A facile aromatisation of 1,4-dihydropyridines by ammonium nitrate in acetic acid

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The oxidation of 1,4-dihydropyridines to pyridines with ammonium nitrate as an oxidant in the presence of acetic acid proceeds in excellent yield.

Keywords: 1,4-dihydropyridines, ammonium nitrate, acetic acid, aromatisation

The chemistry of dihydropyridines was reviewed in 1972 by Kuthan[1] and in 1988 by Stout.[2] These compounds have medicinal interest.[3] Current studies in dihyropyridine chemistry involve synthesising NADH mimics, and utilising them in a variety of synthetic reactions.

Substituted 1,4-DHP's are analogues of NADH-coenzymes and are an important class of drugs.[4] These substituted pyridines are useful as anti-hypoxics and anti-ischaemics[5,6] and some compounds have acaricidal, insecticidal, bactericidal, and herbicidal activity.[7,8] Oxidation of a 1,4-DHP to a pyridine is important in the synthesis of the respective radiolabelled compounds. 1,4-Dihydropyridine based drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver.[9]

1,4-DHPs have a wide range of biological activity[10-12] and find use as calcium channel blockers[13] as exemplified by nifedipine, nitrendipine, nimodipine and amlodipine.

The oxidation of 1,4-DHPs to the corresponding pyridine derivatives is well documented but many of the reported procedures either use strong oxidants like HNO_3,[14] CrO_3,[15] $KMnO_4$,[16] under severe conditions or need excess reagent like CAN,[17] PCC[18] or expensive Pd/C catalyst,[3] bismuth nitrate,[19] or cumbersome workup procedures.[18]

In view of the above limitations and in continuation of our interest[20-22] in developing mild and efficient protocols for the oxidation of dihydropyridines to pyridine, we thought that NH_4NO_3 could serve as an efficient reagent for this transformation (Scheme 1).

We now report an efficient oxidation of 1,4-dihydropyridines to pyridines with inexpensive and readily available ammonium nitrate in acetic acid at reflux temperature.

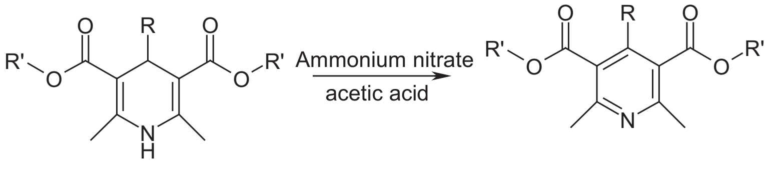
1,4-Dihydropyridines were synthesised according to the reported procedure.[23]

Our initial attempts to effect the oxidation of the simple 4-phenyl-1,4-dihydropyridine as a test case with a stoichiometric amount of ammonium nitrate in various solvents, such as $CHCl_3$, CH_3COCH_3, CCl_4 at room as well as at elevated temperature showed an insignificant formation of the corresponding pyridines. However, oxidation of 4-phenyl-1,4-dihydropyridine was observed when the reaction was performed with a stoichiometric amount of ammonium nitrate in acetic acid at reflux temperature, affording the corresponding pyridine in 45% yield. After increasing the oxidant to two equivalents, quantitative formation of the product was observed. The combination of ammonium nitrate and acetic acid is critical for the success of the reaction as no reaction was observed with only ammonium nitrate or acetic acid separately (Table 1).

This success led us to study a variety of 1,4-dihydropyridines having various substituents at 4-position. A series of 1, 4-dihydropyridines were subjected to the oxidation reaction in the presence of ammonium nitrate in acetic acid at reflux temperature to furnish corresponding pyridines in excellent yields (Table 2).

In the oxidative reactions of the 1,4-dihydropyridines to pyridines it was previously observed that dealkylated[16,24] products were obtained with oxidants such as $KMnO_4$ and Clay MnO_2. One of the salient feature of our reaction is the retention of alkyl substituent at 4-position (Table 2, entry 7, 8). This result is in stark contrast to most of the reported reagents which lead to dealkylation.

In summary, we have described a practical, efficient and inexpensive pathway for the oxidation of 1,4-dihydropyridines in excellent yields using ammonium nitrate as an oxidant in presence of acetic acid. The availability of ammonium nitrate and the ease of the reaction should find a widespread use as the method of choice to effect such transformation.



Scheme 1

Table 1 Oxidation of 4-phenyl-1,4-dihydropyridine with ammonium nitrate in different solvent at reflux temperature

No.	DHP mmol	Ammonium nitrate/equiv	Solvent	Reaction time/h	Yield/%
1	1	0.0	Acetic acid	2	00
2	1	1.0	Acetic acid	2	45
3	1	2.0	Acetic acid	2	97
4	1	1.0	Water	2	00

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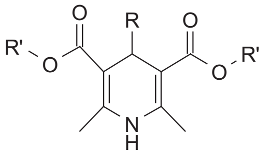
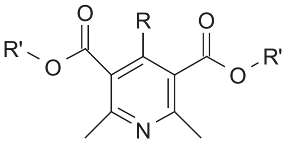
Table 2 Oxidation of 1,4-dihydropyridines with ammonium nitrate in acetic acid at reflux temperature

						
Entry no.	R	R'	R	R'	Yield/%	M.p./°C (lit^{ref})
1	C_6H_5	$-C_2H_5$	C_6H_5	$-C_2H_5$	97	64^{25}
2	H	$-C_2H_5$	H	$-C_2H_5$	90	70^{26}
3	$4-OCH_3-C_6H_4$	$-C_2H_5$	$4-OCH_3-C_6H_4$	$-C_2H_5$	92	58^{27}
4	$4-CH_3-C_6H_4$	$-C_2H_5$	$4-CH_3-C_6H_4$	$-C_2H_5$	89	72^{25}
5	$2-Cl-C_6H_5$	$-C_2H_5$	$2-Cl-C_6H_5$	$-C_2H_5$	91	62^{28}
6	$3-NO_2-C_6H_5$	$-C_2H_5$	$3-NO_2-C_6H_5$	$-C_2H_5$	91	61^{29}
7	$-(CH_2)_3CH_3$	$-C_2H_5$	$-(CH_2)_3CH_3$	$-C_2H_5$	86	Oil^{20}
8	$-CH_3$	$-C_2H_5$	$-CH_3$	$-C_2H_5$	88	Oil^{27}
9	$-C_6H_5$	$-CH_3$	$-C_6H_5$	$-CH_3$	90	136^{20}
10	$4-OCH_3-C_6H_5$	$-CH_3$	$4-OCH_3-C_6H_5$	$-CH_3$	95	155^{20}
11	–H–	CH_3	–H–	CH_3	90	100^{30}
12	$4-CH_3-C_6H_5-$	CH_3	$4-CH_3-C_6H_5-$	CH_3	92	91^{30}
13	$3-NO_2-C_6H_5$	$-CH_3$	$3-NO_2-C_6H_5$	$-CH_3$	88	121^{30}
14	$2-Cl-C_6H_5-$	CH_3	$2-Cl-C_6H_5-$	CH_3	90	71^{20}

Experimental

Typical procedure for oxidation of dihydropyridines with ammonium nitrate

1,4-Dihydropyridine (1 mmol), ammonium nitrate (2 mmol) and acetic acid (2 ml), were refluxed for 2 h. After completion of the reaction, it was neutralised with aq.10% $NaHCO_3$ and extracted with ethyl acetate, dried (anhydrous sodium sulfate) and filtered. Evaporation of solvent yielded the pyridines in 86–95% yield (Table 2, Entry 1–14)**.** All the products were identical in melting point and ^{1}H NMR with the reported in literature [20,25-30].

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