirred in ethanol. After 10 h, only 50% of product was obtained after crystallization of the crude product from ethanol. To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of 5.81 mmol of guanidine hydrochloride under similar conditions. Surprisingly, a significant improvement was observed and the yield of product was dramatically increased but the product has less biological activity. Later, the author synthesized 1, 4-dihydropyridine derivatives containing high biological activity using heterocyclic aldehydes (2a-e) (Scheme 1).

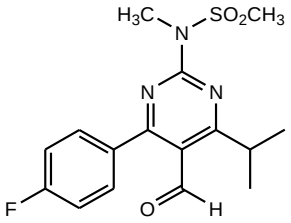
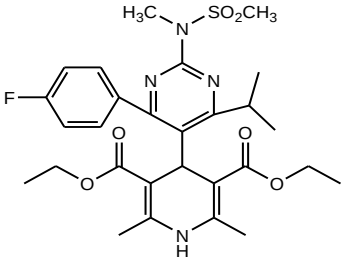
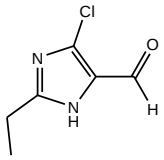
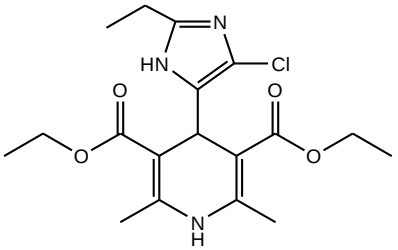


Scheme 1: Reported synthetic scheme for dihydropyrimidines derivatives

Encouraged by this success, we attempted the reaction of ethyl acetoacetate, ammonium acetate with different hetero atom containing aldehyde derivatives with organocatalysts guanidine hydrochloride, furnishing the respective of dihydropyridine derivatives which is shown in Table 2. It is noteworthy to mention that the structural variation of the aldehyde and substituents on the aromatic ring show obvious effect on this conversion because the desired products were obtained with high biological activities.

Table 2: Synthesis of 1,4-dihydropyridine derivatives by using different heterocyclic aryl aldehydes through, Hantzsch reaction using guanidine hydrochloride as a catalyst

Entry	Aldehyde (R)	Product	Time	Yield (%)
1	 **2a**	 **1a**	3 h	92%
2	 **2b**	 **1b**	2 h	90%
3	 **2c**	 **1c**	3 h	82%

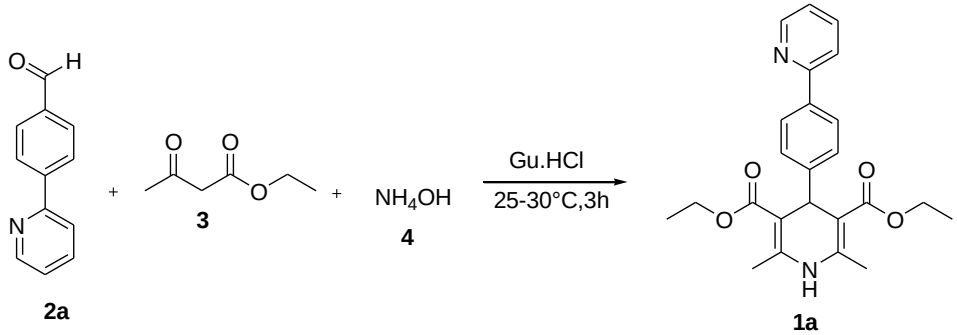
4	 **2d**	 **1d**	2.5 h	85%
5	 **2e**	 **1e**	2 h	80%

In entry (1), the 4-(2-pyridyl)benzaldehyde is a six membered heterocyclic compound containing one nitrogen atom which is called as pyridine has considerable interest in different areas such as medicinal, pesticide, polymer and material science. In entry (2), the 1, 3-diphenyl pyrazole-4-carbaldehyde contains pyrazole nucleus which has great significance in the field of pharmacy as well as to develop newer anti-cancer agent. In entry (3), the 4-imidazol-1-yl benzaldehyde contains a five membered heterocyclic ring containing two nitrogen atoms which is called as imidazole and are an important class of heterocyclics and include many substances of both biological and chemical interest. They are part of a large number of highly significant biomolecules such as the essential amino acid histidine and related compounds, biotin, and the imidazole alkaloids. In entry (4), the N-[4-(4-fluorophenyl)-5-formyl-6-isopropyl-pyrimidin-2-yl]-N-methyl-methane sulphonamide contains a six membered heterocyclic ring containing two nitrogen atoms which is called as pyrimidine and heterocyclics containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [24,25]. Substituted pyrimidines occur widely in living organisms and were some of the first compounds studied by the organic chemists [26] and are an important class of heterocyclics and include many substances of both biological and chemical interest. They are part of a large number of highly significant bio molecules such as the essential amino acid histidine and related compounds, biotin, and the imidazole alkaloids. In entry(5), the 4-chloro-2-ethyl-1H-imidazole-5-carbaldehyde is a fused hetero aromatic system which has been the subject of substantial attention by synthetic and medicinal chemists because of the role of this hetero aromatic ring in many biological systems.

RESULTS AND DISCUSSION

Solvents and reagents were obtained from commercial source and used without purification. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) using aluminium sheets coated with silica gel F_{254} (Merck) with yielding under short wavelength UV lamp detection. The IR spectra (ϑ_{max}, cm^{-1}) were recorded in solid state KBr dispersion using Perkin Elmer FTIR spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker-Avance 300 and 500 MHz spectrometers using Deuterated Dimethyl Sulfoxide (DMSO-d_6) or Deuterated Chloroform ($CDCl_3$) as the solvent and Tetramethylsilane (TMS) as an internal standard. The chemical shifts were reported in δ (ppm) relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. Melting points were determined on Pohlman melting point apparatus (Model No MP96) by open capillary method and are uncorrected.

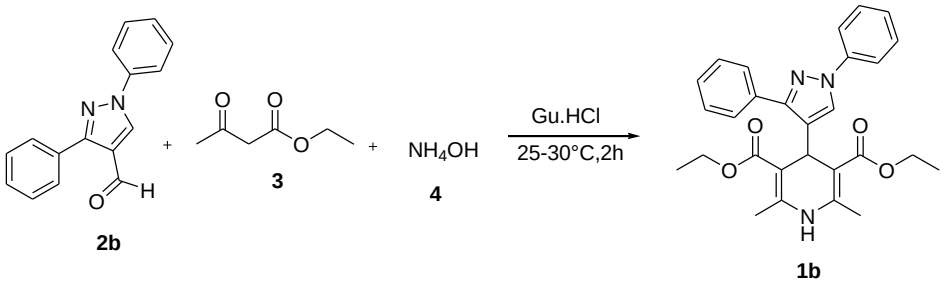
Synthesis of diethyl 2, 6-dimethyl-4-[4-(2-pyridyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (compound 1a)



2a **3** **4** **1a**

To a solution of 4-(2-pyridyl) benzaldehyde (10 g, 54.6 mmol) in ethyl acetoacetate (14.137 g, 108.57 mmol), ammonium acetate (4.187 g, 54.318 mmol) and guanidine hydrochloride (0.555 g, 5.81 mmol) was added at room temperature. The reaction mass was stirred for 3 h at room temperature to complete the reaction. After evaporation of solvent, the product was crystallized from ethanol to give a white colored solid product 26.05 g (92%), m.p.: 240-245°C. Mass for $C_{24}H_{26}N_2O_4$ $(M + H)^+$ Calcd: 407.4718, found: 407. ^{1}H-NMR (500 MHz, DMSO), δ (ppm): 8.54 (d, J=7.5 Hz, 1H, Ar), 7.83 (d, J=8 Hz, 2H, Ar), 7.44 (d, J=7.5 Hz, 1H, Ar), 7.45 (dd, J=8Hz, 1H, Ar), 7.19 (d, J=7.5 Hz, 2H, Ar), 6.92 (dd, J=8 Hz, 1H, Ar), 4.40 (s, J=7 Hz, 1H, Ar-CH-), 4.20 (q, J=7.5 Hz, 4H, OCH_2CH_3), 1.73 (s, 6H, J=7Hz, CH_3-C=C-), 1.35 (t, J=7 Hz, 6H, O-CH_2-CH_3). ^{13}C-NMR (125 MHz, DMSO), δ (ppm): 167.228, 154.87, 149.326, 143.87, 141.153, 137.246, 133.345, 128.501, 127.56, 124.64, 120.824, 102.62, 61.672, 16.437, 14.297. IR (KBr pellet): 3350, 3030, 2960, 2920, 2872, 2852, 1730, 1650, 1600, 1580, 1500, 1450, 1250, 1200, 830 cm^{-1}.

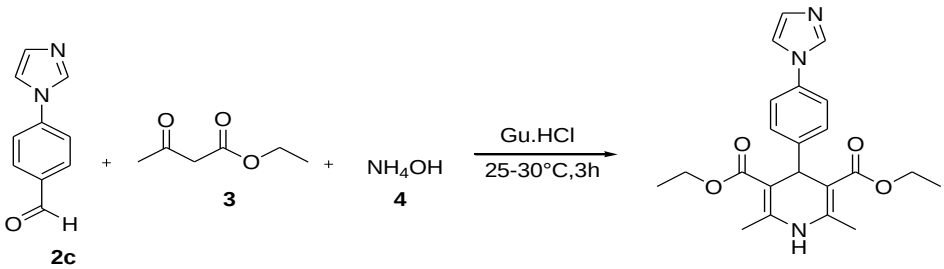
Synthesis of diethyl 4-(1,3-diphenylpyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(compound 1b)



2b **3** **4** **1b**

To a solution of 1,3-diphenyl pyrazole-4-carbaldehyde (10 g, 40.3 mmol) in ethyl acetoacetate (14.13 g, 108.57 mmol), ammonium acetate (4.187 g, 54.318 mmol) and guanidine hydrochloride (0.555 g, 5.81 mmol) was added at room temperature. The reaction mass was stirred for 2 h at room temperature to complete the reaction. After evaporation of solvent, the product was crystallized from ethanol to give a yellow colored solid 25.491 g (90%) mp: 305-310°C. Mass for $C_{28}H_{29}N_3O_4$ $(M + H)^+$ Calcd: 472.5469, found: 472.5348. ^{1}H-NMR (500 MHz, DMSO), δ (ppm): 7.625 (s, J=7Hz, 1H, N-CH=C-Ar), 7.438 (d, J=8 Hz, 2H, Ar), 7.35 (m, J=7.5 Hz, 5H, Ar), 7.328 (d, J=7.5 Hz, 2H, Ar), 4.345 (s, J=7Hz, 1H, =C-CH), 4.129 (q, J=7.5 Hz, 4H, OCH_2CH_3), 1.761 (s, J=7Hz, 6H, CH_3-C=C-). ^{13}C-NMR (125 MHz, DMSO), δ(ppm): 139.729, 129.989, 129.692, 129.13, 128.634, 128.545, 127.76, 127.501, 127.153, 126.828, 126.62, 126.495, 125.762, 122.927, 121.587, 120.839, 66.63, 52.232, 46.347, 39.833, 39.67, 39.5, 39.337, 39.167, 14.368. IR (KBr pellet): 3478, 3371, 3000, 2951, 1720, 1630, 1616, 1549, 1280, 1248, 1149 cm^{-1}.

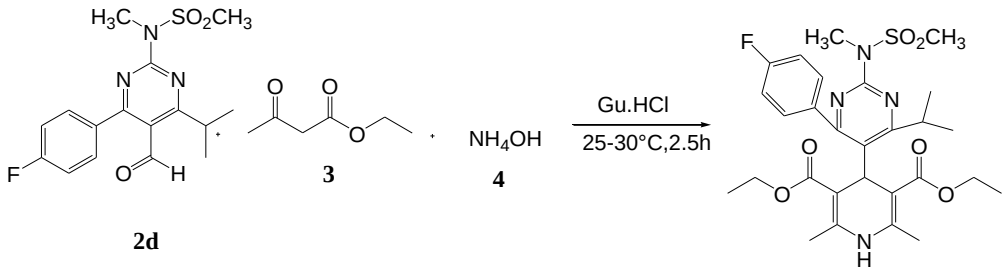
Synthesis of diethyl 4-(4-imidazol-1-ylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (compound 1c)



2c **3** **4** **1c**

To a solution of 4-imidazol-1-yl benzaldehyde (10 g, 58.1 mmol) in ethyl acetoacetate (14.137 g, 108.57 mmol), ammonium acetate (4.187 g, 54.318 mmol) and guanidine hydrochloride (0.555 g, 5.81 mmol) was added at room temperature. The reaction mass was stirred for 3 h at room temperature to complete the reaction. After evaporation of solvent, the product was crystallized from ethanol to give a yellow colored solid 23.225 g (85%), m.p: 238-240°C. Mass for $C_{22}H_{25}N_3O_4$ $(M + H)^+$Calcd: 396.4516, found: 396. ^{1}H-NMR (500 MHz, DMSO), δ (ppm): 8.034 (s, 1H, -N=CH-N-), 7.462 (d, J=7 Hz, 1H, N-CH=C-), 7.273 (d, J=7.5 Hz, 1H, N-CH=C-), 7.138 (m, 5H, Ar), 4.43 (s, 1H, -CH-Ar), 4.129 (q, J=7.5 Hz, 4H), 1.71 (s, 1H, -CH-), 1.398 (t, J=7 Hz, 3H, OCH_2-CH_3).^{13}C-NMR (125 MHz, DMSO) δ (ppm): 167.213, 150.709, 148.023, 135.78, 123.463, 102.309, 61.76, 26.796, 16.35, 14.32, 14.23. IR (KBr pellet): 3450, 3350, 2952, 2910, 2873, 2852, 1735, 1640, 1610, 1465, 1452, 1375, 1300 cm^{-1}.

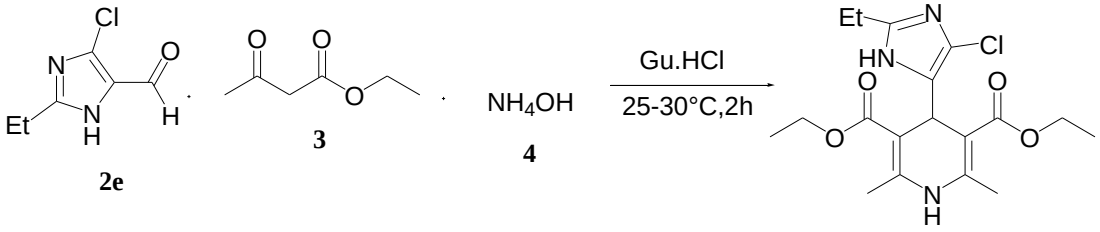
Synthesis of diethyl 2,6-dimethyl-4-(2-(methyl (methyl sulfonyl) amino)pyrimidin-5-yl]-1,4-dihydropyridine-3,5-dicarboxylate (compound 1d)



2d **3** **4** **1d**

To a solution of N-[4-(4-fluorophenyl)-5-formyl-6-isopropyl-pyrimidin-2-yl]-N-methyl-methane sulphonamide (10 g, 28.5 mmol) in ethyl acetoacetate (14.137 g, 108.57 mmol), ammonium acetate (4.187 g, 54.318 mmol) and guanidine hydrochloride (0.555 g, 5.81 mmol) was added at room temperature. The reaction mass was stirred for 2.5 h at room temperature to complete the reaction. After evaporation of solvent, the product was crystallized from ethanol to give a yellow colored solid 24.075 g (80%), m.p: 282 -284°C. Mass for $C_{28}H_{34}N_4O_6FS$ $(M + H)^+$Calcd: 591.1081, found: 591. ^{1}H-NMR (500 MHz, DMSO), δ (ppm): 7.463 (d, J=8Hz, 2H, Ar), 7.021 (d, J=7.5 Hz, 2H, Ar), 4.430 (s, 1H, -CH-C=C-), 4.196 (q, J=7.5 Hz, 4H, -OCH_2-CH_3-), 3.123 (m, 1H, -CH-$(CH_3)_2$), 2.843 (2, 3H, CH_3SO_2), 2.479 (s, 3H, CH_3-N-), 1.711 (s, 1H, -CH-), 1.302 (t, J=7Hz, 6H, -OCH_2CH_3). ^{13}C-NMR (125 MHz, DMSO) δ (ppm): 170.108, 167.213, 166.901, 166.546, 161.910, 150.712, 129.191, 128.729, 116.85, 116.09, 102.321, 61.723, 39.09, 33.373, 31.012, 30.712, 23.702, 16.317, 14.272. IR (KBr pellet):3350, 3025, 2950, 2872, 1735, 1600, 1570, 1500, 1452, 1450, 1385, 1375, 1365, 1250, 1210 cm^{-1}.

Synthesis of diethyl 4-(4-chloro-2-ethyl-1H-imidazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (compound 1e)



2e **3** **4** **1e**

To a solution of 4-chloro-2-ethyl-1H-imidazole-5-carbaldehyde (10 g, 63 mmol) in ethyl acetoacetate (14.137 g, 108.57 mmol), ammonium acetate (4.187 g, 54.318 mmol) and guanidine hydrochloride (0.555 g, 5.81 mmol) was added at room temperature. The reaction mass was stirred for 2 h at room temperature to complete the reaction. After evaporation of solvent, the product was crystallized from ethanol to give a white colored solid product 22.659 g (82%), mp: 220-222 °C. Mass for $C_{18}H_{24}N_3O_4Cl$ $(M + H)^+$Calcd: 382.8538, found: 382. ^{1}H-NMR (500 MHz, DMSO), δ (ppm): 13.43 (s, 1H, -NH-), 7.201-7.117 (m, 15H, Ar), 6.843 (d, J=7.5 Hz, 2H, Ar), 5.825 (s, 2H, NH_2), 5.53 (s, 2H, N-CH_2-Ar), 4.631 (q, J=7.5 Hz, 2H, OCH_2CH_3), 4.43 (s, 1H, -CH-C=C-), 3.668 (s, 3H, OCH_3), 2.59 (q, J=7.5 Hz, 2H, CH3-CH2), 1.398 (t, J=7 Hz, 3H, OCH2-CH3), 1.241 (t, J=7.7 Hz, 3H, CH3-CH2).^{13}C-NMR (125 MHz, DMSO) δ (ppm): 145.119, 129.989, 129.692, 129.13, 128.634, 128.545, 127.76, 127.501, 127.153, 126.828, 126.62, 126.495, 125.762, 122.927, 121.587, 120.839, 66.63, 52.232, 46.347, 39.833, 39.67, 39.5, 39.337, 39.167, 14.368. IR (KBr pellet):3478, 3371, 3000, 2951, 1720, 1630, 1616, 1549, 1280, 1248, 1149 cm^{-1}.

CONCLUSION

In conclusion, aryl heterocyclic aldehydes (2a-e) were used as starting materials for the synthesis of new biologically active heterocyclic dihydropyridine derivatives (1a-e) by using ethyl acetoacetate 3 and ammonium acetate 4 in presence of organocatalysts guanidine hydrochloride. The newly synthesized compounds are characterized by spectral data. The outcome of this experiment has resulted in excellent yield generation within a short span of time. This method has inherent advantages like simplicity of performance, solvent free condition, low cost, eco- friendly, and the catalyst is readily available and inexpensive, conveniently be handled and easily removed from the reaction mixture. The use of heterocyclic aryl aldehydes in this process has enhanced the biological activity of desired product, dihydropyridine derivatives.

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