Solid state oxidation of 1,4-dihydropyridines to pyridines using phenyliodine(III) bis(trifluoroacetate) or elemental sulfur

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A solventless oxidation of 1,4-dihydropyridines is effected by phenyliodine(III) bis(trifluoroacetate) (PIFA) at room temperature or elemental sulfur under microwave irradiation conditions. Dealkylation at the 4-position in the cases of ethyl, isopropyl and benzyl substituted dihydropyridine derivatives with PIFA is circumvented by an alternative general procedure using elemental sulfur which provides pyridines in good yields.

Introduction

Hantzsch 1,4-dihydropyridines have been widely used in the treatment of hypertension and angina pectoris.[1] The oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives occurs initially during the first pass metabolism in the liver. The pyridine derivatives are then further metabolized leading to the cleavage of the ester groups.[2] Due to the relevance of this oxidative event to the biological NADH redox process and the metabolic studies that require reference standards,[3–5] this transformation has attracted the attention of several research groups. A variety of reagents have been utilized for this oxidative conversion: nitric acid,[2] manganese dioxide–bentonite clay,[6] chromium trioxide,[7] potassium permanganate,[8] pyridinium chlorochromate,[9] ceric ammonium nitrate (CAN),[10] clayfen,[11] bismuth trinitrate,[12] and ruthenium trichloride.[13] However, most of these reactions require an extended period of time for completion, utilize strong oxidants in large excess and afford only modest yields of the products. Ring-nitrated byproducts are generated when oxidation of phenols is carried out with metallic nitrates,[12] and solvent-dependent oxidation of a 2-methyl group occurs in some cases.[10] Importantly, the use of almost all these reagents has one major limitation which is the dealkylation of substituents at the 4-position, especially when secondary alkyl or benzyl groups are present.[2,6,8,9,12,13]

In continuing our efforts to develop environmentally benign protocols that proceed under solvent-free conditions using microwave (MW) irradiation,[14,15] herein we wish to report two solid state oxidative methods for the conversion of 1,4-dihydropyridines to pyridines which employ either phenyliodine(III) bis(trifluoroacetate) (PIFA) at room temperature or elemental sulfur under microwave irradiation conditions.

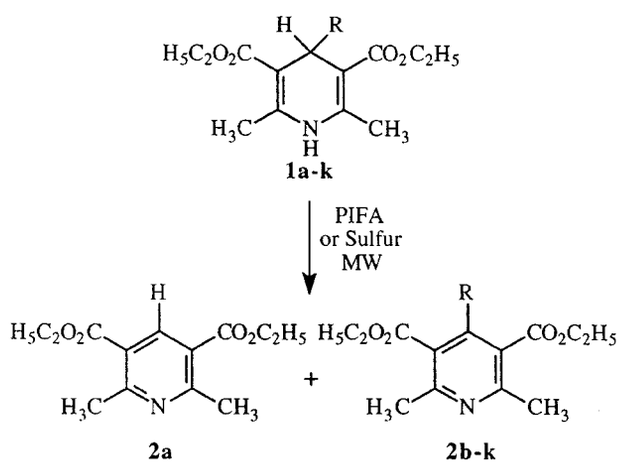
Results and discussion

In view of our interest in the synthetic use of the nonmetallic, hypervalent iodine oxidant reagents,[16] we explored the oxidation of 1,4-dihydropyridines with iodobenzene diacetate. This reagent affords a complex mixture with a small amount of the unreacted starting material remaining at the end of the reaction. The corresponding fluorinated reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA), worked very well using our conditions and simply requires mixing of a 1,4-dihydropyridine derivative with 1.2 equivalents of the reagent at room temperature to produce the corresponding pyridines in a clean reaction (Scheme 1). The oxidation proceeds smoothly with 1,4-dihydropyridine substrates bearing substituents at the 4-position such as hydrogen, methyl, aryl and heterocyclic groups. However, in the case of the 4-ethyl analogue a mixture of alkylated and dealkylated products is obtained and with 4-isopropyl and 4-benzyl derivatives, dealkylation occurs exclusively (Table 1).

Table 1 Solid state oxidation of 1,4-dihydropyridines to pyridines with PIFA

Entry	R	Final product (s)	Yield (%)[a]	Mp/°C[b] Found	Mp/°C[b] Reported
1	H	**2a**	82	70–71	70–71[19]
2	CH_3	**2b**	76	oil	oil[20]
3	CH_3CH_2	**2a** + **2c**	20 + 68		
4	$CH(CH_3)_2$	**2a**	80	70–71	70–71[19]
5	C_6H_5	**2e**	90	62–63	62–64[20]
6	$C_6H_5CH_2$	**2a**	85	70–71	70–71[19]
7	4-$CH_3C_6H_4$	**2g**	88	73–74	72–73[20]
8	4-$NO_2C_6H_4$	**2h**	85	113–14	115[21]
9	2-Furyl	**2i**	82	oil	oil[23]

[a] Yields refer to isolated pure products. [b] Products exhibited physical and chemical properties in accordance with the assigned structures.



Scheme 1

In order to obtain the desired pyridine derivatives bearing 4-isopropyl and 4-benzyl substituents, and to develop a general approach for this oxidative conversion, we explored the utility of elemental sulfur[17] which has recently been used under solvent-free conditions for the assembly of heterocyclic com-

Table 2 Oxidation of 1,4-dihydropyridines to pyridines with sulfur/microwaves

Entry	R	Final product	Time/min	Yield (%)[a]	Mp/°C[b] Found	Mp/°C[b] Reported
1	H	**2a**	5.0	80	72	70–71[19]
2	CH_3	**2b**	5.0	72	oil	oil[20]
3	CH_3CH_2	**2c**	5.0	70	oil	oil[19]
4	$CH(CH_3)_2$	**2d**	5.5	68	oil	oil[17]
5	C_6H_5	**2e**	6.0	85	62–63	62–64[20]
6	$C_6H_5CH_2$	**2f**	6.0	74	45	46[17]
7	4-$CH_3C_6H_4$	**2g**	6.0	82	73–74	72–73[20]
8	4-$NO_2C_6H_4$	**2h**	6.0	80	113–14	115[21]
9	4-HOC_6H_4	**2i**	7.0	72	172–73	171–73[22]
10	Styryl	**2j**	6.0	74	163–64	162–65[20]
11	2-Furyl	**2k**	6.0	76	oil	oil[23]

[a] Yields refer to isolated pure products. [b] Products exhibited physical and chemical properties in accordance with the assigned structures.

pounds.[18] The oxidation of 1,4-dihydropyridines with sulfur occurs readily and requires mixing the substrates with 1.3 equivalents of sulfur followed by exposure to microwave irradiation for 5–6 min. This protocol readily oxidizes alkyl, aryl, styryl and heterocyclic analogues of dihydropyridines to the corresponding pyridine derivatives in good yields (Table 2). Also, this procedure accommodates the challenging cases of substrates bearing secondary alkyl or benzyl substituents at the 4-position and tolerates a variety of functional groups in the aryl ring such as hydroxy and olefinic moieties (entries 9 and 10, Table 2). The identity and purity of products in these cases is confirmed by ^{1}H NMR analysis (see Experimental section).

Our results reveal that the aromatization of 4-isopropyl- or 4-benzyl-1,4-dihydropyridines in the presence of PIFA may occur *via* an ionic route to produce **2a**. This can be rationalized taking into account the fact that the ionic pathway proceeds with the expulsion of the 4-substituent when it is an isopropyl or benzylic group because of the stability of the resulting carbonium ion. However, when sulfur was employed we observed the liberation of hydrogen sulfide requiring the abstraction of hydrogen instead of the alkyl group.

The effect of microwave irradiation in this reaction has been investigated by comparing reactions carried out by traditional heating methods and in a microwave oven. The former reaction (**1b**, entry 2) was conducted in an oil bath at 160 °C and required 35 min for completion. In the reaction performed in the microwave oven the temperature also reached 160 °C after 3.0 min of irradiation at full power. However, in this experiment, microwave heating only required 5 min for completion of the reaction.

In conclusion, we have developed simple, rapid and practical methods for the oxidation of 1,4-dihydropyridines to pyridines that can be conducted at room temperature or can be safely accelerated by microwave irradiation under solvent-free conditions. The utility of inexpensive elemental sulfur under solvent-free conditions makes this protocol more economical and environmentally friendly.

Experimental

Melting points were determined on a Mel-Temp II hot stage apparatus using a Fluke 51 K/J digital thermometer and are uncorrected. An unmodified household microwave oven (900 W) equipped with a turntable was used for microwave heating while using elemental sulfur as an oxidant. The average bulk temperature at the end of the reaction was measured by inserting a thermometer in the alumina bath housing the reaction vessel. ^{1}H NMR spectra were recorded on a JEOL 300 MHz spectrometer using $CDCl_3$ as solvent and compared with reported values wherever recorded. The multiplicities are abbreviated as singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). The coupling constants (J) values are recorded in Hz. All the starting 1,4-dihydropyridines were prepared according to literature procedure.[2]

General procedure for the oxidation of 1,4-dihydropyridines 1 with PIFA

1,4-Dihydropyridines (1 mmol) and PIFA (1.2 mmol) were mixed thoroughly using a vortex mixer at room temperature. After 15 minutes the reaction mixture was poured into water and the product extracted into methylene chloride (2 × 10 ml). The combined extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was passed through a small bed of silica gel using hexane–EtOAc (9:1) as eluent to afford the corresponding pyridine derivative **2**.

General procedure for the oxidation of 1,4-dihydropyridines 1 with sulfur

1,4-Dihydropyridines (1 mmol) and elemental sulfur (1.3 mmol) were mixed thoroughly using a vortex mixer. The mixture was transferred into a glass tube and exposed to microwave irradiation in an alumina bath placed inside the MW oven. Intermittent heating with a time interval of 2 min (Table 2) was used when the bulk temperature reached 160 °C. The crude product was dissolved in methylene chloride (5 ml) and purified by chromatography on a silica gel column; elution with hexane–EtOAc (9:1) afforded pure pyridine derivatives **2**.

Diethyl 2,6-dimethyl-4-isopropylpyridine-3,5-dicarboxylate 2d. Yield 68%; oil (lit.,[17] oil); δ_H (300 MHz) 1.25 (6H, d, J 7.20, $CH(CH_3)_2$), 1.36 (6H, t, J 7.20, OCH_2CH_3), 2.50 (6H, s, 2-CH_3, 6-CH_3), 2.92 (1H, septet, $CH(CH_3)_2$), 4.37 (4H, q, J 7.20 and 6.90, OCH_2CH_3).

Diethyl 2,6-dimethyl-4-benzylpyridine-3,5-dicarboxylate 2f. Yield 74%; mp 45 °C (lit.,[17] 46 °C); δ_H (300 MHz) 1.15 (6H, t, J 7.20, OCH_2CH_3), 2.52 (6H, s, 2-CH_3, 6-CH_3), 4.15 (4H, q, J 7.20 and 6.90, OCH_2CH_3), 4.03 (2H, s, 4-CH_2Ar), 7.05–7.25 (5H, m, Ar-H).

Diethyl 2,6-dimethyl-4-(4-hydroxyphenyl)pyridine-3,5-dicarboxylate 2i. Yield 72%; mp 172–73 °C (lit.,[22] 171–73 °C); δ_H (300 MHz) 1.00 (6H, t, J 7.20 and 6.90, OCH_2CH_3), 2.58 (6H, s, 2-CH_3, 6-CH_3), 4.06 (4H, q, J 7.20 and 6.90, OCH_2CH_3), 6.77 (2H, d, J 7.50, 2′-H, 6′-H), 7.11 (2H, d, J 8.47, 3′-H, 5′-H).

Diethyl 2,6-dimethyl-4-(4-styryl)pyridine-3,5-dicarboxylate 2j. Yield 74%; mp 163–64 °C (lit.,[20] 162–65 °C); δ_H (300 MHz) 1.27 (6H, t, J 7.20, OCH_2CH_3), 2.56 (6H, s, 2-CH_3, 6-CH_3), 4.32 (4H, q, J 7.20 and 6.90, OCH_2CH_3), 6.79 (1H, d, J 16.50, =CH), 7.09 (1H, d, J 16.50, =CH), 7.26–7.42 (5H, m, ArH).

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