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Oxidative aromatization of some 1,4-dihydropyridine derivatives using $NaBrO_3$

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Abstract

In this study, oxidation of some 3,5-diacyl or 3,5-diester 1,4-dihydropyridines to corresponding pyridine derivatives using sodium bromate in the presence of NH_4Cl, $NaHSO_4$ and Bu_4NHSO_4 under thermal conditions has been investigated. The yield and structure of formed products is similar under all conditions; however, the reaction is accelerated in the presence of Bu_4NHSO_4 and $NaHSO_4$. In addition, oxidation of 3,5-diester 1,4-dihydropyridines, against 3,5-diacetyl 1,4-dihydropyridines using sodium bromate in the presence of tetrabutylammonium hydrogen sulfate leads to the corresponding pyridines in shorter reaction times than sodium hydrogen sulfate. The cheapness of reagent, high yielding, easy work up and mild condition make this method a useful addition to the available methods in organic synthesis.

Keywords: 1,4-Dihydropyridine; aromatization; sodium bromate.

Introduction

Hantzsch 1,4-dihydropyridines have been widely used in 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 importance of this oxidative event in the biological system, the study of oxidation of 1,4-dihydropyridines has

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attracted the attention of several research groups. In addition aromatization of 1,4-dihydropyridines provides a good method for the synthesis of 4-substituted pyridine which are difficult to access via the friedel crafts alkylation.

In the course of our study with 1,4-dihydropyridines [3-8], we investigate oxidations of 1,4-dihydropyridines using $NaBrO_3$ in the presence of NH_4Cl, $NaHSO_4$ and Bu_4NHSO_4. The oxidation with bromate ion, BrO_3^-, results in bromide ion formation, which can be safely treated or recycled. Thus such oxidations are recognized as friendly to the environment. Standard redox potential of the bromate is 0.61 V in neutral and alkaline aqueous solution while in aqueous acidic media it is 1.52 V [9,10]. Therefore, pH of the media affects standard redox potential and oxidation ability of BrO_3^- ion. Furthermore, nature and strength of the acid used, is important for oxidation of organic compounds using bromate.

Sodium bromate is a cheap and a commercially available compound. However, sodium bromate is usually used in aqueous media in the presence of co reactants such as NH_4Cl [11], $AlCl_3$ [12], $KHSO_4$ [13], CAN [14], $Mg(HSO_4)_2$ [15] and $NaHSO_4$. H_2O [16] for the oxidation of organic compounds.

Oxidation of 3,5-diester 1,4-dihydropyridines by tetraethyl ammonium bromate [17], potassium bromate in the presence of $SnCl_4$ [18], potassium bromate in the presence of sodium bisulfite [19], and sodium bromate in the presence of $NaHSO_3$ [20] have been reported. The present study describes a convenient and efficient method for the oxidation of 3, 5-diacyl or 3, 5-diester 1,4-dihydropyridines with $NaBrO_3$ in the presence of NH_4Cl, $NaHSO_4$ and Bu_4NHSO_4 and explains the effect of the type and the nature of the 3,5-substituents on the rate of oxidation.

Experimental

General

All Hantzsch 1,4-dihydropyridines have been synthesized according to the known procedure [21-23]. All products were known and their physical and spectroscopic data were compared with those of authentic samples [23-29]. Melting points were determined with Barnstead Electrothermal and are uncorrected. IR spectra were recorded on Shimadzu IR-470 spectrometer, ^{1}HNMR data were obtained using a

Brüker 300 MHz spectrometer in $CDCl_3$. UV spectra were measured on a R.R. China, Agilent 8453 spectrometer.

General procedure for oxidation of 1,4-dihydropyridines using $NaBrO_3$ in the presence of NH_4Cl, $NaHSO_4$ and Bu_4NHSO_4

To each of Hantzsch 1,4-dihydropyridines (5 mmol) and $NaBrO_3$ (0.75 g, 5 mmol) solution in aqueous acetonitrile (CH_3CN/H_2O = 22.5:7.5 mL) was added NH_4Cl (0.9 g, 17 mmol) or $NaHSO_4$ (0.6 g, 5 mmol) or Bu_4NHSO_4 (1.7 g, 5 mmol). The mixture was stirred at 80 ºC for time reported in Tables 1-3. The progress of reaction was followed by TLC. After the reaction was completed, the mixture was washed with aqueous $Na_2S_2O_3$ and extracted with methylene dichloride (2 ×20 mL). The combined organic layer was dried over $MgSO_4$ and after filtration, the solvent was evaporated. The product was purified by recrystallization from petroleum ether / ethyl acetate.

Diethyl-2,6-dimethyl pyridine-3,5-dicarboxylate (2a)

M.P.°C : 67-68; ^{1}H NMR(300 MHz , $CDCl_3$): δ =1.40 (t, J= 7 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 2.84 (s, 6H, 2 and 6 -CH_3) , 4.38 (q, J= 7 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$), 8.67 ppm (s, 1H, 4-H); IR (KBr): $\tilde{\nu}$ = 1717 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log ε) = 273 nm (3.52) .

Diethyl-4-methyl-2,6-dimethyl pyridine-3,5-dicar boxylate (2b)

Oil; ^{1}H NMR(300 MHz , $CDCl_3$): δ =1.36 (t, J= 6.5 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 1.52 (s, 3H, 4-CH_3) , 2.37 (s, 6H, 2 and 6 -CH_3) , 4.10 ppm (q, J= 6.5 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 1731 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log ε) =254 nm (3.44).

Diethyl-4-phenyl-2,6-dimethyl pyridine-3,5-dicar boxylate (2c)

M.P.°C : 64-66; ^{1}H NMR(300 MHz , $CDCl_3$): δ = 0.86 (t, J= 6.5 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 2.58 (s, 6H, 2 and 6 -CH_3) , 3.97 (q, J= 6.5 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$), 7.28 ppm (m, 5H, C_6H_5); IR (KBr): $\tilde{\nu}$ = 1726 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log ε) = 236 nm (3.75).

Diethyl-4-(4'-chlorophenyl)-2,6-dimethyl pyridine-3,5-dicarboxylate (2d)

M.P.°C : 67-68; ^{1}H NMR(300 MHz , $CDCl_3$): δ = 0.96 (t, J= 7.1 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 2.61 (s, 6H, 2 and 6 -CH_3) , 4.03 (q, J= 7.1 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$), 7.25 ppm (d d, 4H, C_6H_4Cl); IR (KBr): $\tilde{\nu}$ =1716 (C=O)

cm^{-1}; UV/vis (MeOH): λ_{max} (log £) = 212 nm (4.47).

Diethyl-4-(4'-metoxyphenyl)-2,6-dimethyl pyridine-3,5-dicarboxylate (2e)

M.P.°C : 59-61; ^{1}H NMR(300 MHz , $CDCl_3$): δ = 0.99 (t, J= 7.1 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 2.63 (s, 6H, 2 and 6 -CH_3) , 3.95 (s, 3H, 4′-OCH_3),4.05 (q, J= 7.1 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$), 7.30 ppm (d d, 4H, $C_6H_4OCH_3$); IR (KBr): $\tilde{v}$ =1697 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log£) = 243 nm (4.96).

Diethyl-4-(3'-nitrophenyl)-2,6-dimethyl pyridine-3,5-dicarboxylate (2f)

M.P.°C : 62-64; ^{1}H NMR(300 MHz , $CDCl_3$): δ = 1.01 (t, J= 7.0 Hz , 6H , $CO_2CH_2\mathbf{CH_3}$) , 2.68 (s, 6H, 2 and 6 -CH_3) , 4.06 (q, J= 7.1 Hz , 4H , $CO_2\mathbf{CH_2}CH_3$), 7.25 ppm (m, 4H, $C_6H_4NO_2$); IR (KBr): $\tilde{v}$ =1722 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log£) = 257 nm (4.75).

3,5-Diacetyl-2,6-dimethyl pyridine (2g)

M.P.°C : 66-67; ^{1}H NMR (300 MHz, $CDCl_3$): δ =2.62 (s, 6H, 2-and 6-CH_3), 2.77 (s, 6H, 3-and 5-$COCH_3$), 4.30ppm (s, 1H, 4-H); IR (KBr): $\tilde{v}$ = 1681 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log£) = 246 nm (4.14).

Diacetyl-4-phenyl-2,6-dimethyl pyridine (2h)

M.P.°C : 186-188; ^{1}H NMR (300 MHz, $CDCl_3$): δ =2.19 (s, 6H, 2-and 6-CH_3), 2.44 (s, 6H, 3-and 5-$COCH_3$), 7.36ppm (m, 5H, C_6H_5); IR (KBr): $\tilde{v}$ = 1699 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log £) = 258 nm (4.28).

3,5-Diacetyl-4-(4'-chlorophenyl)-2,6-dimethyl pyridine (2i)

M.P.°C : 171-174; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.86 (s, 6H, 2-and 6-CH_3), 2.43 (s, 6H, 3-and 5-$COCH_3$), 7.22ppm (dd, 4H, C_6H_4Cl); IR (KBr): $\tilde{v}$ =1704 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log £) = 275 nm (4.39).

3,5-Diacetyl-4-(4'-metoxyphenyl)-2,6-dimethy l pyridine (2j)

M.P.°C : 165-166; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.88 (s, 6H, 2-and 6-CH_3), 2.48 (s, 6H, 3-and 5- $COCH_3$), 3.83(s, 3H, 4-OCH_3), 7.04ppm (dd, 4H, $C_6H_4OCH_3$); IR (KBr): $\tilde{v}$ =1696 (C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log£) = 239 nm (4.42).

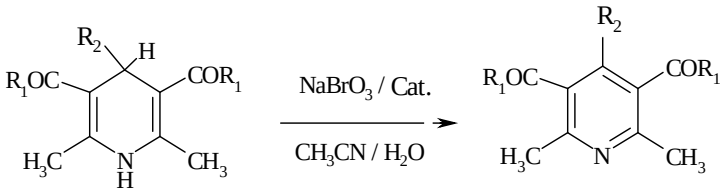
3,5-Diacetyl-4-(3'-nitrophenyl)-2,6-dimethyl pyridine (2k)

M.P.°C : 124-125; ^{1}H NMR (300 MHz, $CDCl_3$): δ =2.18 (s, 6H, 2-and 6-CH_3), 2.58 (s, 6H, 3-and 5-$COCH_3$), 7.65ppm (m, 4H, $C_3H_4NO_2$); IR (KBr): $\tilde{v}$ =1696

(C=O) cm^{-1}; UV/vis (MeOH): λ_{max} (log £) = 257 nm (4.73).

Results and discussion

A long series of 1,4-dihydropyridines were synthesized to investigate their conversion to the corresponding pyridines with sodium bromate. For optimization of the reaction condition, we accomplish some experimental, with diethyl-2,6-dimethyl-4-phenyl-1,4 dihydropyridine-3,5-dicarboxylate as a typical compound. We use different solvents such as EtOAc, H_2O, CH_3CN, EtOH, CH_3CN: H_2O (3:1), and also, we use different amounts of sodium bromate in the presence of different amount of NH_4Cl, $NaHSO_4$.and Bu_4NHSO_4. The molar ratio of substra / $NaBrO_3$/ NH_4Cl 1: 1: 3, substra / $NaBrO_3$/ $NaHSO_4$ 1: 1: 1 and substra / $NaBrO_3$/ Bu_4NHSO_4 1: 1: 1 in aqueous acetonitrile (CH_3CN /H_2O = 3 : 1) at 80 ºC, is the best optimal for the oxidation of these compounds (Scheme 1).



1 **2**

Scheme 1. Oxidative aromatization of 1,4-dihydropyridine derivatives using $NaBrO_3$

The results of oxidation of 1,4-dihydropyridine by $NaBrO_3$ / NH_4Cl, $NaBrO_3$ / $NaHSO_4$ and $NaBrO_3$ / Bu_4NHSO_4 are summarized in Tables 1-3.

Table 1. Oxidative aromatization of some 1,4-dihydropyridines using sodium bromate in the presence of ammonium chloride

Comp.	R_1	R_2	Product (%)[a]	Time (h)
1a	OC_2H_5	H	2a (66)	1.7
1b	OC_2H_5	CH_3	2b (82)	1.5
1c	OC_2H_5	C_6H_5	2c (97)	2
1d	OC_2H_5	4-ClC_6H_4	2d (75)	1.25
1e	OC_2H_5	4-$OCH_3C_6H_4$	2e (90)	1.6
1f	OC_2H_5	3-$NO_2C_6H_4$	2f (75)	2.17
1g	CH_3	H	2g (98)	5
1h	CH_3	C_6H_5	2h (88)	10
1i	CH_3	4-ClC_6H_4	2i (79)	18
1j	CH_3	4-$OCH_3C_6H_4$	2j (81)	9
1k	CH_3	3-$NO_2C_6H_4$	2k(78)	30

[a]Isolated yield

Table 2. Oxidative aromatization of some 1,4-dihydropyridines using sodium bromate in the presence of sodium hydrogen sulfate

Comp.	R_1	R_2	Product (%)[a]	Time (min)
1a	OC_2H_5	H	**2a** (70)	90
1b	OC_2H_5	CH_3	**2b**(90)	120
1c	OC_2H_5	C_6H_5	**2c** (95)	150
1d	OC_2H_5	4-ClC_6H_4	**2d**(80)	180
1e	OC_2H_5	4-$OCH_3C_6H_4$	**2e** (90)	70
1f	OC_2H_5	3-$NO_2C_6H_4$	**2f**(73)	130
1g	CH_3	H	**2g** (98)	20
1h	CH_3	C_6H_5	**2h** (90)	30
1i	CH_3	4-ClC_6H_4	**2i** (76)	120
1j	CH_3	4-$OCH_3C_6H_4$	**2j** (69)	35
1k	CH_3	3-$NO_2C_6H_4$	**2k**(83)	30

[a]Isolated yield

Table 3. Oxidative aromatization of some 1,4-dihydropyridines using sodium bromate in the presence of tetrabutylammonium hydrogen sulfate

Comp.	R_1	R_2	Product (%)[a]	Time (min)
1a	OC_2H_5	H	**2a** (90)	25
1b	OC_2H_5	CH_3	**2b** (79)	100
1c	OC_2H_5	C_6H_5	**2c** (86)	45
1d	OC_2H_5	4-ClC_6H_4	**2d** (95)	120
1e	OC_2H_5	4-$OCH_3C_6H_4$	**2e (**73**)**	40
1f	OC_2H_5	3-$NO_2C_6H_4$	**2f (**83**)**	30
1g	CH_3	H	**2g (**92**)**	30
1h	CH_3	C_6H_5	**2h (**81**)**	60
1i	CH_3	4-ClC_6H_4	**2i (**70**)**	240
1j	CH_3	4-$OCH_3C_6H_4$	**2j (**88**)**	55
1k	CH_3	3-$NO_2C_6H_4$	**2k (**67**)**	45

[a]Isolated yield

The presented data in Tables 1-3 indicate that sodium bromate in the presence of catalysts such as; ammonium chloride, sodium hydrogen sulfate and tetrabutylammonium hydrogen sulfate is able to convert 1,4-dihydropyridines to their corresponding pyridines in good yields. As can be seen from these tables, oxidation of **1a-1k** under all conditions yields **2a-2k** to retention of the substituent in position 4. The presented data in Tables 1-3 indicate that, compounds **1a** and **1g** with no substituent in position 4 of

dihydropyridine ring convert to the corresponding pyridines in shorter reaction time than other 3,5-diester and 3,5-diacetyl 1,4-dihydropyridines respectively. the reaction is facilitated by electron releasing groups on 4-substituent of dihydropyridine ring in the presnece of ammonium chloride. Furthermore, we do not find any correlation between substituent in position 4 of dihydropyridine ring and reaction times in the presence of other catalysts.

The consumed amount of ammonium chloride is more than sodium hydrogen sulfate or tetrabutylammonium hydrogen sulfate in this reaction, so oxidation using sodium bromate in the presence of ammonium chloride is slower than other catalysts. As shown in Tables 1-3 the oxidation of 3,5-diester 1,4-dihydropyridines (**1a-1f**), against 3,5-diacetyl 1,4-dihdropyridines (**1g-1k**) using sodium bromate in the presence of tetrabutylammonium hydrogen sulfate, lead to the corresponding pyridines in shorter reaction times than sodium hydrogen sulfate. As we know, hydrogen sulfate ion is stronger acid than ammonium ion. In addition, tetrabutylammonium bromate as a phase transfer reagent was produced in situ from tetrabutylammonium hydrogen sulfate and sodium bromate which was suitable for application in two-phase system. Standard redox potential of the bromate ion is variable in neutral, alkaline and acidic media. Therefore, pH of the media affect standard redox potential and oxidation ability of bromate ion. However. the kinetics and mechanism of the oxidation of these compounds by bromate has not been investigated in this study.

Conclusion

In conclusion, we have described a convenient and practical route for the oxidation of 1,4-dihydropyridines to the corresponding pyridines. Furthermore, the cheapness of reagent, high yielding, easy work up and mild condition makes this method a useful addition to the available methods in organic synthesis.

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