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Synthesis of some novel and water-soluble 2,4,6-substituted 3,5-dihydroxymethylpyridines

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The reduction of 2,4,6-sustituted pyridine-3,5-dicarboxylate derivatives to give novel and water-soluble corresponding 2,4,6,-substituted 3,5-dihydroxymethylpyridines was achieved in good yields using lithium aluminum hydride at 0-30°C in dry THF.

Keywords: Pyridine derivatives, Esters, Lithium aluminum hydride, Reduction

INTRODUCTION

The pyridine ring has found as a most prevalent heterocyclic ring in biological active compounds, drugs and medicinal chemistry[1-14]. In pragmatical industry, the pyridine ring forms the nucleus of over 7000 existing drugs.[7,8] Keeping in view the above-mentioned applications of this important ring, the synthesis of some pyridine derivatives which can be probe in biological media is a topic of current interest. Reduction of ester groups of organic materials with $LiAlH_4$, which is a known procedure,[14-18] increases their water solubility. In view of this report and also as a continuation of our work on the synthesis of pyridine derivatives,[19] the present work aimed at designing and synthesizing of some water-soluble pyridine derivatives, which could function in an organic solvent-free solution and thereby could function in biological systems.

EXPERIMENTAL

All chemicals were purchased from Merck company. Hantzsch 1,4-dihydropyridines were prepared using the appropriate aldehyde, ammonium carbonate and ethyl acetoacetate.19 Diethyl 2,6-dimethyl-4-arylpyridine-3,5-dicarboxylates were prepared from corresponded 1,4-dihydropyridines by oxidation with H2O2-AcOH/NaI. Column chromatography was carried out on flash silica gel (230-400 mesh, Merck) using the indicated eluent. The spectroscopic data of synthesized compound were assigned by IR and NMR spectroscopy. IR spectra were recorded on Brucker spectrometer FT-IR. NMR spectra were obtained using 9.4 T vertical bore spectrometer (1H 400 MHz; 13C 100 MHz) or 11.7 T vertical bore spectrometer (1H 500 MHz; 13C 125 MHz; 19F 470 MHz). 1H and 13C chemical shifts are referenced to TMS as an internal standard, 19F to a dilute solution of trifluoroacetic acid (TFA) in capillary column as an external reference. Chemical shifts are given as δ ppm values and J values are given in hertz (Hz).The elemental analysis was carried out in Microanalytical Lab, Department of Chemistry, Tarbiyat Moallem University, Tehran, Iran.

3,5-Dihydroxymethyl-4-(phenyl)-2,6-dimethylpyridine (5a).

To a magnetically stirred slurry of LiAlH4 (2.2 mmol, 0.083 g) in anhydrous THF (5.0 mL), a solution of diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (1 mmol, 0.33 g) in anhydrous THF (5.0 mL) was added drop-wise at 0 °C for 5 min. The reaction mixture was further stirred magnetically for 2.5 h at 30 °C. Excess LiAlH4 was quenched by adding saturated aqueous sodium sulfate solution and the reaction mixture was filtered. The solid cake was washed with THF and the filtrate concentrated under reduced pressure. The latter was extracted with chloroform (2×25 mL) and water (12.5 mL) and dried (Na2SO4), organic layer was concentrated under reduced pressure to give a crud mass, which was

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chromatographed over SiO2 column using chloroform/ethyl acetate (30:70) as eluent to give 3,5-dihydroxymethyl-2,6-dimethyl-4-phenylpyridine as a pale yellow oil, Yield 87%. FT-IR: νmax (neat): 3322 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.70 (s, 6H, 2×CH3), 3.54 (s, 2H, 2×OH), 4.38 (s, 4H, 2×CH2), 7.22-7.48 (m, 5Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 19.9, 58.7, 127.6, 128.6, 129.5, 137.6, 150.3, 156.7 ppm. Anal. Calcd. for C15H17NO2: C, 74.03; H, 7.04. Found: C, 73.85; H, 7.34.

3,5-Dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (5b)

Reduction of diethyl 2,6-dimethyl-4-(2-fluorophenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine as pale yellow oil, Yield 83%. FT-IR: νmax (neat): 3161 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.71 (s, 6H, 2×CH3), 3.70 (s, 2H, 2×OH), 4.32-4.45 (m, 4H, 2×CH2), 7.22-7.27 (m, 3Harom), 7.44-7.45 (m, 1Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 22.5, 58.6, 115.3 (2JC-F= 21.0 Hz), 124.0 (4JC-F= 2.6 Hz), 124.9 (J= 20 Hz), 130.1 (3JC-F= 3.6 Hz), 130.2 (3JC-F= 7.9 Hz), 132.0, 143.7, 156.5, 159.5 (1JC-F= 246 Hz) ppm; 19F NMR (470 MHz, D2O): δ -114.69 ppm. Anal. Calcd. for C15H16FNO2: C, 68.93; H, 6.17. Found: C, 69.22; H, 6.24.

3,5-Dihydroxymethyl-4-(3-fluorophenyl)-2,6-dimethylpyridine (5c)

Reduction of diethyl 2,6-dimethyl-4-(3-fluorophenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(3-fluorophenyl)-2,6-dimethylpyridine as pale yellow oil, Yield 84%. FT-IR: νmax (neat): 3350 (OH-stretching); 1H NMR (400 MHz, CDCl3): δ 2.70 (s, 6H, 2×CH3), 3.61 (s, 2H, 2×OH), 4.38 (s, 4H, 2×CH2), 7.00-7.43 (m, 4Harom) ppm; 13C NMR (125 MHz, CDCl3): δ 22.7, 59.2, 115.6 (2JC-F= 20.8 Hz), 116.5 (2JC-F= 22.2 Hz), 125.0 (4JC-F= 2.9 Hz), 128.3, 130.2 (3JC-F= 8.4 Hz), 139.0 (3JC-F= 7.9 Hz), 147.3, 154.1, 162.7 (1JC-F= 246 Hz) ppm; 19F NMR (470 MHz, D2O): δ -113.95 ppm. Anal. Calcd. for C15H16FNO2: C, 68.93; H, 6.17. Found: C, 68.95; H, 6.02.

3,5-Dihydroxymethyl-4-(4-fluorophenyl)-2,6-dimethylpyridine (5d)

Reduction of diethyl 2,6-dimethyl-4-(4-fluorophenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(4-fluorophenyl)-2,6-dimethylpyridine as pale yellow oil, Yield 83%. FT-IR: νmax (neat): 3382 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.65 (s, 6H, 2×CH3), 2.19 (s, 2H, 2×OH), 4.29 (s, 4H, 2×CH2), 7.09 (t, J= 8.7 Hz, 2Harom), 7.22-7.25 (m, 2Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 22.2, 58.5, 115.1 (2JC-F= 22.0 Hz), 128.4, 130.5 (3JC-F= 8.0 Hz), 132.4 (4JC-F= 2.9 Hz), 147.3, 159.3, 162.6 (1JC-F= 248 Hz) ppm; 19F NMR (470 MHz, D2O): δ -115.0 ppm. Anal. Calcd. for C15H16FNO2: C, 68.93; H, 6.17. Found: C, 69.18; H, 5.97.

3,5-Dihydroxymethyl-4-(4-trifluoromethylphenyl)-2,6-dimethylpyridine (5e)

Reduction of diethyl 2,6-dimethyl-4-(4-trifluoromethylphenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.40 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(4-trifluoromethylphenyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 78%. FT-IR: νmax (neat): 3420 (OH-stretching); 1H NMR (400 MHz, DMSO): δ 2.54 (s, 6H, 2×CH3), 4.78 (s, 2H, 2×OH), 4.06 (s, 4H, 2×CH2), 7.46-7.48 (m, 2Harom), 7.79-7.81 (m, 2Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 20.0, 58.5, 124.6, 128.8, 129.2, 129.4, 130.0, 141.8, 149.0, 156.7 ppm; 19F NMR (470 MHz, D2O): δ -109.77 ppm. Anal. Calcd. for C16H16 F3NO2: C, 61.71; H, 5.17. Found: C, 61.55; H, 5.25.

3,5-Dihydroxymethyl-4-(2-pyridyl)-2,6-dimethylpyridine (5f)

Reduction of diethyl 2,6-dimethyl-4-(2-pyridyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.33 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(2-pyridyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 81%. FT-IR: νmax (neat): 3329 (OH-stretching); 1H NMR (400 MHz, CDCl3): δ 2.68 (s, 6H, 2×CH3), 3.68 (s, 2H, 2×OH), 4.30 (s, 4H, 2×CH2), 7.40-7.43 (m, 2Harom), 7.55-7.57 (m, 1Harom), 7.84-7.86 (m, 1Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 19.7, 59.3, 123.3, 124.0, 125.4, 136.8, 148.8, 149.0, 156.2, 157.2 ppm. Anal. Calcd. for C14H16N2O2: C, 68.81; H, 6.60. Found: C, 68.70; H, 6.77.

3,5-Dihydroxymethyl-4-(3-pyridyl)-2,6-dimethylpyridine (5g)

Reduction of diethyl 2,6-dimethyl-4-(3-pyridyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.33 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(3-pyridyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 82%. FT-IR: νmax (neat): 3300 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.70 (s, 6H, 2×CH3), 3.58 (s, 2H, 2×OH), 4.32 (s, 4H, 2×CH2), 7.34-8.54 (m, 4Harom) ppm; 13C NMR

(125 MHz, CDCl3): δ 19.8, 58.2, 125.4, 133.1, 133.8, 145.9, 147.2, 159.3 ppm. Anal. Calcd. for C14H16N2O2: C, 68.81; H, 6.60. Found: C, 68.84; H, 6.79.

3,5-Dihydroxymethyl-4-(4-pyridyl)-2,6-dimethyl-pyridine (5h)

Reduction of diethyl 2,6-dimethyl-4-(4-pyridyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.33 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(4-pyridyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 80%. FT-IR: νmax (neat): 3323 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.62 (s, 6H, 2×CH3), 3.60 (s, 2H, 2×OH), 4.36 (s, 4H, 2×CH2), 7.20-7.26 (m, 2Harom), 8.61-8.64 (m, 2Harom) ppm; 13C NMR (125 MHz, CDCl3): δ 20.0, 67.6, 124.5, 125.9, 144.2, 147.7, 148.8, 156.8 ppm. Anal. Calcd. for C14H16N2O2: C, 68.81; H, 6.60. Found: C, 68.53; H, 6.82.

3,5-Dihydroxymethyl-4-(3-hydroxyphenyl)-2,6-dimethylpyridine (5i)

Reduction of diethyl 2,6-dimethyl-4-(3-hydroxyphenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(3-hydroxyphenyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 80%. FT-IR: νmax (neat): 3441 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.68 (s, 6H, 2×CH3), 3.54 (s, 2H, 2×OH), 4.32 (s, 4H, 2×CH2), 6.28-7.32 (m, 4Harom) ppm; 13C NMR (100 MHz, CDCl3): δ 19.2, 58.3, 115.3, 116.1, 120.1, 124.3, 133.4, 142.0, 150.1, 156.9, 160.4 ppm. Anal. Calcd. for C15H17NO3: C, 69.46; H, 6.60. Found: C, 69.63; H, 6.48.

3,5-Dihydroxymethyl-4-(4-hydroxyphenyl)-2,6-dimethylpyridine (5j)

Reduction of diethyl 2,6-dimethyl-4-(4-hydroxyphenyl)-pyridine-3,5-dicarboxylate (1 mmol, 0.34 g) with LiAlH4 (2.2 mmol, 0.083 g) and work-up as described above gave 3,5-dihydroxymethyl-4-(4-hydroxyphenyl)-2,6-dimethylpyridine as a pale yellow oil, Yield 82%. FT-IR: νmax (neat): 3268 (OH-stretching); 1H NMR (500 MHz, CDCl3): δ 2.63 (s, 6H, 2×CH3), 3.58 (s, 2H, 2×OH), 4.20 (s, 4H, 2×CH2), 7.24-7.56 (m, 4Harom) ppm; 13C NMR (125 MHz, CDCl3): δ 19.8, 58.0, 115.1, 125.4, 131.4, 132.2, 150.5, 156.3, 164.1 ppm. Anal. Calcd. for C15H17NO3: C, 69.46; H, 6.60. Found: C, 69.79; H, 6.72.

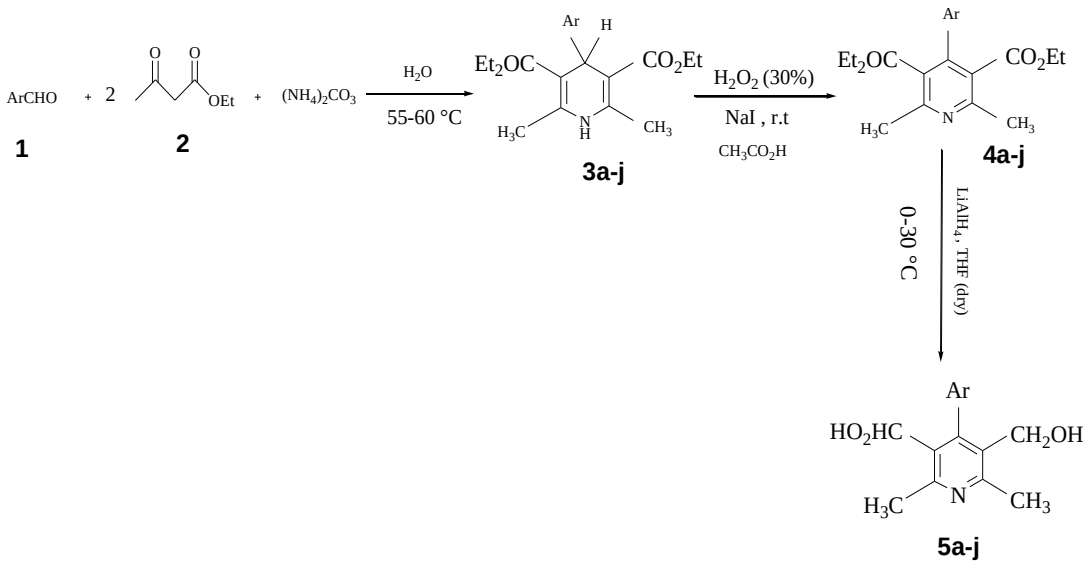
RESULTS AND DISCUSSION

Initially, the condensation of an aromatic aldehyded 1, ethyl acetoacetate 2, and ammonium carbonate resulted in Hantzch 1,4-dihydropyridnes (1,4-DHPs) 3.[19] 1,4-Dihydropyridnes 3 was then converted to corresponding pyridine derivatives 4a-j using H2O2-AcOH/NaI oxidation system[20] as shown in Scheme 1. These synthesized compounds containing one phenyl and two ester groups are not water-soluble. The reduction of two ester groups on the pyridine ring was tested by using molar ratios of diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate/LiAlH4 of 1:2, 1:2.2 and 1:3 equiv, respectively, in anhydrous THF to give 5a-j. It was found that the second ratio is sufficient to carry out the reduction successfully so as to afford the desired product namely 3,5-dihydroxymethyl-2,6-dimethyl-4-phenylpyridine in 87% yield (Table 1, 5a). A reduction in the amount of LiAlH4 from 2.2 to 1.1 equiv showed one ester group is unreacted. An increase in the amount of LiAlH4 from 2.2 to 3 equiv showed no substantial improvement in the yield. The conversion proceeded smoothly within 2.3-2.5 h at 0-30 °C. Under this optimized cost-effective reaction condition, the scope of the reduction of ester groups on the pyridine ring of the diethyl 2,6-dimethyl-4-arylpyridine-3,5-dicarboxylate was explored to prepare the corresponding 3,5-dihydroxymethyl-4-aryl-2,6-dimethylpyridine 5a-j. In all cases, the yield of reaction was 78–87% (Table 1) without further reduction products.

Table 1. Reduction of **4a-j** with $LiAlH_4$ in anhydrous THF at 0-30 °C to give **5a-j**.

Compound **5**	Ar	Time (h)	Yield[a] (%)
a	Ph	2.5	87
b	2-F-ph	2.5	83
c	3-F-ph	2.5	84
d	3-F-ph	2.5	83
e	4-CF_3-ph	2.4	78
f	2-pyridil	2.3	81
g	3-pyridil	2.3	82
h	4-pyridil	2.4	80
i	3-OH-ph	2.5	80
j	4-OH-ph	2.5	82

Yields refer to isolated pure products.



Scheme 1. Synthetic pathway of 3,5-Dihydroxymethyl-4-aryl-2,6-dimethylpyridines 5a-j

3,5-Dihydroxymethyl-4-aryl-2,6-dimethyl-pyridines were easily characterized using elemental analysis, physical and spectral data. They were pale yellow oily liquid and water-soluble compounds.

The IR spectra showed an absorption band at 3100-3500 cm-1 belongs to the stretch vibrations of the two hydroxymethyl groups on the pyridine ring of 5a-j and a further hydroxy group on the phenyl ring. The 1H NMR spectra of the products showed a singlet at 2.54-2.71 ppm region due to the resonance of CH3 protons at C-2 and C-6 positions and another singlet at 4.06-4.38 ppm as a resonance of the methylen protons of the two hydroxymethyl groups. This singlet is indicative of the presence of the hydroxymethyl group on the pyridine ring, which is in support of the expected reaction. The 1H NMR spectrum of 3,5-dihydroxymethyl-4-(2-fluorophenyl)-2,6-dimethylpyridine (Table 1, 5b) showed a multiple signal at 4.32-4.45 ppm, typical of the coupling of fluorine atom with hydroxymethyl group on the pyridine ring.

CONCLUSION

3,5-Dihydroxymethyl-4-aryl-2,6-dimethylpyridines could be synthesized in good yields by reduction of 1 equiv of diethyl 2,6-dimethyl-4-arylpyridine-3,5-dicarboxylate with 2.2 equiv of LiAlH4 in anhydrous THF at 0-30 °C. The advantage of such molecules is their water solubility which, could function effectively in biological systems.

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СИНТЕЗА НА НЯКОИ НОВИ ВОДО-РАЗТВОРИМИ 2,4,6-ЗАМЕСТЕНИ 3,5-ДИХИДРОМЕТИЛ-ПИРИДИНИ

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(Резюме)

Постигната е редукция на 2,4,6-заместени производни на пиридин -3,5-дикарбоксилкатиза получаването на нови и водно-разтворими 2,4,6,-заместени 3,5-дихидроксиметилпиридини с добър добив при използването на литиево-алуминиев хидрид при 0-30°C в сух тетрахидрофуран.