

Oxidation of 1,4-Dihydropyridines under Mild and Heterogeneous Conditions

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A combination of $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ and $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ in the presence of wet SiO_2 was used as an effective oxidizing agent for the oxidation of 1,4-dihydropyridines to their corresponding pyridine derivatives at room temperature with excellent yields.

INTRODUCTION

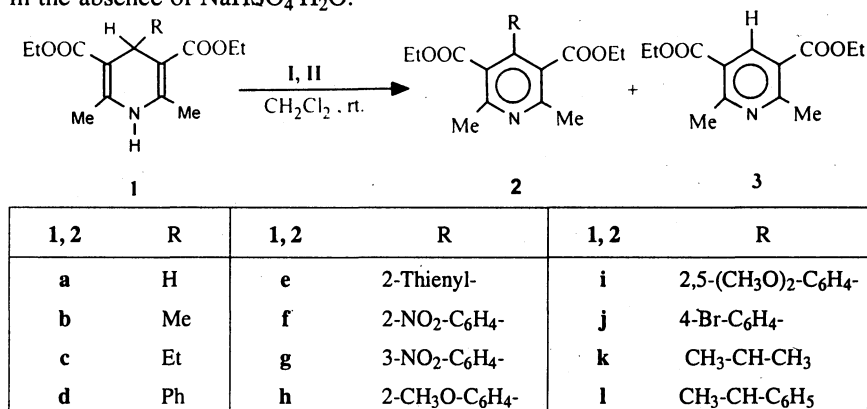
The 4-substituted-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl esters have antihypoxic and anti-ischemic activity; some of the representatives of this class have acaricidal, insecticidal, bacterial and herbicidal activity¹. Several methods have been reported for the aromatization of 1,4-dihydropyridines^{1–11}, but most of them require vigorous conditions. For oxidation of organic functionalities, one turns often to high-valent metal oxides or their mineral salts. Classic reagents of this type are manganese dioxide (MnO_2), potassium permanganate (KMnO_4), chromium trioxide (CrO_3), potassium chromate (K_2CrO_4) and potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$)¹². These are all frequently-used reagents, whether in the laboratory or in industry, and yet they are beset with multiple liability. For satisfactory and reproducible results, these oxidants demand rigorous control of the experimental conditions. The other drawbacks against such oxidants and their use in multistage organic synthesis, in spite of their power, are also their lack of selectivity, strong protic and aqueous conditions, low yields of the products, and tedious work-up¹³. Furthermore, the elevated reflux temperatures required by some oxidation procedures will favour inopportune secondary reactions. Likewise, the presence of strong acids or bases, which are required adjuncts as catalysts for some reactions, often leads to detrimental side reactions¹⁴. Therefore, we were interested to find a new system for the applications of chromium salts to overcome the above limitations. In addition, for our purpose, both clean and easy work-up were also important. Very recently, we among many others have demonstrated that heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction conditions and minimization of

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chemical wastes as compared to their liquid phase counterparts¹⁵. The above facts encouraged us to seek a completely heterogeneous system for the oxidation of 1,4-dihydropyridines, and we have investigated a number of different reaction conditions based upon the *in situ* generation of H_2CrO_4 at the surface of SiO_2 in low concentration by very mild inorganic acidic salt [*e.g.*, $\text{NaHSO}_4\cdot\text{H}_2\text{O}$, $\text{p}K_a$ *ca.* 2] and ammonium dichromate. This work outlines a convenient system for the effective oxidation of 1,4-dihydropyridines (**1**) using chromium salts, which appears to circumvent the drawbacks typically associated with these reagents.

RESULTS AND DISCUSSION

Different kinds of dihydropyridines (**1**) were subjected to oxidation reaction in the presence of $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ (**I**), wet SiO_2 (50% w/w) and inorganic acidic salt [*e.g.*, $\text{NaHSO}_4\cdot\text{H}_2\text{O}$ (**II**)] in dichloromethane (Scheme 1). The oxidation reactions were performed under mild and heterogeneous conditions at room temperature with excellent yields (Table-1). Meanwhile, the reaction did not occur in the absence of $\text{NaHSO}_4\cdot\text{H}_2\text{O}$.



Scheme 1

It was also observed that the oxidation of 1,4-dihydropyridines (Entries 11, 12) bearing alkyl substituents (in which the alkyl moiety which are susceptible for generating stable carbocation) at 4-position give only dealkylated pyridine derivative (**3**). This is in agreement with the observations reported by others who employed different oxidative conditions.³ However, aryl substituted 1,4-dihydropyridines (Entries 4–10) furnished corresponding pyridine derivatives (Table-1).

This oxidation reaction can be readily carried out only by placing $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ (**I**), $\text{NaHSO}_4\cdot\text{H}_2\text{O}$ (**II**), **1**, wet SiO_2 (50% w/w) and CH_2Cl_2 as the solvent in a reaction vessel and efficiently stirring the resulting heterogeneous mixture at room temperature for 30–135 min and the pyridine derivatives (**2** or **3**) can be obtained by simple filtration and evaporation of the solvent. The results and reaction conditions are given in Table-1.

In conclusion, practical and efficient oxidations of 1,4-dihydropyridines have

been achieved by the methodology described. The heterogeneous nature, low cost and the availability of the reagents, easy procedure and work-up make this method attractive for large-scale operations. We believe that the present methodology would be an important addition to existing methodologies.

TABLE-1
OXIDATION OF 1,4-DIHYDROPYRIDINES (I) TO THEIR CORRESPONDING PYRIDINE DERIVATIVES WITH A COMBINATION OF $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ (I), $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ (II) AND WET SiO_2 (50% w/w) IN DICHLOROMETHANE AT ROOM TEMPERATURE

Entry	Substrate	Product ^a	(Reagent/Substrate) ^b		Time (min)	Yield ^{c, d} (%)
			I	II		
1	1a ^c	3	0.25	1	45	97
2	1b	2b	0.25	1	30	98
3	1c	2c	0.25	1	45	96
4	1d	2d	0.40	1.6	135	98
5	1e	2e	0.75	3	45	90
6	1f	2f	0.75	3	45	98
7	1g	2g	0.25	1	30	99
8	1h	2h	0.25	1	45	98
9	1i	1i	0.25	2	60	95
10	1j	1j	0.50	1	75	96
11	1k	3	0.25	1	30	94
12	1l	3	0.25	1	30	97

^aAll of the products are known. ^{1-11, 15b}, ^bWet SiO_2 : substrate (0.2 g : 1 mmol). ^cIsolated yields.

^dThe extra pure pyridine derivatives were obtained by passing the residue through a pad of silica gel. ^eReaction did not occur in the absence of $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, Riedel-dehaen AG and Aldrich chemical companies. The oxidation products were characterized by comparison of their spectral (IR, ^1H NMR, ^{13}C NMR), TLC and physical data with the authentic samples. All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures⁵.

Oxidation of dihydropyridine (1a) to the corresponding substituted pyridine (2a): A typical procedure.

A suspension of compounds 1a (0.331 g, 1 mmol), $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ [(I) 0.063 g, 0.25 mmol], wet SiO_2 (50% w/w) (0.2 g) and $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ [(II) 0.138 g, 1 mmol], in dichloromethane (4 mL) was stirred at room temperature for 30 min. The progress of reaction was monitored by TLC, and then filtered. Anhydrous Na_2SO_4 (3 g) was added to the filtrate. After 15 min dichloromethane (20 mL) was added to the resulting mixture and filtered. Dichloromethane was removed

by a water bath (40–50°C) and simple distillation. The yield was 0.290 g, (97%) of a crystalline pale yellow solid (**2a**), m.p. 68–70°C {Lit. [2], m.p. 72–73°C}. ¹H NMR ((CDCl₃)/TMS: 1.42 (t, 6 H), 2.86 (s, 6 H), 4.36 (q, 4 H), 8.69 (s, 1H) {Lit⁷}.

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