One-pot, multicomponent synthesis of symmetrical Hantzsch 1,4-dihydropyridine derivatives using glycerol as clean and green solvent

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ABSTRACT

Multi component, one pot synthesis of symmetrical 1,4-dihydropyridine derivatives from the condensation of ethyl/methyl acetoacetate, aromatic/aliphatic aldehyde and ammonium acetate has been described using glycerol, as economical, easily available and environmentally benign reagent. The targeted molecules were obtained in high purity and excellent yield without use of any additional catalyst and methodology from readily available starting materials.

1. Introduction

The chemistry of 1,4-dihydropyridines (1,4-DHP’s) found birth in 1882 with Hantzsch condensation [1]. After Hantzsch, multifarious new methods have been nurtured for the synthesis of original molecule. 1,4-DHP’s attracted more attention, thanks to its presence in the coenzyme, diphosphopyridine nucleotide [DPNH] [2] and identification as bio-active material. In the present scenario many representatives have been commercialised such as nifedipine [3], felodipine [4], nicardipine [5], amlodipine [6] and even more have made their presence felt in the market [7] in the treatment of angina and hypertension. The activity profiles of 1,4-DHP’s were further expanded as they were detected to possess anti-tumor [8], anti-inflammatory [9], anticonvulsant activity [10], antitubercular activity [11,12] cerebral antischismic activity in the treatment of Alzheimer’s disease, PAF-acether antagonists [13]. Invention and execution of various new methodologies have engendered for the synthesis of symmetrical 1,4-DHP’s. Off late many supported catalysts have been brought into use such as silica supported 12-tungstophosphoric acid [14]. Organo catalyst [15], TBA2[WO4]2 [16], Y(OTf)3 [17] and use of nanoparticles also provided swiftness and higher degree of efficiency to the reaction such as Silicotungstic acid dispersed in the micropores if Cr-pillared clay [18], MgO [19] and cobalt [20] nanoparticles with the use of many instruments like microwave [18,19,21-24], sonicator [25] turn out to exemplify. The above mentioned protocols have advantages over one another as they improve the Hantzsch condensation in terms of reaction time and yield [24]. However, the use of expensive catalysts and solvents does not allow the process to stay within the peripheries of a limited budget. In addition to this considering environmental and time perspective the process of combining solvent and catalysts cannot be believed to be undoubtedly beneficial, the recovery of catalysts requiring a lot of solvent, time and purification based upon special methods could be termed as potent reasons. In the recent past reactions mediated with glycerol astonishing attention as glycerol is a solvent which is easily available and costs virtually nothing. In addition to this it does not distort the environmental processes. Not a long time ago, it was found that glycerol has been used for Heck and Suzuki coupling [26-28], Michael addition [29], Fridel-Crafts type addition, epoxide ring opening [30], synthesis of xanthenes [31] and very recently for the production of benzodiazepines and octahydroacridines [32,33]. Understanding the magnanimity of both 1,4-DHP’s and glycerol, a new clean and green protocol has been discussed. In this effort, we synthesize 1,4-DHP’s using glycerol as green solvent without amalgamating any catalyst (Scheme 1). The present protocol is found to be much efficient over other procedure.
2. Experimental

2.1. Instrumentation

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. 1H NMR spectra were recorded in DMSO-d6 on a Bruker Avance II 400 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The mass spectrum and IR spectra were recorded at LC-MS Spectrometer Model Q-ToF Micro Waters and Perkin-Elmer Spectrum II infra-red spectrophotometer, respectively. Elemental analyses (C, H, and N) were performed using a Thermo Scientific elemental analyser.

2.2. Synthesis

2.2.1. Synthesis of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

In a conical flask benzaldehyde (0.01 mol), ethyl acetate (0.02 mol) and ammonium acetate (0.02 mol) were taken in a pre-heated glycerol (10 mL) and stirred at 90 ºC for the stipulated time (vide Table 1). After the completion of reaction (vide TLC), reaction mixture was cooled to room temperature and added 50 mL ice-cold water, solid separated out. Filtered and dried, recrystallized from ethanol to afford compound 4a, 94% yield, m.p.: 159-160 ºC (Entry 1, Table 2).

Similarly, other aldehydes 2b-k were reacted with ethyl/methyl acetocetate and ammonium acetate to afford a various 1,4-dihydropyridines derivatives 4b-q and 5a-k (Table 2). Data obtained using advanced spectral technique for some selected compounds have been summarized.

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*Yield refer to combined amounts of different crops.

Diethyl 2,6-dimethyl-4-(3,4-dimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d): Yield: 95%. M.p.: 148-150 ºC. FT-IR (KBr, v, cm⁻¹): 3341 ν(N-H Str.), 1704 ν(C=O Str.). 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.23 (t, 6H, 2×CH3), 2.31 (s, 6H, 2×CH3), 3.79 (s, 3H, OCH3), 3.85 (s, 3H, OCH3), 4.12 (q, 4H, 2×CH2CH3), 4.90 (s, 1H, C=H), 5.80 (br s, 1H, N-H), 6.73-6.89 (m, 3H, Ar-H). MS (El, m/z (%)): 390 (M⁺, 26). Anal. Calcd. for C21H27NO6: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.75; H, 6.97; N, 3.58%.

Diethyl 2,6-dimethyl-4-(3,4-3,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4e): Yield: 91%. M.p.: 184-186 ºC. FT-IR (KBr, ν, cm⁻¹): 3356 ν(N-H Str.), 1704 ν(C=O Str.). 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.21 (t, 6H, 2×CH3), 2.30 (s, 6H, 2×CH3), 3.78 (s, 3H, OCH3), 3.82 (s, 6H, 2×OCH3), 4.11 (q, 4H, 2×CH2CH3), 4.93 (s, 1H, C=H), 5.91 (br s, 1H, N-H), 6.52 (s, 2H, Ar-H). MS (El, m/z (%)): 420 (M⁺, 26). Anal. Calcd. for C22H29NO7: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.71; H, 6.05; N, 3.84%.

Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4f): Yield: 93%. M.p.: 155-156 ºC. FT-IR (KBr, v, cm⁻¹): 3343 ν(N-H Str.), 1703 ν(C=O Str.). 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.25 (t, 6H, 2×CH3), 2.36 (s, 6H, 2×CH3), 4.11 (q, 4H, 2×CH2CH3), 5.01 (s, 1H, C=H), 6.08 (br s, 1H, N-H), 7.10-7.57 (m, 4H, Ar-H). MS (El, m/z (%)): 375 (M⁺, 26). Anal. Calcd. for C19H18N2O6: C, 60.93; H, 5.90; N, 7.47%. Found: C, 60.92; H, 5.91; N, 7.47%.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4h): Yield: 92%. M.p.: 159-160 ºC. FT-IR (KBr, v, cm⁻¹): 3350 ν(N-H Str.), 1699 ν(C=O Str.). 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.27 (t, 6H, 2×CH3), 2.33 (s, 6H, 2×CH3), 4.13 (q, 4H, 2×CH2CH3), 5.09 (s, 1H, C=H), 6.09 (br s, 1H, N-H), 7.16-7.44 (m, 4H, Ar-H). MS (El, m/z (%)): 375 (M⁺, 25). Anal. Calcd. for C20H18N2O6: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.92; H, 5.91; N, 7.44%.

Diethyl 2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4i): Yield: 90%. M.p.: 138-139 ºC. FT-IR (KBr, v, cm⁻¹): 3339 ν(N-H Str.), 1699 ν(C=O Str.). 1H NMR (400 MHz, DMSO-d6, δ ppm): 1.19 (t, 6H, 2×CH3), 2.31 (s, 6H, 2×CH3), 4.07 (q, 4H, 2×CH2CH3), 5.08 (s, 1H, C=H), 5.97 (br s, 1H, N-H), 7.29-7.58 (m, 4H, Ar-H). MS (El, m/z (%)): 364 (M⁺, 23). Anal. Calcd. for C21H17ClNO2: C, 62.72; H, 6.09; N, 3.85. Found: C, 62.71; H, 6.05; N, 3.84%.

Diethyl 2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4j): Yield: 93%. M.p.: 147 ºC. FT-IR (KBr, v, cm⁻¹): 3332 ν(N-H Str.), 1693 ν(C=O Str.).
Table 2. Synthesis of symmetrical 1,4-dihydropyridine derivative.

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Products were characterized with spectral techniques and compared with authentic samples.

Yield refer to combined amounts of different crops.
pyridine 4.17 (q, 4H, 2 × CH₂), 4.99 (s, 1H, C−H), 6.07 (br s, 1H, N−H), 7.12−7.51 (m, 4H, Ar−H). MS (EI, m/z (%)): 347 [M+ 24]. Anal. calc. for C₁₂H₁₅NO₆: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.94; H, 5.22; N, 8.08%.

Dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydopyridine-3,5-dicarboxylate (5d): Yield: 93%. MP: 152−153 °C.

 FT-IR (KBr, v cm⁻¹): 3342 ν(N−H), 1707 ν(C=O). MS (EI, m/z (%)): [M+ 40] 1170 ν(C=O), 970 ν(C=O), 790 ν(C=O), 670 ν(C=O), 570 ν(C=O), 470 ν(C=O), 370 ν(C=O), 270 ν(C=O). Anal. calc. for C₁₅H₁₇NO₆: C, 65.23; H, 5.21; N, 7.59. Found: C, 65.20; H, 5.20; N, 7.48%.

3. Results and discussion

Condensation of ethylacetacetate (1), benzaldehyde (2a) and ammonium acetate [3] were carried out in glycerol at different temperatures (70−110 °C). It was observed that 90 °C is the optimal temperature for the synthesis of 1,4-dihydopyridines. Further rise in temperature had a negligible impact on rate and yield of the reaction (Table 1).

The structure of the compound 4a was confirmed with the use of spectral techniques. In IR spectrum absorption at 3340 cm⁻¹ represents the N−H stretching, a strong absorption for COO groups was observed at 1730−1760 cm⁻¹. In 1H NMR spectra peaks for five aromatic protons are observed at 6.71−7.33 ppm, singlet at 8.06 ppm for 2H−proton, singlet at 8.16 ppm for 2H−proton and a singlet for two −CH₂ groups was observed at 5.43 ppm. Spectral data of compound 4a fully supports the structure assigned to it. Similarly, other dialkyldimethyl-4-aryl-1,4-dihydopyridine-3,5-dicarboxylate 4b and 5a have been synthesized by the condensation of ethyl/methyl acetacetate (1), aldehyde (2) and ammonium acetate (3) in glycerol. The results are summarized in Table 2.

In the proposed mechanism, for the synthesis of dihydropyridines follow the addition of compound 1 and 3 to give compound 6 by the removal of an acetic acid molecule and at the same time Knoevenagel condensation between compounds 1 and 2 to give compound 7, which upon Michael addition with compound 6 produce compound 8 then followed.
by cyclization to produce 9 and rearrange to yield the 1,4-DHP molecule (4a-s and 5a-j) (Scheme 2).

Reactions proceeded smoothly with aldehydes carrying electron withdrawing as well as electron donating substituents (Table 2). This method endures various functionalities like nitro, ether, halogen etc. on the aldehydes. Efficacy of this method is fairly general and affords the resultant products in excellent yield (85-95%) and products are obtained by simple workup.

4. Conclusion

The present procedure is an effective method for production of tetra substituted 1,4-dihydropyridine from readily available starting materials in a single step with inherent flexibility and diversity. This method was efficacious to reduce labor, cost, waste production and also devoid of harsh reaction conditions. The target compounds were obtained in an acceptable yield with simple recrystallization as a purification step.

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References