THE PREPARATION OF N´-ALKYLNICOTINIUM SALTS

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Abstract --- Treatment of N-benzyl-N´-alkylnicotinium dihalides with triphenylphosphine provided a synthetic route to N´-alkylnicotinium salts.

Nicotine(**1**) has two kinds of tertiary nitrogens, one in pyridine (N) and the other in pyrrolidine ring (N´). Selective N-quaternization has been carried out by the reaction of nicotine hydrochloride with alkyl halides. On the other hand, there has been no method for selective N´-quaternization. The reaction of **1** with stoichiometric amount of alkyl halide gave only N-alkylnicotinium salt, and with excess amount of alkyl halide N,N´-dialkyl salt was obtained.[1)]In this paper, we wish to report a method to prepare N´-alkylnicotinium salts.

Two methods for N-dealkylation of N,N´-dialkylnicotinium salts were attempted. One was pyrolysis, and the other was cleavage reaction with triphenylphosphine reported by Kutney *et al*.[2)] The former method was, however, not successful for this case, and the result is discussed briefly at latter part in this report. On the other hand, the latter method was satisfactory for this purpose. In order to know which alkyl group had the most facility in this cleavage reaction, several N-alkylnicotinium salts were allowed to react with triphenylphosphine. The yields of **1** are listed in Table 1.

Table 1 Dealkylation of N-alkylnicotinium salts with PPh_3

R	Yield of nicotine(%)
CH_3	46
C_2H_5	0
$n-C_3H_7$	0
$iso-C_3H_7$	0
$CH_2=CHCH_2$	16
CH_2Ph	92
CH_2CH_2Ph	0

On the basis of the result, benzyl group was chosen for leaving group, and the synthesis of N´-alkylnicotinium salt was performed by the reaction of

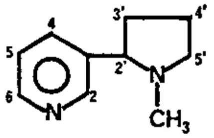
Table 2 Reaction of **2** with alkyl halides

RX	solvent	time(h)	Yield(%)
CH_3I	a)	4	99.3
C_2H_5I	b)	8	99.1
$n-C_3H_7I$	b)	8	79.1
$iso-C_3H_7I$	a)	16	79.9[c]
$CH_2=CHCH_2Br$	a)	4	99.6
$PhCH_2CH_2Br$	b)	8	99.1

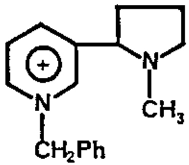
a) diglyme/CH_3CN = 2 : 1

b) diglyme/CH_3CN = 1 : 1

c) about 10% debenzylated product was contained.



nicotine (1)



(2)

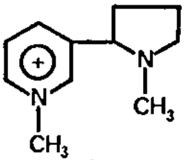
N-benzyl-N′-alkylnicotinium dihalides with triphenylphosphine, as exampled below. To a solution of 5.0 mmol of N-benzylnicotinium bromide(**2**) (which was obtained by the reaction of **1** with 1 equiv. of benzyl bromide) in 20 ml of 1:1 diglyme-acetonitrile was added dropwize 10.0 mmol of ethyl iodide at room temperature. The reaction mixture was refluxed for 8h, and extracted with water. The water extract was washed with dichloromethane, and concentrated <u>in vacuo</u> to give a brown oil. The ^1H NMR data showed that the residue was N-benzyl-N′-ethylnicotinium salt. The yields and the reaction conditions are listed in Table 2.

As shown in Table 2, the reaction of **2** with alkyl halides gave diquaternary salts in high yield. The effects of solvent, temperature, and reaction time in the reaction of **2** with ethyl iodide was examined. Each experiment was carried out in diglyme-acetonitrile solution. The conversion of **2** was 30% in 0:1 diglyme-acetonitrile solution (refluxed for 24h), 60% in 1:1 solution (2h), 85% in 1:2 solution (8h), and 99% in 1:1 solution (8h). When this reaction was further continued for over 20h in 2:1 solution, trace amount of the debenzylated product was obtained.

The cleavage reaction with triphenylphosphine was carried out in dimethylformamide (DMF) as follows. To a solution of 5.0 mmol of diquaternary salt in 10 ml of DMF was added 6.0 mmol of triphenylphosphine at room temperature. After refluxing for 3h, the reaction mixture was poured into ether. After removal of ether layer, the residual oily mixture was washed with ether and extracted with water. The extract was washed with dichloromethane and

Table 3 ^1H NMR chemical shifts (ppm from TMS)

	3	4	5	6	7	8	9
N′	2.26	2.87	3.07	3.07,3.30	2.70	3.10,3.20	3.03
	—	3.20	4.90	4.90	5.26	5.18	5.70
2′	3.55	5.16	4.72~5.08	4.78~5.10	4.85	5.18	4.85
3′	1.75	2.10	2.28	2.18	2.20	2.25	2.25
4′	2.25	2.80	2.70	2.85	2.75	2.75	2.75
5′	2.44,3.25	3.90	3.46~4.00	3.42~3.98	3.63~4.20	3.29~4.20	3.20~4.00
2	9.10	8.87	8.90	8.93	8.82	8.95	8.75
4	8.49	8.12	8.29	8.22	8.25	8.44	8.15
5	8.12	7.50	7.85	7.85	7.77	7.55	7.70
6	9.28	8.68	8.90	8.93	8.82	8.95	8.75
N	4.70	—	—	—	—	—	—
			1.86	2.50	1.92	3.54	5.70~5.80
				1.13		7.26~7.62	



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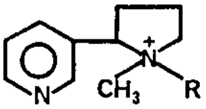

R=(4) CH_3, (5) C_2H_5, (6) n-C_3H_7,
(7) iso-C_3H_7, (8) $PhCH_2CH_2$
(9) $CH_2=CHCH_2$,

concentrated *in vacuo* to give a brown oil. The residue was identified on the basis of its ^1H NMR spectrum, which is shown in Table 3. The chemical shifts of nicotine moiety in 5~9 were extremely close to those of N′-methylnicotinium salt(4), but not to those of N-methyl salt(3). Thus, the structures of 5~9 were determined to be N′-alkyl derivatives.

The cleavage reactions proceeded regioselectively, and gave N′-alkylnicotinium salts in high yields, which are listed in Table 4.

Preparation of N′-alkylnicotinium salt was initially attempted by the pyrolysis with and without solvent to cleave N-alkyl group in the N,N′-dialkyl salt. In order to examine the ease of cleavage, the pyrolysis of several

N-alkylpyridinium salts was performed. Methyl- and benzylpyridinium salts were not pyrolyzed at 230°C, and ethyl, n-propyl, and iso-propyl salts gave hydropyridinium salts in 18%, 75%, and 84% yields at the same temperature, respectively. In the case of β-phenylethylpyridinium bromide, pyridine hydrobromide was obtained in 100% yield at 200°C. Therefore, pyrolysis of N-β-phenylethyl-N′-alkylnicotinium dihalide was attempted. However, this attempt resulted in the formation of a complex mixture of unidentified compounds at any temperature.

Table 4 Debenzylation of diquaternary salts with PPh_3

R	Yield of N′-alkylnicotinium salts(%)
CH_3	80.8
C_2H_5	87.1
n-C_3H_7	70.5
iso-C_3H_7	68.6
$CH_2=CHCH_2$	97.4
$PhCH_2CH_2$	82.7

Thus, it is concluded that at present the N′-alkylation of N-benzylnicotinium halides followed by debenzylation with triphenylphosphine is the best way to obtain a N′-alkylnicotinium salts.

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2) J. P. Kutney and R. Greenhouse, Synth. Commun., **5**, 119 (1975).

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