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THE ZINCKE'S REACTION: A NEW ALTERNATIVE FOR THE PREPARATION OF 1-[2-(3-INDOL)ETHYL]-ALKYLPYRIDINIUM CHLORIDE DERIVATIVES

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Abstract. The Zincke's salts **3** (**a-f**) were prepared and used for the synthesis of 1-[(2-(3-indol)-ethyl]alkylpyridinium chloride derivatives **5** (**a-f**) in high yields.

The Zincke's salts are compounds that react under appropriate conditions with primary amines to generate the corresponding pyridinium chloride derivatives.[1] The Zincke's salts **3** (**a-f**) were reacted with tryptamine and the pyridinium chloride derivatives **5** (**a-f**) were obtained. These compounds can be used for the preparation of the corresponding 1, 2 and 1, 4- dihydropyridines or 2-pyridones derivatives [2, 3, 4] which are suitable intermediates for the synthesis of alkaloids.[5, 6, 7, 8].

Normally, the synthetic approach for the preparation of pyridinium bromide derivatives involves moderate heating at 50° for several hours of a small excess of the

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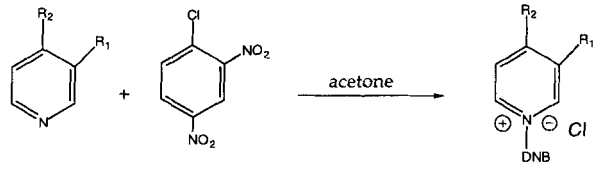
pyridine or alkylpyridine derivative with tryptophyl bromide, or by letting the mixture stand at room temperature for several days.[9]

In the present report we describe an efficient two step route for the preparation of pyridinium chloride derivatives **5 (a-f)** via Zincke's reaction. The first step was carried out refluxing 1 eq. of pyridines **1 (a-f)** in dry acetone or methanol, with 1 eq. of 1-chloro-2,4-dinitrobenzene 2 (ClDNB).[10] The reaction afforded the corresponding Zincke's salts **3(a-f)** with average yields above 86% (Scheme 1). The relevant physical and spectroscopic data and yields of **3 (a-f)** are shown in Table 1.



1 (a-f) 2 Cl-DNB **3 (a-f)**
Zincke's salts

Scheme 1

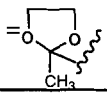
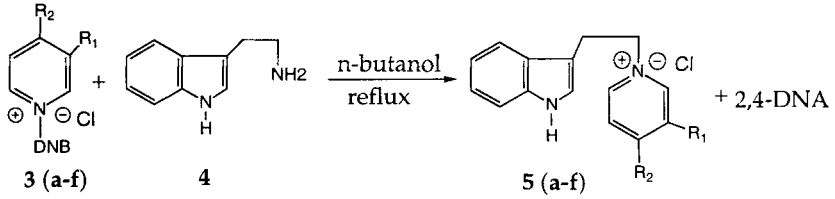
a)	$R_1 = H$	$R_2 = H$	**d)**	$R_1 = CH_2CH_3$	$R_2 = H$
b)	$R_1 = H$	$R_2 = CH_3$	**e)**	$R_1 = CH_3$	$R_2 = CH_3$
c)	$R_1 = CH_3$	$R_2 = H$	**f)**	$R_1 =$ 	$R_2 = H$

Table 1

Table 1. Zincke's[1] salts 3	yield (%)	m.p.°C.	FAB
a	90	202-203	246(M^+, 100), 80($C_5H_5N^+$, 10)
b	90	reddish paste	260(M^+, 100), 94($C_6H_8N^+$, 8)
c	92	206-207	260(M^+, 100), 94($C_6H_8N^+$, 8)
d	85	194-196	274(M^+, 100), 108($C_7H_{10}N^+$, 14)
e	90	yellow paste	274(M^+, 100), 108($C_7H_{10}N^+$, 39)
f	80	green paste	332(M^+, 100), 166($C_9H_{12}NO_2^+$, 51)

1. The synthesis of **3b** and **3e** were carried out in methanol.

In the second step, 1 eq. of a n-butanol solution of the Zincke's salts **3 (a-f)** and 1 eq. of tryptamine **4** was refluxed for 12 hours affording compounds **5 (a-f)** after removal of excess 2, 4-dinitroaniline (2, 4-DNA) by extraction with dichloromethane (Scheme 2). The physical and relevant spectroscopic data and yields of **5(a-f)** are shown in the Tables 2, 3 and 4. For tryptamine moiety ^{13}C assignments see FIG 1.



Scheme 2

a, b, c, d, e, f: same as in Scheme 1

Table 2

Compd 5	yield (%)	m.p.° 4	FAB
a	85	228-230	223 (M^+ 80), 144 ($C_{10}H_{10}N^+$, 100)
b	85	194-197	237 (M^+ 90), 144 ($C_{10}H_{10}N^+$, 100)
c	80	199-200	237 (M^+ 80), 144 ($C_{10}H_{10}N^+$, 100)
d	85	140-142	251(M^+ 95), 144($C_{10}H_{10}N^+$ 100)
e[3]	80	230-237	251(M^+ 95), 144($C_{10}H_{10}N^+$ 100)
f	80	yellowish paste	309(M^+, 100), 144($C_{10}H_{10}N^+$ 65)

3. The synthesis of **5e** was carried out in dichloromethane; 4. Lit.[9] m.p reported for bromide derivatives: **a)** 230-232° **b)** 199-201°, **c)** 204-206°, **d)** 154-156° and **e)** 215-222°

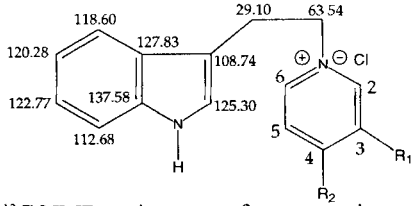


FIG. 1 ^{13}C NMR assignments for tryptamine moiety.

Table 3. ^{13}C NMR (CD_3OD)

Compd 5[5]	a	b	c	d	e	f
C-2	145.77	146.00	144.54	142.20	143.39	143.20
C-3	129.24	130.10	127.08	129.40	139.89	137.60
C-4	147.10	158.40	145.58	146.20	160.67	144.80
C-5	129.24	130.10	127.28	129.29	129.53	127.88
C-6	145.77	146.00	145.20	145.80	141.81	144.70
R_1			18.71	26.53(CH_2) 14.33(CH_3)	17.10	65.25-63.04 (2 OCH_2) 27.24 (CH_3)
R_2		20.21			20.41	

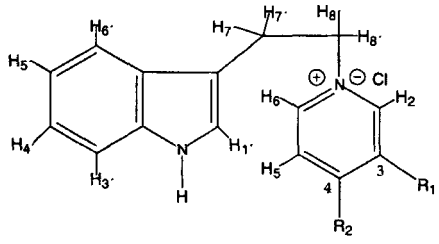
5. The tryptamine moiety of products showed an average variation of 0.3 ppm in ^{13}C NMR. **a, b, c, d, e, f** ere the same as in Scheme 2.

Table 4. ^{1}H (CD_3OD)

Compd 5[6]	a	b	c	d	e	f
H-2	20 (t, 1H)	8.90 (d, 2H) (H-2, H-6)	8.16 (s,1 H)	8.13 (s, 1H)	8.85 (s, 1H)	8.19 (s, 1H)
H-3	7.70 (t, 1H)	7.93 (d, 2H) (H-3, H-5)				
H-4	8.30 (m, 1H)		8.10 (d, 1H)	8.90 (d, 1H)		8.43 (d, 1H)
H-5	7.70 (t, 1H)		7.60 (t, 1H)	7.65 (t, 1H)	7.87 (d, 1H)	8.10 (t, 1H)
H-6	8.20 (t, 1H)		8.12 (d, 1H)	8.18 (d,1H)	8.77 (d, 1H)	8.87 (d, 1H)
R_1		R_1= H3	2.12(s, 3H, Me)	0.95 (t, 3H, Me) 2.25(q, 2H, CH_2)	2.50 (s,3H, Me)	3.92 (t, 2H) 3.87(t, 2H) 1.40 (s, 3H, Me)
R_2		2.70(s, 3H, Me)	R_2= H4	R_2= H4	2.61(s, 3H, Me)	R_2= H4

6. The tryptamine moiety of products showed average differences of 0.2 ppm in the ^{1}H NMR spectra.

Table 4. ^{1}H NMR (CD_3OD)



H-1´	6.93 (s, 1H)
H-3´	7.33 (d, 1H)
H-4´	7.06 (t, 1H)
H-5´	6.77 (t, 1H)
H-6´	7.18 (d, 1H)
H-7´	4.25 (m, 2H)
H-8´	4.90 (m, 2H)

EXPERIMENTAL.

The NMR spectra were obtained on a Bruker AC 200 and AM 400 instrument. The spectra were recorded at 25° in CD_3OD using TMS as internal standard. The Fast Atom Bombardment (FAB) spectra were measured on a Kratos MS-80.

Typical Procedures.

1- (2′-4′- Dinitrophenyl) pyiridinium chloride 3a. To a solution of **1a** (1.0 mL, 12.36 mmol of pyridine recently distilled in 25 mL of dry acetone) a solution of 1-chloro- 2,4-dinitrobenzene 2 (2.49 g, 12.36 mmol in 50 mL of dry acetone) in a 150 mL round bottom flask was added. dropwise with magnetic stirring at 35°. After 8 h of reflux the reaction was completed. The remaining solvent was removed in vacuo to obtain the Zincke's salt **3a**. The crude product was recrystallized from ethanol-diethylether. Yield 90%, mp. 202-203°. Compounds **3 (b-f)** were prepared following the same procedure.

1-[2-(3-Indol) ethyl] pyridinium chloride 5a. To a solution of **3a** in a 150 mL round bottom flask at 70° (1.0 g , 3.55 mmol in 30 mL of n-butanol) a solution of tryptamine **4** (0.507 g , 3.55 mmol in 40 mL of n-butanol) was added dropwise vigorous stirring and refluxed for 12 h. Thereinafter, the solvent was removed *in vacuo* rendering a viscous residue which was dissolved in 15 mL of water, filtered and the water solution washed with dichloromethane (5x20 mL). To the water solution free of 2,4-dinitroaniline 50 mL of toluene was added. The azeotrope toluene-water was removed under reduced pressure, affording the salt **5a**. The product was recrystallized from methanol-acetone. Yield 85%; mp. 228-230°. Compounds **5 (b-f)** were prepared following the same procedure.

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