Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines by SiO_2/P_2O_5-SeO_2 under Mild and Heterogeneous Conditions

Satya Paul,* Shivani Sharma, Monika Gupta, Deepak Choudhary, and Rajive Gupta

*Department of Chemistry, University of Jammu, Jammu-180 006, India. *E-mail: paul7@rediffmail.com*
Received October 18, 2006

Key Words : 1,4-Dihydropyridines, Aromatization, Selenium dioxide, SiO_2/P_2O_5, Heterogeneous conditions

The oxidation of Hantzsch 1,4-dihydropyridines to corresponding pyridines has been extensively studied in view of the pertinence of the reaction to the metabolism of Hantzsch esters and the calcium channel blocking drugs used in the treatment of various cardiovascular disorders.[1] Consequently, this aromatization reaction continues to attract the attention of researchers for the discovery of milder and general protocols applicable to a wide range of 1,4-dihydropyridines.

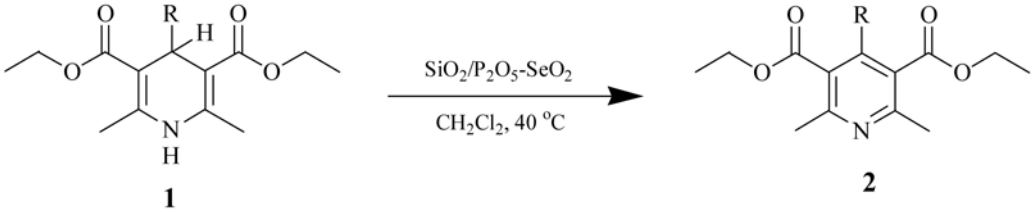
Numerous reagents and procedures have been recommended for this purpose such as manganese dioxide or DDQ,[2] nitric oxide,[3] bismuth nitrate pentahydrate,[4] PCC,[5] tetra kis-pyridine cobalt (II) dichromate (TPCD),[6] nicotinium dichromate,[7] N_2O_4 complex of 18-crown-6,[8] MCl_x/$NaNO_2$/wet SiO_2,[9] silica chloride/$NaNO_2$/wet SiO_2,[10] H_2O_2/$Co(OAc)_2$,[11] $NaHSO_4/Na_2Cr_2O_7$/wet SiO_2,[12] peroxy-disulfate-cobalt (II),[13] $Zr(NO_3)_4$,[14] hypervalent iodine reagents,[15] Co(II) catalyzed auto-oxidation,[16] sodium nitrite or nitrates,[17] I_2-MeOH[18] and heteropolyacid/$NaNO_2$/wet SiO_2.[19] A literature survey showed that three other systems that have been used for dehydrogenation of 1,4-dihydropyridines are catalysis by cytochrome P-450,[20] electrochemical,[21] and a homogeneous complex of palladium as catalyst.[22] Recently, selenium dioxide[23] in acetic acid has been reported for the oxidation of 1,4-dihydropyridines. Although variety of reagents are capable of effecting these oxidations, this transformation is not always so easy and can be a difficult step if the substrate have functional groups within the molecule sensitive to the oxidizing agent and reaction conditions. Most of the reported reagents produce by-products which are difficult to remove. Therefore, the development of more effective method for the aromatization of 1,4-DHP's under milder conditions is still necessary.

The introduction of supported reagents for bringing about various chemical transformations has provided an attractive option for organic synthesis.[24] These reagents not only modify the activity but also may impart product selectivity. In addition, the work-up procedure becomes quite easier.

Keeping in view our interest in oxidation processes,[25] we have developed a practical and general approach for the oxidative conversion of 1,4-dihydropyridines (**1a-m**) to corresponding pyridines (**2a-m**) using SiO_2/P_2O_5-SeO_2 as reagent system under stirring in CH_2Cl_2 at 40 °C (Scheme 1).

Results and Discussion

Recently, SiO_2/P_2O_5-HNO_3 has been used for the oxidation of sulfides to corresponding sulfoxides.[26] Keeping in view the mildness of this reagent system, we have tried to carry out the aromatization of 4-phenyl-1,4-dihydropyridine (**1a**) by simple grinding in a pestle and mortar at room temperature in solvent-free conditions. It was found that oxidation did take place but in addition to oxidation, ring nitration was also observed. The reagent SiO_2/P_2O_5 is quite stable and can be stored in a desiccator for several weeks. So, we decided to carry out oxidation of 4-phenyl-1,4-dihydropyridine using SiO_2/P_2O_5 reagent and SeO_2 as oxidizing agent by grinding at room temperature in solvent-free conditions. It was found that reaction did take place but didn't proceed to completion



1 **2**

2a: R = C_6H_5
2b: R = 4-$MeOC_6H_4$
2c: R = 4-HO-3-$MeOC_6H_3$
2d: R = 3,4-$(MeO)_2C_6H_3$
2e: R = 3,4-$(OCH_2O)C_6H_3$
2f: R = 4-ClC_6H_4
2m: R = *n*-C_3H_7
2g: R = 3-$(NO_2)C_6H_4$
2h: R = 4-$(NO_2)C_6H_4$
2i: R = C_6H_5CH=CH
2j: R = 4-FC_6H_4
2k: R = 2-Furyl
2l: R = 2-Thienyl

Scheme 1

Table 1. Aromatization of Hantzsch 1,4-dihydropyridines to corresponding pyridines with SiO_2/P_2O_5-SeO_2 at 40 °C

Product[a]	Time[b] (min)	Yield[c] (%)	mp (°C) (Found/Lit.)
2a	30	90	68-69/63-65[23]
2b	30	88	57-58/55-57[23]
2c	35	85	156-57/159-60[23]
2d	25	92	62-63[27]
2e	35	87	97-99[27]
2f	45	88	78-79/63-65[23]
2g	30	85	60-61/60-62[13]
2h	40	82	113-14/114-16[28]
2i	30	85	161-62/162-64[23]
2j	30	88	88-89/88-90[23]
2k	45	82	37-39/38-41[28]
2l	50	80	75-77/76-79[28]
2m[d]	50	75	liq./yellow oil[13]

[a]All products were characterized by ^{1}H NMR, IR, mass spectral data and comparison with authentic samples prepared according to literature methods. [b]Time at which 100% conversion of 1,4-dihydropyridine was observed on TLC. [c]Isolated yield. [d]4-Dealkylated product (15%, based on separation by column chromatography) was also formed.

even after 5 h of grinding (monitored by TLC). We then decided to carry out oxidation with SiO_2/P_2O_5-SeO_2 reagent system by stirring in CH_2Cl_2 at different temperatures including room temperature under heterogeneous conditions. It was found that the oxidation reaction proceeds efficiently at 40 °C as evaluated qualitatively by TLC.

A series of 1,4-dihydropyridines were synthesized to investigate their conversion to corresponding pyridines. Initially, 4-phenyl-1,4-dihydropyridine (**1a**) was used as a substrate to test the feasibility of SiO_2/P_2O_5-SeO_2 for the oxidation. After carrying out series of reactions under different conditions, it was found that for 1 mmole of each of **1a** and SeO_2, 0.3 g of SiO_2/P_2O_5 and 5 mL of methylene chloride was required to proceed the reaction under mild conditions and gave high efficiency in terms of yield and reaction time. Using similar conditions, other dihydropyridines (**1b-m**) were oxidized and excellent results were obtained (Table 1). However, in the case of 1-propanal (Table 1, product **2m**), 4-dealkylated product (15%) was also formed. In general, the reaction was fast and work-up procedure was straight forward requiring simple filtration followed by removal of the solvent under reduced pressure. Finally pure products (**2a-m**) were obtained by passing through column of silica gel and elution with pet. ether: EtOAc.

Experimental Section

General. Silica gel (K100, 0.063-0.200 mm) was purchased from Merck, Germany and phosphorus pentoxide from Himedia, India. Melting points were determined on a Tempo melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard and IR spectra was recorded using KBr disc on Perkin Elmer FTIR spectrophotometer. The mass spectral data was obtained on a JEOL JMS-D 300 spectrometer. The reactions were monitored qualitatively by TLC.

Preparation of silica supported phosphorus pentoxide (SiO_2/P_2O_5). Silica gel (10 g, K100, 0.063-0.200 mm) was mixed with phosphorus pentoxide (2 g) and grinded in a pestle and mortar for 15 minutes. The homogeneous powder was stored in a vacuum desiccator and can be used for several weeks.

Oxidative aromatization of 1,4-dihydropyridines with SiO_2/P_2O_5-SeO_2. General procedure. A suspension of 1,4-dihydropyridine **1** (1 mmol), re-sublimed selenium dioxide (1 mmol) and SiO_2/P_2O_5 (0.3 g) in CH_2Cl_2 (5 mL) was stirred at 40 °C for an appropriate time (monitored by TLC, Table 1). After completion of the reaction, the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (2 × 5 mL). The product obtained after removal of the solvent under reduced pressure was purified by passing through column of silica gel and elution with pet. ether: EtOAc.

The structures of the products were confirmed by ^{1}H NMR, IR, mass spectral data and comparison with authentic samples prepared according to the literature methods.

Conclusion

In conclusion, we have found that SiO_2/P_2O_5-SeO_2 is an efficient reagent for the aromatization of 1,4-dihydropyridines to corresponding pyridines under mild and heterogeneous conditions. The salient features of our method are: it is simple, rapid, cost-effective, general and selective. In addition, this could be a valuable addition to the existing methods for the oxidation of 1,4-dihydropyridines.

Acknowledgement. One of the authors (MG) is thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for awarding Senior Research Fellowship (SRF).

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27. Selected analytical data: **2d**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.01-1.17 (t, 6H, 2x $-CH_2CH_3$, J = 7.2 Hz), 2.53 (s, 6H, 2x $-CH_3$), 3.96 (s, 6H, 2x $-OCH_3$), 4.01-4.19 (q, 4H, 2x $-CH_2CH_3$, J = 6.9 Hz), 6.77-6.98 (m, 3H, H_{arom}); IR (KBr ν_{max} in cm^{-1}): 3060, 2800, 1735, 1440, 1210, 1100; m/z $(M+1)^+$: 388. **2e**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.03-1.18 (t, 6H, 2x $-CH_2CH_3$, J = 7.1 Hz), 2.5 (s, 6H, 2x $-CH_3$), 4.05-4.20 (q, 4H, 2x $-CH_2CH_3$, J = 7.0 Hz), 5.95 (s, 2H, -OCH_2O-), 6.6-7.2 (m, 3H, H_{arom}); IR (KBr ν_{max} in cm^{-1}): 3055, 2815, 1730, 1450, 1190; m/z $(M+1)^+$: 372.
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