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N-Amination of 2,6-Di-*tert*-butylpyridine

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Summary. Despite its low nucleophilicity 2,6-di-*tert*-butylpyridine (*DTBP*) easily undergoes N-amination. Other hidered pyridines react similarly. Comparison of the NMR carbon chemical shifts of 2,6-disubstituted 1-aminopyridinium perchlorates and those of the respective 1-methylpyridinium salts shows that the changes are parallel. 1-Amino-2,6-di-*tert*-butylpyridinium perchlorate does not react with *p*-dimethylaminobenzaldehyde. However, other hindered 1-(4′-dimethylaminobenzylideneamino)pyridinium salts were obtained by a standard procedure.

Keywords. 2,6-Di-*tert*-butylpyridine; N-Amination; 1-Amino-2,6-di-*tert*-butylpyridinium perchlorate; Steric hindrance.

N-Aminierung von 2,6-di-*tert*-Butylpyridin

Zusammenfassung. Trotz seiner geringen Nucleophilie ist an 2,6-Di-*tert*-butylpyridin (*DTBP*) leicht eine N-Aminierung durchzuführen. Andere gehinderte Pyridine reagieren ähnlich. Ein Vergleich der NMR-Kohlenstoffverschiebungen von 2,6-disubstituiertem 1-Aminopyridiniumperchlorat mit denjenigen der entsprechenden 1-Methylpyridiniumsalze zeigt, daß die Änderungen parallel verlaufen. 1-Amino-2,6-di-*tert*-butylpyridiniumperchlorat reagiert nicht mit *p*-Dimethylaminobenzaldehyd, hingegen wurden andere gehinderte 1-(4′-Dimethlylaminobenzylidenamino)pyridiniumsalze über Standardmethoden erhalten.

Introduction

2,6-Di-*tert*-butylpyridine (*DTBP*) is an unusual base [1]. As a result of steric crowding at the nitrogen atom, it does not coordinate with Lewis acids, e.g. boron trifluoride [2], or undergo quaternization under ordinary conditions [2, 3]. Also 2,6-diisopropylpyridine reacts very slowly with methyl iodide [3, 4] but numerous pyridinium salts containing bulky substituents in positions 2 and 6 of the pyridine ring are known compounds [5–13]. Use of stronger alkylating agents produces the respective 2,6-di-*tert*-butylpyridinium salts in low yield [14, 15]. Reaction of *DTBP* with methyl iodide carried out under high pressure [16] gave the respective 1-methylpyridinium salt which was later found to be 2,6-di-*tert*-butylpyridinium hydroiodide [3]. As a matter of fact, both 1-hydrogen and 1-methyl derivatives are formed from similar starting materials at high pressure [17, 18]. As shown by its melting point, 1-methyl-2,6-di-*tert*-butylpyridinium iodide obtained in such a manner [18] is probably still contaminated by the respective hydroiodide. The former

compound was also the product of the ion exchange in the respective fluorosulfonate which, in turn, was obtained from *DTBP* and methyl fluorosulfonate at atmospheric pressure [14]. It should be mentioned that highly hindered N-methylpyridinium salts, like those discussed above, can also be formed from 1,2,6-trimethylpyridinium iodide by consecutively addition of sodium hydride and methyl iodide [15].

As expected, the steric strain in the N-methyl salts of *DTBP* changes the bond angles, but in the crystal only slight deformation of the pyridine ring was detected [14].

It should be mentioned that 4,5-dimethylacridine, which is isosterical to *DTBP*, gives the HCl salt, but fails to react with boron trifluoride [19]. It undergoes quaternization with methyl fluorosulfonate under pressure [18].

The rate of S_N2 reactions depends on the nucleophilicity of the attacking species [20, 21]. Shielding of the lone electron pair of the nucleophile by neighbouring groups affects the process. It can be easily seen in quaternization of α-substituted pyridines [22, 23]. These compounds also act as nucleophiles in reactions with compounds containing N-bonded leaving groups [24]. Thus, the corresponding N-aminopyridinium salt was obtained from 2,6-dimethylpridine and O-(2,4-dinitrophenyl)hydroxylamine [25]. Though similar syntheses of more hindered pyridinium salts were not studied, they can be obtained from the respective pyrylium salts and hydrazines [26, 27]. The present paper is concerned with the formation of 1-aminopyridinium salts carrying bulky alkyl or aryl groups in the positions 2 and 6 of the pyridine ring by use of some O-substituted hydroxylamines as aminating agents. Some properties of the products will be also discussed here.

Experimental Part

Some starting pyridines and quinolines were commercially available (Fluka, Aldrich, ICN). The procedure described for 2,6-lutidine [28] was used in preparation of 2,6-di-*n*-propyl- and 2,6-diisopropylpyridine (yield 42 and 31%, respectively). Their physical constants agree with those available in literature [2, 4]. The Skraup method [29] was applied in preparation of 8-ethylquinoline.

O-Tosyl- (*TSH*) [30] and O-mesitylenesulfonylhydroxylamines (*MSH*) [24] were prepared starting from the respective ethyl O-(arylsulfonyl)acetohydroxamates. *Warning*: Pouring of the dioxane solution of *TSH* into water must be done very slowly with vigorous mechanical stirring to get the precipitate in form of large crystals. Otherwise the product decomposes on the funnel due to very slow filtration. It should be immediately dissolved in methylene chloride and used in reactions just as the solution.

1-Aminopyridinium Arylsulfonates

A solution of ca 0.11 mol of *TSH* or *MSH* in methylene chloride was added slowly with stirring to the solution of 0.1 mol of pyridine in 30 ml of the same solvent cooled in ice. The solvent was removed and the residue extracted with ether. The non-extractable residue was recrystallized from ethyl acetate-methanol (2:1). The crystals were obtained only for 2,6-dimethyl derivatives.

Mesitylenesulfonate: yield 56%, m.p. 180.5–181.5 °C (lit. 180–181 °C [31, 32]).

Tosylate: yield 77%, m.p. 148–149 °C (lit. 147 °C [33]).

The crude salts were used directly in the next step.

1-Aminopyridinium Perchlorates

Method A. (Compare Ref. [34]): To the above obtained arylsulfonate dissolved in a small amount of methanol, 70% perchloric acid (14 ml) was added. After cooling the crystals formed were filtered off, washed with ether and recrystallized from methanol (see Table 1 for yields and m.p.'s).

Method B. Strong basic Amberlite or Dowex [Cl^-] was used to substitute the arylsulfonate anion by the chloride one [35]. A slight excess of an aqueous solution of silver perchlorate was added to the solution of the chloride obtained above. Precipitated silver chloride was filtered off and water evaporated *in vacuo*. The residue was recrystallized from methanol (see Table 1).

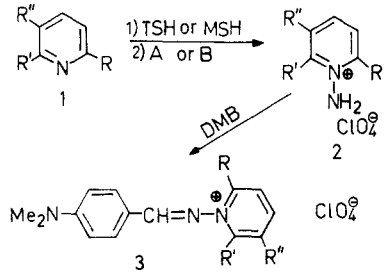
1-(4'-Dimethylaminobenzylideneamino)pyridinium Perchlorates

These compounds are the products of condensation of 1-aminopyridinium perchlorates with *p*-dimethylaminobenzaldehyde (*DMB*) [36]. Their NMR spectra will be discussed in our next paper [37].

Satisfactory C, H, N and Cl analyses were obtained for all new compounds. C-13 NMR spectra in *DMSO*-d_6 were recorded as before [38].

Results and Discussion

Unlike other 2,6-dialkylpyridines, *DTBP* does not form perbromide after addition of bromine [2]. Its methylation was reported (see Introduction) to proceed with difficulties. *DTBP* can attach only very small atoms such as hydrogen [2] and fluorine [39]. The steric requirements, *A*, of methyl, bromine, fluorine and hydrogen substituents are equal to 1.7, 0.4, 0.2 and 0, respectively [23]. The primary amino



TSH, MSH – O-Tosyl- and O-(mesitylenesulfonyl)hydroxylamine, respectively
A, B – See Experimental for the method used
DMB – p-dimethylaminobenzaldehyde

	–R	–R'	–R''
a	–Me	–Me	–H
b	–*n*-Pr	–*n*-Pr	–H
c	–*i*-Pr	–*i*-Pr	–H
d	–*t*-Bu	–*t*-Bu	–H
e	–Ph	–Ph	–H
f	–H	–CMe=CH–CH=CH–	
g	–H	–CEt=CH–CH=CH–	
h	–H	*ortho*-C_6H_4–CH=CH–	

group, NH_2, is smaller than methyl but bulkier than bromine and has $A = 1.2$ [23]. It was found to be easily attached to the aza atom in 2,6-di-*tert*-butylpyridine (see Experimental).

O-Arylsulfonylhydroxylamines are powerful aminating agents [24]. Application of such NH_2 synthons transforms tertiary amines, R_3N, into the respective hydrazinium cations $R_3N^+-NH_2$. Thus, 1-aminopyridinium salts can be obtained directly from the respective pyridines. The compounds undergo decomposition but these processes are slow and there is no problem in having them pure for at least two weeks. They undergo reaction with aldehydes to give the respective N-methylene derivatives [36].

As is known (see Introduction), the reactions of the aza atom in highly hindered pyridines proceed with difficulty. In the present paper, however, selected pyridines were transformed into the respective 1-aminopyridinium perchlorates. Since purification of such salts very often was not possible, they were analysed as the products of reaction with *p*-dimethylaminobenzaldehyde (*DMB*).

The synthesis results are given in Table 1. As seen, both aminating agents, i.e. O-tosyl- (*TSH*) and O-(mesitylenesulfonyl)hydroxylamines (*MSH*), are effective in preparation of the salts **2**. The yield depends only slightly on the substituent present in the pyridine ring. However, only starting materials were recovered in the reaction of **1d** with *DMB* (reflux in EtOH, 12 h). The respective dimethyl-, di-*n*-propyl-, diisopropyl- and diphenyl-1-aminopyridinium salts were successfully condensed with *DMB*. 8-Alkylquinolines as well as 7,8-benzoquinoline give the respective 1-aminoquinolinium salts which were transformed into benylidene derivatives **3** (see Table 1). As reported [40], the rotational barriers of the N-methly group in

Table 1. The yields and m.p.'s of 1-amino-, **2**, and 1-(4'-dimethylaminobenzylideneamino)pyridinium perchlorates, **3**[a]

No.	**2**			**3**
	Method	Yield (%)	m.p. (°C)	Yield (%)
a	B	63	130.5–131	48
b	A	60	96–98	37[b]
	B	–	oil	
c	A	–	oil	19[b]
	B	–	oil	
d	A	62	228.5–230	0[c]
e	A	71	187–189	50
	B	69	186–189	
f	B	–	oil	34[b]
g	B	–	oil	35[b]
h	B	–	oil	32[b]

[a] The melting points of compounds **3** are given in Ref. [36]

[b] Overall yield from **1**

[c] See Discussion

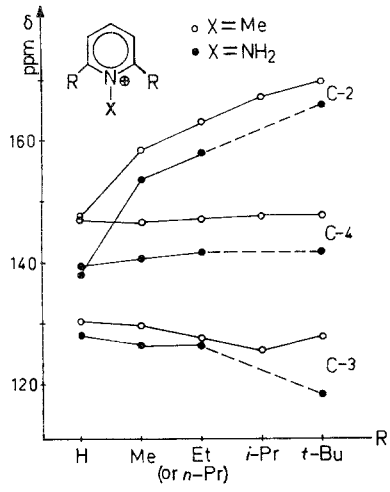


Fig. 1. Effect of increasing steric requirements of an alkyl group on carbon chemical shifts of 2,6-disubstituted 1-methyl- and 1-amino-pyridinium cations

unsubstituted, 8-methly and 7,8-benzo-1-methylquinolinium iodides amount to 1.98, 2.42 and 4.44 kcal/mol, respectively. Though one would expect different reactivities of the aza atom in the quinolines used, both 8-alkyl- and 7,8-benzo-1-(4′-dimethylaminobenzylideneamino)quinolinium perchlorates, **3f**, **3g** and **3h**, are formed in approximately the same yield (see Table 1).

Both *tert*-butyl and phenyl are bulky groups but they have different shapes. Steric effects of the latter depend on its conformation with respect to the rest of the molecule. It is known [41] that 1-methyl-2,6-diphenylpyridinium iodide is formed from 2,6-diphenylpyridine and methyl iodide at 100 °C. The data in Table 1 show that similar reaction with *TSH* and *MSH* proceeds, too. Though *DTBP* hesitates to react with alkylating agents, in reaction with *TSH* it gives **2d** in quite resonable yield (see Table 1).

Effect of the substituent on C-13 NMR spectra of compounds **2** can be seen in Fig. 1 and Table 2. A downfield shift of signal of the *ipso*, i.e. 2 and 6, carbons change in the order *t*-Bu > *n*-Pr > Me > H.

However, the $\delta_{C\text{-}4}$ value is only slightly dependent on the substituent. As seen in Fig. 1, the signals of the carbon atoms of the 1-amino-2,6-dialkylpyridinium cations are shifted upfield as compared to the 1-methyl-2,6-dialkylpyridinium compounds.

Table 2. Carbon chemical shifts (δ, ppm) of 2,6-disubstituted 1-aminopyridinium perchlorates **2** (R″ = H) *DMSO-d*$_6$

No.	R = R′	C-2(6)	C-3(5)	C-4	Substituent carbons			Ref.
					C-α	C-β	C-γ	
–	H	138.08	127.94	139.41	–	–	–	38
2a	Me	153.74	126.46	140.66	19.69	–	–	38
2b	*n*-Pr	157.89	126.56	141.55	34.03	20.28	13.62	38
2d	*t*-Bu	165.83	118.51	141.50	36.98	29.39	–	[a]

[a] Present paper

In general, the substituent chemical shifts in the spectra of salts **2** in *DMSO-*d_6 are parallel to those of the respective 1-methylpyridinium perchlorates in D_2O [14] (see Fig. 1). However, some perturbations can be seen for the $\delta_{C\text{-}3(5)}$ values.

Finally, it may be noted that 1-amino-2,6-di-*tert*-butylpyridinium perchlorate **2d** melts at a higher temperature than other 1-amino-2,6-dialkylpyridinium salts. Characteristic absorption bands in its IR spectrum (KBr disc) are: 3368 (NH_2) and 624 cm^{-1} (ClO_4^-).

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