



NOTE

Novel Oxidation of 1,4-Dihydropyridines

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A one-pot method for the oxidation of 1,4-dihydropyridines to pyridines using magnesium bromide and hydrogen peroxide at convenient temperature in excellent yields has been described.

Key Words: Oxidation, $H_2O_2/MgBr_2$ oxidant, 1,4-Dihydropyridines, Pyridines.

1,4-Dihydropyridines are valuable compounds and useful in synthetic, therapeutic and bioorganic chemistry¹⁻⁴. 1,4-Dihydropyridines heterocyclic compounds are important constituents that often exist in biological products and synthetic compounds of medicinal interest⁵. The 4-substituted Hantzsch dihydropyridines, analogues of NADH coenzymes, are important classes of drugs⁶. Amlodipine besylate, nifedipine and related dihydropyridines are Ca^{2+} channel blockers that are the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension. The aromatization of Hantzsch 1,4-dihydropyridines has been considered because these Ca^{2+} channel blockers are oxidized to the corresponding pyridines by the action of cytochrome P-450 in the liver. These compounds undergo oxidation to form pyridine derivatives in body⁷.

In recent years several groups have reported various new oxidation methods which include oxidation with ferric or cupric nitrates on a solid support (claycop)⁸, ceric ammonium nitrate⁹, clay-supported cupric nitrate accompanied by ultrasound-promotion¹⁰, manganese dioxide or DDQ¹¹, nitric oxide¹², bismuth nitrate pentahydrate¹³, PCC¹⁴, tetrakis-pyridine cobalt(II)dichromate (TPCD)¹⁵, nicotiniumdichromate¹⁶, S-nitrosoglutathion¹⁷, N_2O_4 complex of 18-crown¹⁸, diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents¹⁹, $KMnO_4$ ²⁰, CrO_3 ²¹, HNO_3 ²², HNO_2 ²³, tert-butylhydroperoxide²⁴, silica gel-supported ferric nitrate (silfen)²⁵, N_2O_3 ²⁶, photochemical oxidation²⁷, $H_2O_2/Co(OAc)_2$ ²⁸, peroxydisulfate-cobalt(II)²⁹, $Zr(NO_3)_4$ ³⁰, hypervalent iodine reagents³¹, Co(II) catalyzed auto oxidation³², anodic oxidation³³, I_2-MeOH ³⁴ and selenium dioxide³⁵.

Previously, the synthesis of 1,4-dihydropyridines is reported³⁶⁻³⁸ multicomponent reaction in solvent free by

microwave irradiation and conventional heating. Herin we reported a new route to oxidize and aromatize of 1,4-dihydropyridine derivatives.

General methods: All reagents and solvents were purchased from commercial sources and used as received. The 4-dihydropyridines were synthesized from a combination of ethyl acetoacetate, aldehyde and ammonium acetate under mild and solvent-free conditions (Hantzsch reaction)³⁹. Melting points were determined on a Electrothermal 9100 melting-point apparatus and are uncorrected. 1H NMR spectra were recorded on Bruker AV-300 or Varian Mercury Plus 300 spectrometer in $CDCl_3$ and chemical shifts are in ppm (δ) relative to internal TMS. Mass spectra (MS) were determined on a FINNIGAN-MAT 8430 mass spectrometer by direct inlet at 70 eV. All products were identified by comparison of their 1H NMR, MS spectra and the melting point with those of the authentic samples.

Typical synthesis of compounds 5a-5e: In a typical reaction a mixture of $MgBr_2$ (0.03 mmol) and aq. 30 % H_2O_2 (2.16 mmol) was prepared. The mixture was stirred at room temperature for 20 min and then a solution of 1,4-dihydropyridine (0.6 mmol) in CH_3CN (5 mL) was added. The resulting mixture was stirred for 2 h at 60 °C. After completion of the reaction (monitored by thin-layer chromatography), the mixture was poured into H_2O (15 mL) and extracted with Et_2O (3×15 mL). The combined extracts were dried over anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure followed by short-column chromatography (silica gel, petroleum ether-ethylacetate, 5:1 v/v) afforded the pure pyridine product.

Compound 5a: Colourless solid, yield: 90 %, m.p. 69-70 °C, 1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, 6H, $J = 7.2$ Hz),

2.86 (s, 6H), 4.40 (q, 4H, $J = 7.2$ Hz), 8.68 (s, 1H); MS (EI, 70 eV): m/z (%) 251 (39.8, $[M]^+$), 206 (100), 195 (19.6), 178 (53.8), 150 (29.0), 106 (21.6).

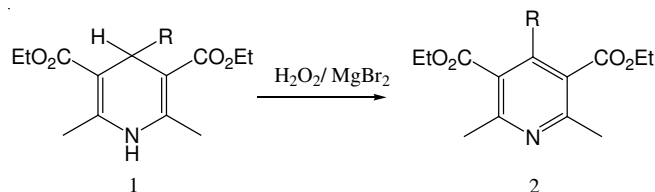
Compound 5b: Pale yellow oil, yield: 85 %, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.27 (t, 6H, $J = 6.9$ Hz), 2.16 (s, 3H), 2.40 (s, 6H), 4.30 (q, 4H, $J = 6.9$ Hz); MS (EI, 70 eV): m/z (%) 265 (31.4, $[M]^+$), 236 (45.9), 220 (100), 208 (43.2), 192 (25.9), 77 (34.5).

Compound 5c: Colourless solid, yield: 84 %, m.p.: 60–62 °C, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 0.85 (t, 6H, $J = 7.2$ Hz), 2.57 (s, 6H), 3.96 (q, 4H, $J = 7.2$ Hz), 7.21 (d, 2H), 7.32 (t, 3H); MS (EI, 70 eV): m/z (%) 327 (71.2, $[M]^+$), 282 (48.1), 254 (42.4), 236 (100), 209 (29.4), 139 (33.8), 77 (18).

Compound 5d: Pale yellow solid, yield: 78 %, m.p. 66–67 °C, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 0.93 (t, 6H, $J = 7.2$ Hz), 2.57 (s, 6H), 4.00 (q, 4H, $J = 7.2$ Hz), 7.16 (d, 2H, $J = 8.4$ Hz), 7.35 (d, 2H, $J = 8.4$ Hz); MS (EI, 70 eV): m/z (%) 361 (100, $[M]^+$), 316 (74), 288 (50), 270 (66), 139 (72), 84 (59), 77 (7).

Compound 5e: Pale yellow solid, yield: 83 %, m.p.: 163–164 °C, $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.27 (t, 6H, $J = 7.2$ Hz), 2.56 (s, 6H), 4.32 (q, 4H, $J = 7.2$ Hz), 6.79 (d, 1H, $J = 16.5$ Hz), 7.10 (d, 2H, $J = 16.5$ Hz), 7.26–7.42 (m, 5H); MS (EI, 70 eV): m/z (%) 353 (78, $[M]^+$), 308 (26), 278 (100), 263 (17), 250 (21), 234 (41), 165 (44), 152 (24), 105 (19), 77 (19).

The literature review shows that the combination system of H_2O_2 and MgBr_2 has been used for the oxidation alcohols to their corresponding carbonyl compounds³⁸. In continuation of these works, we decided to examine the capability of the $\text{H}_2\text{O}_2/\text{MgBr}_2$ for the aromatization of Hantzsch 1,4-dihydropyridines. Reaction conditions were optimized and the usefulness of this synthetic method was studied by subjecting a variety of Hantzsch 1,4-dihydropyridines to the $\text{H}_2\text{O}_2/\text{MgBr}_2$ as shown in **Scheme-I**.



Scheme-I

The results of this investigation are summarized in Table-1. As shown, all reactions were carried out within 2 h and the pyridine products were obtained in good to excellent yields.

TABLE-1
AROMATIZATION OF HANTZSCH
1,4-DIHYDROPYRIDINES BY $\text{H}_2\text{O}_2/\text{MgBr}_2$

Entry	Oxidized products	R	Yield (%)	m.p. (°C)
1	5a	H	90	69-70
2	5b	Me	85	Oil
3	5c	C_6H_5	84	60-62
4	5d	4-Cl- C_6H_4	78	66-67
5	5e	$\text{PhCH}=\text{CH}_2$	83	163-164

Conclusion

This article described a novel and mild method for the aromatization of Hantzsch 1,4-dihydropyridines using the

$\text{H}_2\text{O}_2/\text{MgBr}_2$ system at 60 °C. The cheapness, easy availability of the reagents, mild reaction conditions and excellent yield of the products are the advantages that make this protocol a useful addition to the existing methodologies.

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