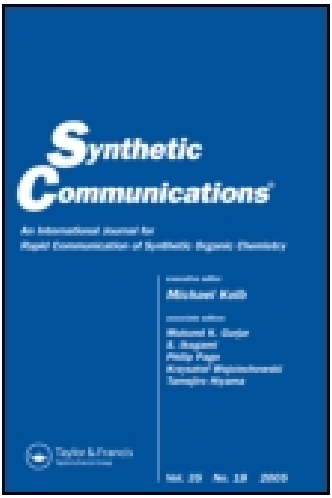

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CHEMOSELECTIVE OXIDATION OF 1,4-DIHYDROPYRIDINES WITH $[NO^{+}.CROWN.H(NO_3)_2^{-}]$

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ABSTRACT

An ionic complex has been obtained from N_2O_4 in the presence of the macrocyclic ether 18-crown-6. This crystalline compound was used as an effective oxidizing agent for the oxidation of dihydropyridines to their corresponding pyridine derivatives at room temperature with excellent yields.

Amlodepine besylate, Nifedepine, and related dihydropyridines are Ca^{2+} channel blockers, and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension. In the human body, it has been observed that these

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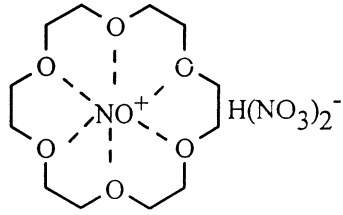
compounds undergo oxidation to form pyridine derivatives. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. Additionally, dihydropyridines are often produced in a synthetic sequence, which have to be oxidized to pyridines.[1,2]

The oxidation of dihydropyridines (**1**) is an old reaction in general organic chemistry. Even in recent years, several groups have reported new methods for aromatization, including oxidation with ferric or cupric nitrates on a solid support,[3,4] ceric ammonium nitrate,[5] clay-supported cupric nitrate accompanied by ultrasound-promotion,[6] pyridinium chlorochromate,[7] *tert*-butylhydroperoxide,[1,2] and photochemical oxidation.[8] There has also been reported a general method using nitric acid.[9] Very recently, Ohsawa et al. reported an excellent procedure for this transformation. They have demonstrated the remarkably practical use of NO gas as a clean and efficient oxidant for this purpose.[10]

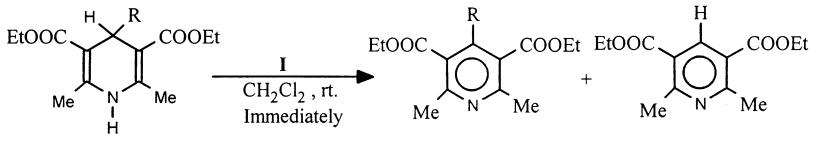


I

We decided to seek a completely homogeneous system for dihydropyridine oxidation, and we have investigated a number of different reaction conditions based upon the in situ generation of NO^+. In continuing of our study about the applications of NOX,[11–23] N_2O_4,[24–28] metal nitrate dinitrogen tetroxide complexes[29–35] and complexation of transition metals with microcyclic ethers,[36] we have found that 18-crown-6 gives an ionic complex of N_2O_4 gas [NO^+.crown.$H(NO_3)_2^-$] in quantitative yields. However, in this article we report a simple and convenient method for the effective conversion of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) under mild and homogeneous conditions.

Different types of dihydropyridines (**1**) were subjected to oxidation reaction in the presence of [NO^+.crown.$H(NO_3)_2^-$] in dichloromethane (Scheme 1). The oxidation reactions were performed under mild and completely homogeneous conditions at room temperature with quantitative yields.

It was also observed that the oxidation of 1,4-dihydropyridines (**1i**) bearing alkyl substituents (alkyl moieties may be responsible for generating



1 2 3

1, 2	R	1, 2	R	1, 2	R
a	H	**d**	2-Thienyl-	**g**	2-CH_3O-C_6H_4-
b	Me	**e**	2-NO_2-C_6H_4-	**h**	2,5-$(CH_3O)_2$-C_6H_4-
c	Ph	**f**	3-NO_2-C_6H_4-	**i**	CH_3-CH-C_6H_5

Scheme 1.

stable carbocations) at the 4-position gives only dealkylated pyridine derivative (**3**). This is in agreement with the observation made by others employing different oxidative conditions.[1,2] However, aryl-substituted 1,4-dihydropyridines (**1c**–**h**) furnished the corresponding pyridine derivatives.

The present oxidation reaction can be readily carried out only by placing $[NO^+.crown.H(NO_3)_2^-]$, **1** and dichloromethane as the solvent in a reaction vessel and efficiently stirring the resulting homogeneous mixture at room temperature. The reactions were completed immediately. The solvent was evaporated and the extra pure pyridine derivatives (**2** or **3**) can be obtained by passing the residue through a pad of silica gel.

In conclusion, practical, chemoselective, and efficient oxidation of 1,4-dihydropyridines was achieved by the present methodology. $[NO^+.crown.H(NO_3)_2^-]$, with its easy preparation and handling, can act as a relatively stable and efficient reagent as a source for the delivery of nitrosonium ion (NO^+) under mild and homogeneous conditions. Meanwhile, 18-crown-6 can be recycled and reused. The 18-crown-6 is completely soluble in dichloromethane and also more reactive than those reagents that were reported previously.[1–14] We believe that the present methodology would be an important addition to existing ones.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG, and Aldrich. The oxidation products were characterized by comparison of their spectral (IR, ^1H NMR, ^{13}C NMR, and TLC) and physical data with the authentic samples. All Hantzsch 1,4-dihydropyridines were synthesized

by the reported procedures.[6,37] [NO^+.crown.$H(NO_3)_2^-$] was synthesized according to the reported procedure,[38] but a partial difference exists between our applying method and those reported by others because we used N_2O_4 gas instead of liquid N_2O_4. Dinitrogen tetroxide (N_2O_4) gas was generated in situ according to our previously reported procedure[24–34] as follows.

Generation of NO_2-N_2O_4 Gas

Lead(II) nitrate (50 g) was crashed into powder and dried in an oven at 120°C for three days. The resulting powder was transferred into a one-necked round-bottomed flask (250 mL) equipped with an air condenser and a gas trap containing P_2O_5. The flask was heated by a Bunsen burner to generate brownish-red NO_2-N_2O_4 gas, which was used immediately for the subsequent preparation of the [NO^+.crown.$H(NO_3)_2^-$].

Preparation of [NO^+.Crown.$H(NO_3)_2^-$]

A solution of 18-crown-6 (5.286 g, 0.02 mol) in CH_2Cl_2 (10 mL) was prepared in a three-necked round-bottomed flask (50 mL), which was equipped with a magnetic stirrer, gas inlet tube, thermometer, and a drying tube, and was cooled to −10°C with an ice-salt bath, while being stirred. Generation NO_2-N_2O_4 gas was bubbled through this solution for 30 min. The solvent was evaporated under vacuum at 20°C to give [NO^+.crown.$H(NO_3)_2^-$] as a pale yellow deliquescent solid compound, 8.380 g, (~100%), m.p. 50°–55°C [lit.[38] m.p. 53°–55°C]. ^{1}H NMR (FT-90 MHz, $CDCl_3$/TMS): 3.536 (s, 24H), 11.464 (s, 1H).

Oxidation of Dihydropiridine (1a) to Substituted Pyridine (2a): A Typical Procedure

A solution of compound **1a** (0.253 g, 1 mmol) and **I** [NO^+.crown.$H(NO_3)_2^-$, 0.419 g, 1 mmol] in dichloromethane (2 mL) was stirred at room temperature [the progress of the reaction was monitored by TLC and ^{1}H NMR, the progress of the reaction by ^{1}H NMR based upon the disappearance of the singlet at $\delta = 5.00$–5.35 (CH-4 in dihydropiridine structure **1**)]. The reaction was completed immediately. Dichloromethane was removed by water bath (40°–50°C) and simple distillation.

The residue was passed through a pad of silica gel [eluent: petroleum ether]. The yield was 0.248 g, (98%) of a crystalline pale yellow solid (**2a**),

m.p. 69°–72°C [lit.[3] m.p. 72°–73°C]. ^{1}H NMR (FT-90 MHz, $CDCl_3$/TMS): δ 1.42 (t, 6H), 2.86 (s, 6H), 4.36 (q, 4H), 8.69 (s, 1H) [lit.[7]].

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