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L-Proline catalyzed one pot synthesis of novel 1,4-dihydro pyridine derivatives

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ABSTRACT

*Multi component, one pot synthesis of diethyl/ dimethyl 4-(2-butyl-4-chloro-1H-imdazol-5-yl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylayte derivatives **3(a–f)** form the condensation of N-alkyl-2-butyl-4-chloro-1H-imidazole-5-carbaldehydes **1(a–c)**, methyl/ethyl acetoacetate **(2)**, ammonium carbonate has been described using L-proline as a environmentally benign catalyst. L–proline catalyzed reaction provides a green and inexpensive preparation method for synthesis of above compounds.*

Keyword: *N*-alkyl-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehydes, ethylaceto acetate, green synthesis, L-proline, 1,4,dihydropyridines.

INTRODUCTION

In 1882, Arthur Hantzsch [1] described first synthesis of 1,4–dihydro pyridine derivatives, which exhibit significant pharmacological properties such as vasodilator, anti-hypertensive, anti-tumor, anti-mutagenic and anti diabetic agents [2]. DHPs also used in the treatment of cardio vascular disease as calcium channel blockers [3]. More than fifteen commercially available important drugs like felodipine [4], amlodipine [5], nifedifine [6] containing the 1,4–dihydro pyridine as common parent nucleus. Literature survey reveals that several attempts have made to improve the hantzsch reaction using various alternative catalysts and greener methodologies. Use of various reagents like $[TBA]_2[W_6O_{19}]$ [7], $Yb(OTf)_3$ [8], MgO [9], PEG [10] have its own merits and demerits with respect to reaction time and yields. Consequently, there is scope for further work towards mild conditions and better yields.

As a part of our research for new biological active heterocyclic systems relating to 1,4–DHP derivatives, we report herein the one pot synthesis of novel 1,4–dihydro pyridine derivatives using L–proline as catalyst, which is efficient, bifunctional, eco-friendly and useful in several organic transformations[11,12] .

MATERIALS AND METHODS

Chemistry

Melting points are uncorrected and are determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel–G and spotting was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase, ^{1}H NMR on VARIAN 400 MHz instrument, Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$+1 or $M^{+\cdot}$-1 values.

General preparation of compounds 3(a–f) under conventional method
A mixture of **1** (2.5 gm,13.4 mmol), ethylacetoacetate (3.84 gm, 29 mmol), ammonium acetate (1.07gm,14 mmol) in the presence of catalytic amount of acetic acid (3 mL) in ethanol (40 mL) for 8–10 hr at refluxing temperature. At the end of this period, a white coloured solid separated out and was filtered, washed and dried to obtain crude **3(a–f)**. The crude product that obtained was then purified by column chromatography (ethyl acetate: hexane, 95:5 to 5:95).

General preparation of compounds 3(a–f) using L–proline
A mixture of **1** (2.5 gm, 13.4 mmol), ethyl acetoacetate (3.84 gm, 29 mmol), ammonium acetate (1.07gm, 14 mmol) in the presence of catalytic amount of L–proline (0.8 mol%) in ethanol (40 mL) for 4–5 hr at room temperature. At the end of this period, a white coloured solid separated out and was filtered, washed and dried to obtain crude **3(a–f)**. The crude product that obtained was then purified by column chromatography (ethyl acetate: hexane, 95:5 to 5:95).

Table-1 Synthesis of 1,4 di hydro pyridine derivatives 3(a–f)

Entry	Substrates	Catalyst	Compounds	% Of yield	Time (hr)	Temperature	M.P.
1a **2a**	R=H R^1=CH_3	L–proline	**3a**	94	4	28 ± 2˚C	210 ˚C
1b **2a**	R=CH_3 R^1= CH_3	L–proline	**3b**	96	4	28 ± 2˚C	48 ˚C
1c **2a**	R=methyl sulfonyl R^1=CH_3	L–proline	**3c**	93	5	28 ± 2˚C	39 ˚C
1a **2b**	R=H R^1=C_2H_5	L–proline	**3d**	92	4	28 ± 2˚C	220 ˚C
1b **2b**	R=CH_3 R^1=C_2H_5	L–proline	**3e**	91	5	28 ± 2˚C	49 ˚C
1c **2b**	R=methyl sulfonyl R^1=C_2H_5	L–proline	**3f**	94	6	28 ± 2˚C	38 ˚C
1a **2a**	R=H R^1=CH_3	Acetic acid	**3a**	88	7	78 ± 2˚C	212 ˚C
1b **2a**	R=CH_3 R^1=CH_3	Acetic acid	**3b**	86	7	78 ± 2˚C	46 ˚C
1c **2a**	R=methyl sulfonyl R^1=CH_3	Acetic acid	**3c**	90	8	78 ± 2˚C	39 ˚C
1a **2b**	R=H R^1=C_2H_5	Acetic acid	**3d**	85	7	78 ± 2˚C	223 ˚C
1b **2b**	R=CH_3 R^1=C_2H_5	Acetic acid	**3e**	88	8	78 ± 2˚C	47 ˚C
1c **2b**	R=methyl sulfonyl R^1=C_2H_5	Acetic acid	**3f**	87	8	78 ± 2˚C	38 ˚C

Diethyl-4-(2-butyl-4-chloro-*1H*-imidazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate (3a)
White solid; yield 85%, m. p. 210 ˚C; IR: 3336 (broad, –NH–), 1657-1669 cm^{-1} (sharp, –CO–); ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 0.86-0.90 (t, 3H, -CH_3), 1.23-1.31 (t, 6H, 2 × CH_3), 1.33-1.37 (m, 2H, -CH_2), 1.62 (m, 2H, -CH_2), 2.32 (s, 6H, 2 × CH_3), 2.74 (t, 2H, Ar-CH_2), 4.22 (q, 4H, 2 × CH_2), 5.03 (s, 1H, Ar-H),6.42 (s,1H, -NH), 7.2 (s,1H,-NH) MS (ESI) *m/z* 409.1 [M]+. Anal. Calcd for $C_{20}H_{28}ClN_3O_4$: C, 58.60; H, 6.89; N, 10.25. Found: C, 58.49; H, 6.77; N, 10.16%.

Diethyl-4-(2-butyl-4-chloro-1-methyl-*1H*-imidazol-5-yl)-2, 6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3b)
White solid; yield 88%, m. p. 48 ˚C; IR: 3022-2847 cm^{-1} (broad, –NH–), 1672 cm^{-1} (sharp, –CO–); ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 0.86-0.90 (t, 3H, -CH_3), 1.23-1.31 (t, 6H, 2 × CH_3), 1.33-1.37 (m, 2H, -CH_2), 1.62 (m, 2H, -CH_2), 2.32 (s, 6H, 2 × CH_3), 2.74 (t, 2H, Ar-CH_2), 4.19 (q, 4H, 2 × CH_2), 3.74 (s, 3H, N-CH_3), 5.05 (s, 1H, Ar-H), 6.42 (s,1H, -NH); MS (ESI) *m/z* 423.2 [M]+. Anal. Calcd for $C_{21}H30ClN_3O_4$: C, 59.50; H, 7.13; N, 9.91. Found: C, 59.40; H, 7.02; N, 9.83%.

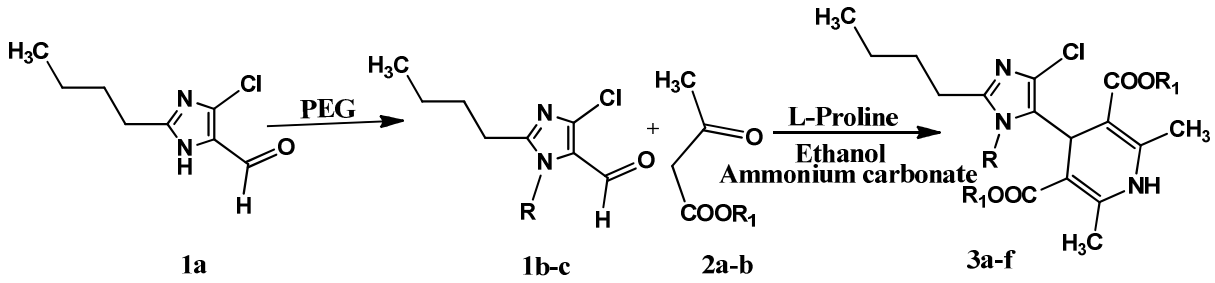
Diethyl-4-(2-butyl-4-chloro-1-(methylsulfonyl)-*1H*-imidazol-5-yl)-1-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3c)
White solid; yield 87%, m. p. 39 ˚C; IR: 3018-2855 cm^{-1} (broad, –NH–), 1678 cm^{-1} (sharp, –CO–); ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 0.86-0.90 (t, 3H, -CH_3), 1.23-1.31 (t, 6H, 2 × CH_3), 1.33-1.37 (m, 2H, -CH_2), 1.62 (m, 2H, -CH_2), 2.32 (s, 6H, 2 × CH_3), 2.74 (t, 2H, Ar-CH_2), 2.82 (s, 3H, methyl sulfonyl), 4.19 (q, 4H, 2 × CH_2), 3.74 (s, 3H,

N-CH_3), 5.05 (s, 1H, Ar-H), 6.42 (s,1H, -NH); MS (ESI) *m/z* 487.1 [M]+. Anal. Calcd for $C_{21}H_{30}ClN_3O_6S$: C, 51.69; H, 6.20; N, 8.61. Found: C, 60.22; H, 7.24; N, 9.48%.

Dimethyl-4-(2-butyl-4-chloro-*1H*-imdazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate (3d)
White solid; yield 88%, m. p. 220 ˚C; IR: 3333 cm^{-1} (broad, –NH–), 1669 cm^{-1} (sharp, –CO –); ^{1}H NMR (400 MHz, DMSO): δ_{ppm} 0.87-0.84 (t, 3H, -CH_3), 1.27 (m, 2H, -CH_2), 1.54 (m, 2H, -CH_2), 2.22 (s, 6H, 2Ar-CH_3), 2.48 (t, 2H, Ar-CH_2), 3.53 (s, 6H, 2 × O-CH_3), 4.90 (s, 1H, Ar-H), 8.89 (s, 1H, -NH), 11.46 (s,1H,-NH) ; MS (ESI) *m/z* 381.2 $[M]^+$. Anal. Calcd for $C_{18}H_{24}ClN_3O_4$: C, 56.62; H, 6.34; N, 11.00. Found: C, 56.51; H, 6.27; N, 10.81 %.

Dimethyl-4-(2-butyl-4-chloro-1-methyl-*1H*-imdazol-5-yl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (3e)
White solid; yield 86%, m. p. 49 ˚C; IR: 3022-2842 cm^{-1} (broad, –NH–), 1682 cm^{-1} (sharp, –CO–); ^{1}H NMR (400 MHz, DMSO): δ_{ppm} 0.86-0.83 (t, 3H, -CH_3), 1.28 (m, 2H, -CH_2), 1.54 (m, 2H, -CH_2), 2.24 (s, 6H, 2Ar-CH_3), 2.46 (q, 2H, Ar-CH_2), 3.54 (s, 6H, 2 × O-CH_3), 3.89 (s, 3H, N-CH_3), 4.91 (s, 1H, Ar-H), 8.91 (s, 1H, -NH); MS (ESI) *m/z* 395.1 [M]+. Anal. Calcd for $C_{19}H_{26}ClN_3O_4$: C, 57.64; H, 6.62; N, 10.61. Found: C, 57.53; H, 6.54; N, 10.49 %.

Dimethyl-4-(2-butyl-4-chloro-1-methylsulfinyl-*1H*-imdazol-5-yl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (3f)
White solid; yield 90%, m. p. 38˚C; IR: 3018-2842 cm^{-1} (broad, –NH–), 1682 cm^{-1} (sharp, –CO–); ^{1}H NMR (400 MHz, DMSO): δ_{ppm} 0.88-0.85 (t, 3H, -CH_3), 1.29 (m, 2H, -CH_2), 1.56 (m, 2H, -CH_2), 2.24 (s, 6H, 2Ar-CH_3), 2.49 (q, 2H, Ar-CH_2), 2.64 (s, 3H, sulfonyl CH_3), 3.55 (s, 6H, 2 × O-CH_3), 4.91 (s, 1H, Ar-H), 8.92 (s, 1H, -NH); MS (ESI) *m/z* 459.1 [M]+. Anal. Calcd for $C_{19}H_{26}ClN_3O_6S$: C, 49.62; H, 5.70; N, 9.14. Found: Found: C, 49.52; H, 5.68; N, 9.02 %.



Scheme 1: Synthesis of title compounds: (i) PEG, corresponding Alkylating agents, 50°C, 15-30 min. (ii) L-Proline, ammonium carbonate, ethanol, room temperature for 4-5hr

RESULTS AND DISCUSSION

Chemistry

2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde **(1a)** on *N*-alkylation using PEG[13] as medium for 15-30 min at ambient temperature, resulting in the formation of *N*-alkyl-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehydes **1(b–c)** in 90-92% yield. Latter on reaction with methyl/ethyl acetoacetate (**2**) and ammonium carbonate in the presence of L–proline in ethanol for 5 hr at room temperature resulted diethyl-4-(2-butyl-4-chloro-*1H*-imidazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **3**(**a**–**f**) in excellent yield 87-92% (**Table 1**).

Alternatively, **3(a–f)** could also be prepared in a one pot process by the reaction of *N*-alkyl-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehydes **1(a–c)** with methyl/ethyl acetoacetate (**2**) and ammonium carbonate in the presence of catalytic amount of acetic acid in ethanol for 8–10 hr at refluxing temperature resulted the title compounds. This methodology required longer reaction time, poor yields and harsh conditions. The compounds thus obtained were found to be identical with **3(a–f)** obtained above in all respects. The compounds were characterized by IR, ^{1}H NMR and mass spectral techniques. Synthesis of above title compounds **3(a–f)** are shown in scheme-1.

CONCLUSION

In conclusion, a series of new chemical entities, diethyl/dimethyl 4-(2-butyl-4-chloro-*1H*-imidazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **3(a–f)** have been synthesized. Instead conventional catalysts, we employed L-proline the preparation of diethyl/dimethyl 4-(2-butyl-4-chloro-*1H*-imidazol-5-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **3(a–f)** with excellent yields and shorter reaction time.

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