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Aromatization of 1,4-dihydropyridines with selenium dioxide

Xiao-hua Cai, Hai-jun Yang, and Guo-lin Zhang

Abstract: 1,4-Dihydropyridines were aromatized to corresponding pyridines using stoichiometric selenium dioxide at ambient temperature in a yield of 87%~98%.

Key words: 1,4-dihydropyridines, aromatization, oxidation, pyridine derivatives, selenium dioxide.

Résumé : Les 1,4-dihydropyridines sont aromatisés en pyridines correspondantes avec des rendements allant de 87 %~98 % par traitement avec une quantité stoechiométrique de dioxyde de sélénium, à la température ambiante.

Mots clés : 1,4-dihydropyridines, aromatisation, oxydation, dérivés de la pyridine, dioxyde de sélénium.

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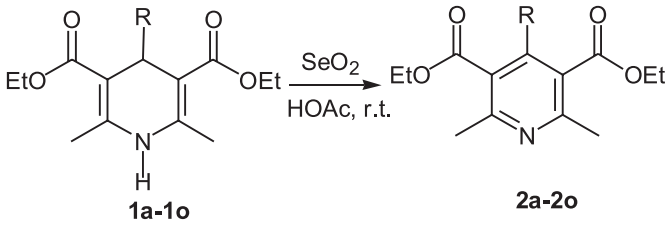
Introduction

1,4-Dihydropyridines are calcium antagonists (1), antitubercular agents (2), and neuropeptide Y Y1 receptor antagonists (3). They possess neuroprotective (4), platet anti-aggregration (5), and antidiabetic (6) activities. Aromatization of 1,4-dihydropyridines has received considerable attention owing to the fact that 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver (7). In addition, the corresponding pyridine derivatives show antihypoxic and antiischemic activites (8). 1,4-Dihydropyridines can easily be synthesized by Hantzsch condensation of aldehydes, β-keto esters, and ammonia or ammonium acetate (7*b*, 9). 1,4-Dihydropyridines have been aromatized to pyridines by various reagents such as $KMnO_4$ (10), HNO_3 (11), DDQ (12), $NaNO_2$ (13), $Zr(NO_3)_4$ (14), $Cu(NO_3)$ (15), $Bi(NO_3)\cdot 5H_2O$ (16), $Mn(OAc)_3$ (17), $(NH_4)_4Ce(NO_3)_6$ (18), urea nitrate and $K_2S_2O_8$–Co^{2+} (19), Pd/C (20), Pt(II) complex – *h*ν (21), GSNO (22), and O_2 – activated carbon (23). Despite these intensive efforts, most of the reported oxidation procedures require long reaction time, utilize strong oxidants in large excess, and afford products with only modest yields. In particular, the aromatization reaction with these reagents leads to dealkylation of the 4-position or formation of side products (11, 24). Therefore, the development of more effective methods for aromatization of 1,4-dihydropyridines is still necessary.

Scheme 1.



Selenium dioxide was widely used for the oxidation of a methylene group activated allyically or benzylically, or by an adjacent carbonyl group (25). Here, we wish to describe a simple and efficient precodure for the aromatization of 1,4-dihydropyridines with selenium dioxide at room temperature (Scheme 1).

Our initial attempts to aromatize 1,4-dihydropyridines (**1a**) as a test case in EtOH, CH_3CN, or THF at ambient or thermal conditions led to corresponding pyridine **2a** in very low yield (<40%). But the aromatization of **1a** in acetic acid occurred smoothly to give the expected pyridine at room temperature in 96% yield. The success of this reaction prompted us to examine the aromatization of some 4-alkyl, aryl, and alkenyl 1,4-dihydropyridines under the same conditions. All reactions proceeded efficiently within 20~60 min to provide the corresponding pyridines in good yields (87%~98%, Table 1). With respect to the yields of the products, a 1:1 mol ratio of 1,4-dihydropyridines and selenium dioxide in HOAc was optimal. The salient features for this procedure are milder reaction conditions, shorter reaction

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X.-h. Cai. Chengdu Institute of Biology, the Chinese Academy of Sciences, Chengdu 610041, P.R. China and Chengdu Institute of Organic Chemistry, the Chinese Academy of Sciences, Chengdu 610041, P.R. China.
H.-j. Yang, and G.-l. Zhang.[1] Chengdu Institute of Biology, the Chinese Academy of Sciences, Chengdu 610041, China.

[1]Corresponding author (e-mail: zhanggl@cib.ac.cn).

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Table 1. Aromatization of 1,4-dihydropyridines to pyridines by SeO_2 at room temperature.

Product[a]	R	Time (min)	Yield (%)[b]	mp (°C)
2a	C_6H_5	30	96	63–65 (62 to 63 (14))
2b	H	20	97	71–72 (68 to 69 (14))
2c	Me	20	97	Yellow oil (liq (17))
2d	*n*-Propyl	40	92	Yellow oil (yellow oil (19))
2e	C_6H_5-CH_2	40	90	Yellow oil (liq (26))
2f	C_6H_5-CH=CH	50	96	162–164 (162 to 163 (17))
2g	4-F-C_6H_5	40	94	88–90
2h	4-Cl-C_6H_5	50	98	63–65 (65 to 66 (14))
2i	4-MeO-C_6H_5	20	95	55–57 (56–58 (19))
2j	4-HO-C_6H_5	40	94	172 to 173 (171–173 (17))
2k	2-NO_2-C_6H_5	60	89	72 to 73 (74–76 (27))
2l	2-Furyl	60	87	Yellow oil (liq (17))
2m	4-HO-3-MeO-C_6H_5	50	92	159 to 160
2n	4-MeO-3-OH-C_6H_5	30	95	140–142
2o	3,4-2Cl-C_6H_5	40	94	63–65 (66–68 (28))

[a]All known compounds were characterized by comparing their spectral data with those reported.
[b]Isolated yields.

time, higher yield, avoidance of dealkylation or debenzylation at C-4, and stoichiometric oxidants used. Moreover, this is a simple procedure for the separation of the products.

Conclusion

An efficient and simple procedure for the aromatization of 1,4-dihydropyridines to correponding pyridine derivatives with stoichiometric selenium dioxide was developed.

Experimental

In a typical procedure, a mixture of **1a** (165 mg, 0.5 mmol), selenium dioxide (66 mg, 0.5 mmol), and HOAc (4 mL) was stirred at room temperature for 30 min. After completion monitored by TLC, the reaction mixture was quenched with a satd. aqueous $NaHCO_3$ solution and the red solid selenium was filtered off. The filtrate was extracted with Et_2O. The organic layer was washed with water, dried over anhydr. $MgSO_4$, and concentrated to give the pure product **2a** (156 mg, 96%), mp 63–65 °C (lit. value (14) mp 62 to 63 °C). Under similar conditions, various substituted 1,4-dihydropyridines were converted to corresponding pyridines (Table 1).

Diethyl 2,6-dimethyl-4-(*p*-fluorinephenyl)pyridine-3,5-dicarboxylate (2g)

Yellow solid. IR (KBr, cm^{-1}) ν_{max}: 2989, 2928, 2905, 2856, 1736, 1716, 1607, 1559, 1513, 1446, 1385, 1294, 1235, 1163, 1106, 1047, 867, 851, 796. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.02 (t, 6H, J = 7.2 Hz), 2.62 (s, 6H), 4.06 (q, 4H, J = 7.2 Hz), 7.06~7.10 (m, 2H), 7.23~7.26 (m, 2H). *m/z* (ESI): 346 (100%, $[M + 1]^+$), 330 (21%, $[M - CH_3]^+$).

Diethyl 2,6-dimethyl-4-(4-hydroxy-3-methoxyphenyl)pyridine-3,5-dicarboxylate (2m)

Yellow solid. IR (KBr, cm^{-1}) ν_{max}: 3424, 3064, 2997, 2934, 1740, 1721, 1613, 1569, 1514, 1441, 1384, 1281, 1215, 1130, 1043, 1008, 866, 836, 757, 691. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.01 (t, 6H, J = 7.2 Hz), 2.59 (s, 6H), 3.86 (s, 3H, OCH_3), 4.06 (q, 4H, J = 7.2 Hz), 5.68 (br s, 1H, OH), 6.74 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.77~6.79 (m, 2H). *m/z* (ESI): 396 (100%, $[M + Na^+]$), 374 (100%, $[M + 1]^+$).

Diethyl 2,6-dimethyl-4-(3-hydroxy-4-methoxyphenyl)pyridine-3,5-dicarboxylate (2n)

Yellow solid. IR (KBr, cm^{-1}) ν_{max}: 3432, 3045, 2984, 2934, 1738, 1724, 1613, 1559, 1507, 1441, 1382, 1267, 1213, 1130, 1045, 1008, 862, 841, 815, 755, 672. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.02 (t, 6H, J = 7.2 Hz), 2.58 (s, 6H), 3.91 (s, 3H, OCH_3), 4.06 (q, 4H, J = 7.2 Hz), 5.62 (br s, 1H, OH), 6.74 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 6.83~6.87 (m, 2H). *m/z* (ESI): 374 (100%, $[M + 1]^+$).

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