1-ALKOXYMETHYL- AND 1-ALKYLTHIOMETHYL-4-DIMETHYLAMINO-PYRIDINIUM CHLORIDES

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Abstract - $ROCH_2Cl$ or $RSCH_2Cl$ reacts with DMAP to form stable pyridinium chlorides. Reaction of these chlorides with NaOH produces the corresponding 4-pyridones. *N*-Alkoxymethylation of a free NH group of azoles is developed from 1-alkoxymethyl-4-dimethylaminopyridinium intermediates.

Dedicated to Prof. Dr. Alan R. Katritzky on the Occasion of his 65th Birthday.

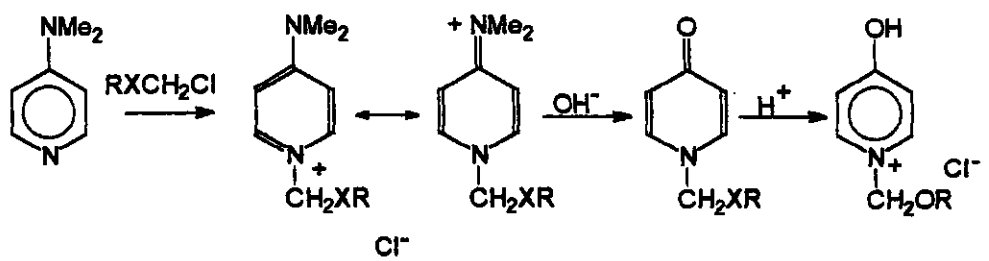
Quaternary pyridinium salts are prepared usually by an electrophilic attack by an alkyl halide at a pyridine nitrogen. Quaternization of pyridine is an example of the Menschutkin reaction. Alkylation of 4-dimethylaminopyridine (DMAP) gives ring alkylation products. DMAP, so-called "a super nucleophile" is very effective in catalyzing acylation.[1] In most such applications 1-acyl-4-dimethylaminopyridinium salts the key intermediates, have not usually been isolated. DMAP reacts vigorously with a variety of electrophiles to give quite stable products at room temperature.[2-8] These pyridinium salts demonstrate biological activity.[3,4]

We now report on the reactions of DMAP with $ROCH_2Cl$ and $RSCH_2Cl$ which have

not been described in the literature. Pyridine and their alkyl derivatives react with $ROCH_2Cl$ and $RSCH_2Cl$ by the S_N1 mechanism.[9,10] Compounds with the group $-CHR^1-OR^2$ linked to a heterocyclic nitrogen atom are of great importance for biochemistry.

Quaternization by $ROCH_2Cl$ and $RSCH_2Cl$ in DMAP. Salts derived from DMAP the following electrophiles have already been reported: RI, RBr, RCl, $ArSO_2Cl$, Ph_3CCl, ROCOCl, Ph_2CHCl, $PhCOCH_2Cl$, PhCH(COPh)Cl and $4\text{-}ClC_6H_4COCH{=}CHCl$.[2-8] We now found that a reaction occurs readily between DMAP and $ROCH_2Cl$ or $RSCH_2Cl$ to give the products (2) (Tables I-III). In general the prepared chlorides were hygroscopic. $ROCH_2Cl$ and $RSCH_2Cl$ are excellent electrophiles in this reaction but very easily hydrolised.

Oxidative deamination. *N*-Alkyl-substituted 4-pyridones such as 1-methoxymethyl-, 1-benzyloxymethyl- and 1-(2-trimethylsilylethoxymethyl)-4-pyridones were prepared by reactions of the sodium salt of 4-pyridone with appropriate electrophiles.[11,12] Now we have found that 1-alkoxymethyl- and 1-alkylthiomethyl-4-dimethylaminopyridinium chlorides (2) can be easily transformed into the corresponding 4-pyridones (3) by a new method (Scheme 1). The procedure involves treatment with aqueous alkali solution at elevated temperature which gives a very good yield.



(1) (2) (3) (4)

Scheme 1

As can be seen from Scheme 1 1-alkoxymethyl-4-pyridones (3) is easily

Table I Preparation of pyridinium chlorides and 4-pyridones

Compound	RX	Yield [%]	mp [°C]	Found [%]			Formula	Required [%]		
				C	H	N		C	H	N
2a	C_2H_5O	92	212-4	55.38	8.02	12.81	$C_{10}H_{17}N_2OCl$	55.42	7.91	12.93
2b	C_3H_7O	79		57.32	8.15	12.29	$C_{11}H_{19}N_2OCl$	57.26	8.30	12.14
2c	C_4H_9O	97	167-9	59.01	8.83	11.59	$C_{12}H_{21}N_2OCl$	58.89	8.65	11.45
2d	$C_{12}H_{25}O$	98	219-21	67.04	10.63	7.99	$C_{20}H_{37}N_2OCl$	67.29	10.45	7.85
2e	C_4H_9S	81	153-5	55.03	7.96	10.83	$C_{12}H_{21}N_2SCl$	55.26	8.12	10.74
2f	$C_6H_{13}S$	75	162-4	58.05	8.56	9.70	$C_{14}H_{25}N_2SCl$	58.21	8.72	9.70
2g	$C_{12}H_{25}S$	85	160-2	67.04	10.41	7.97	$C_{20}H_{37}N_2SCl$	67.29	10.45	7.85
3a	C_4H_9O	88	oil				$C_{10}H_{15}NO_2$			
3b	$C_9H_{19}O$	89	oil				$C_{15}H_{25}NO_2$			
3c	$C_{11}H_{23}O$	91	52-3	72.91	10.23	4.97	$C_{17}H_{29}NO_2$	73.07	10.46	5.01
3d	C_4H_9S	86	oil				$C_{10}H_{15}NOS$			
3e	$C_6H_5CH_2S$	85	oil				$C_{13}H_{13}NOS$			
4	$C_{11}H_{23}O$	95	87-90	64.32	9.80	4.57	$C_{17}H_{30}NO_2Cl$	64.64	9.57	4.43

Table II ^{1}H Nmr data[a] for preparation of pyridinium chlorides and 4-pyridones

Compound	Aromatic-H	$N^{+}CH_2$	$N(CH_3)_2$	Substituent-H
2a[b]	8.51(2H,d,*J* 8)7.15(2H,d,*J* 8)	5.58(2H,s)	3.25(6H,s)	3.54(2H,q,*J* 7)1.15(3H,t,*J* 7)
2b[b]	8.46(2H,d,*J* 8)7.12(2H,d,*J* 8)	5.55(2H,s)	3.23(6H,s)	3.44(2H,t,*J* 7)1.51(2H,m)0.85(3H,t,*J* 7)
2c[c]	8.62(2H,d,*J* 7)7.06(2H,d,*J* 7)	5.70(2H,s)	3.32(6H,s)	3.58(2H,t,*J* 6)1.55(2H,m)1.35(2H,m)0.89(3H,t,*J* 7)
2d[b]	8.46(2H,d,*J* 8)7.13(2H,d,*J* 8)	5.55(2H,s)	3.24(6H,s)	3.51(2H,t,*J* 7)1.47(2H,m)1.27(18H,m)0.88(3H,t,*J* 7)
2e[c]	8.86(2H,d,*J* 8)7.04(2H,d,*J* 8)	5.67(2H,s)	3.32(6H,s)	2.71(2H,t,*J* 7)1.54(2H,m)1.38(2H,m)0.88(3H,t,*J* 7)
2f[b]	8.51(2H,d,*J* 8)7.13(2H,d,*J* 8)	5.50(2H,s)	3.22(6H,s)	2.62(2H,t,*J* 7)1.50(2H,m)1.26(6H,m)0.86(3H,t,*J* 7)
2g[c]	8.09(2H,d,*J* 7)7.08(2H,d,*J* 7)	5.21(2H,s)	3.02(6H,s)	2.45(2H,t,*J* 7)1.43(2H,-)1.30(18H,m)0.90(3H,t,*J* 6)
3a[c]	7.42(2H,d,*J* 7)6.42(2H,d,*J* 7)	5.05(2H,s)		3.45(2H,t,*J* 5.5)1.59(2H,m)1.39(2H,m)0.93(3H,t,*J* 7)
3b[c]	7.46(2H,d,*J* 8)6.40(2H,d,*J* 8)	5.07(2H,s)		3.45(2H,t,*J* 6.5)1.60(2H,m)1.32(12H,m)0.90(3H,t,*J* 7)
3c[c]	7.41(2H,d,*J* 8)6.41(2H,d,*J* 8)	5.04(2H,s)		3.42(2H,t,*J* 6.5)1.60(2H,m)1.30(16H,m)0.90(3H,t,*J* 7)
3d[c]	7.59(2H,d,*J* 7)6.41(2H,d,*J* 7)	4.91(2H,s)		2.55(2H,t,*J* 7)1.58(2H,m)1.38(2H,m)0.91(3H,t,*J* 7)
3e[c]	7.37(7H,m)6.34(2H,d,*J* 7.5)	4.65(2H,s)		3.71(2H,s)
4[c]	8.71(2H,d,*J* 6)7.58(2H,d,*J* 6)	5.84(2H,s)	12.78(1H,OH)	3.62(2H,t,*J* 6)1.59(2H,m)1.25(16H,m)0.90(3H,t,*J* 6)

[a]Chemical shift (δ) in ppm and coupling constants (*J*) in Hz. [b]Solutions in Me_2SO-d_6. [c]Solution in $CDCl_3$.

Table III ^{13}C Nmr data[a] for preparation of pyridinum chlorides and 4-pyridones

Compound	Pyridine ring			N^+-CH_2	$N(CH_3)_2$	Substituent-C
	C-4	C-2,6	C-3,5			
2b[a]	156.3	148.4	107.3	84.7	38.6	70.3;22.0;10.2
2c[b]	156.7	141.4	107.8	85.9	40.6	70.0;31.3;19.1;13.8
2d[a]	156.4	141.4	107.3	84.8	40.0	68.5;39.8;39.5;39.2;31.3;29.0 28.72;28.66;25.4;22.1;14.0
2e[b]	156.2	142.0	107.8	59.2	40.5	31.2;30.9;21.7;13.5
2f[a]	155.9	141.4	107.6	57.6	39.8	30.6;30.4;28.7;27.6;21.9;13.8
2g[b]	156.4	141.4	107.3	59.2	40.0	29.46;29.38;29.28;29.15;28.9 28.7;28.5;22.5;14.0
3a[b]	179.4	138.8	118.6	85.1		69.1;31.33;19.2;13.8
3b[b]	179.2	138.8	118.6	85.0		69.3;31.8;29.4;29.2;29.1;25.9 22.6;14.1
3c[b]	179.3	138.7	118.6	85.1		69.4;32.0;29.6;29.56;29.4;29.3 29.2;26.0;22.7;14.2
3d[b]	178.6	139.2	118.1	57.9		30.53;30.48;21.6;13.3
3e[b]	178.7	138.9	118.4	56.4		148.8;128.7;128.6;127.6;34.7
4[b]	173.1	143.1	115.0	87.0		70.8;31.8;29.5;29.2;29.1;25.8 22.6;14.0

[a]In Me_2SO-d_6 with 39.5 ppm as reference [b]In $CDCl_3$ with 77.0 ppm as reference

transformed to 1-alkoxymethyl-4-hydroxypyridinium chlorides (4) in acidic aqueous solution.

Base-catalysed N-alkoxymethylation of a free NH group of azoles. Most *N*-alkylations of azoles involve two steps: deprotonation and nucleophilic displacement.[13-18] Azoles with N-CH_2-SR and N-CH_2-OR are known but there are described only a few 1-alkoxymethylbenzimidazole.[19-23] We now report another useful synthetic route to *N*-alkoxymethylated azoles by an *N*-alkylation using DMAP as catalyst (Scheme 2). The reactions catalytic were run in one

$$\underset{(5)}{AH} + RXCH_2Cl \xrightarrow[B]{(1)} \underset{(6)}{ACH_2XR}$$

Scheme 2

pot in basic medium at room temperature. The yields of alkoxymethylation azoles were good (Tables IV-VI).

Table IV Perparation of *N*-alkoxymethylated azoles

Azole (6)	Compound	RX	Yield [%]	mp [°C]
Imidazole	6a	C_3H_7S	85	oil
2-phenyl-	6b	C_2H_5O	71	oil
imidazole	6c	C_3H_7O	75	oil
	6d	C_4H_9O	69	oil
Benzotriazole	6e	C_4H_9O	67	oil
	6f	$C_{10}H_{21}O$	66	oil
	6g	$(CH_3)_3CCH_2O$	71	124-6
	6h	$(C_2H_5)_2CHCH_2O$	77	oil
Benzimidazole	6i	C_3H_7O	76	oil
	6j	$(C_2H_5)_2CHCH_2O$	75	oil

Table V ^{1}H Nmr data[a] for *N*-alkoxymethylated azoles

Compound	Aromatic-H	$N-CH_2$	Substituent-H
6a	7.59(1H,s)7.08(2H,s)	4.96(2H,s)	2.45(2H,t,*J* 7)1.60(2H,m)0.97(3H,t,*J* 7)
6b	7.77(2H,m)7.43(3H,m)7.10(2H,d,*J* 7)	5.18(2H,s)	3.51(2H,q,*J* 7)1.17(3H,t,*J* 8)
6c	7.60(2H,m)7.44(3H,m)7.17(1H,s)7.09(1H,s)	5.28(2H,s)	3.47(2H,t,*J* 7)1.65(2H,m)0.94(3H,t,*J* 8)
6d	7.96(1H,m)7.77(1H,m)7.46(2H,m)7.28(1H,m) 7.15(1H,s)7.02(1H,s)	5.27(2H,s)	3.50(2H,t,*J* 7)1.59(2H,m)1.39(2H,m) 0.92(3H,t,*J* 7)
6e[b]	8.13(1H,d,*J* 8)7.96(1H,d,*J* 8)7.65(1H,t,*J* 8) 7.49(1H,t,*J* 8)	6.12(2H,s)	3.49(2H,t,*J* 7)1.43(2H,m)1.23(2H,m) 0.77(3H,t,*J* 7)
6f	8.07(1H,d,*J* 9)7.69(1H,d,*J* 9)7.51(1H,t,*J* 8) 7.39(1H,t,*J* 8)	5.98(2H,s)	3.48(2H,t,*J* 7)1.51(2H,m)1.27(14H,m) 0.88(3H,t,*J* 7)
6g	8.09(1H,d,*J* 8)7.70(1H,d,*J* 8)7.52(1H,t,*J* 8) 7.42(1H,t,*J* 8)	6.00(2H,s)	3.13(2H,s)0.79(9H,s)
6h	8.06(1H,d,*J* 8)7.69(1H,d,*J* 8)7.50(1H,t,*J* 8) 7.38(1H,t,*J* 8)	5.92(2H,s)	3.37(2H,d,*J* 6)1.39(1H,m)1.26(4H,m) 0.71(6H,t,*J* 8)
6i	7.92(1H,s)7.80(1H,m)7.51(1H,m)7.30(2H,m)	5.43(2H,s)	3.31(2H,t,*J* 7)1.53(2H,m)0.83(3H,t,*J* 8)
6j	8.33(1H,s)7.81(1H,m)7.55(1H,m)7.34(2H,m)	5.55(2H,s)	3.30(2H,d,*J*6)1.39(1H,m)1.26(4H,m)0.74(6H,t,*J*8)

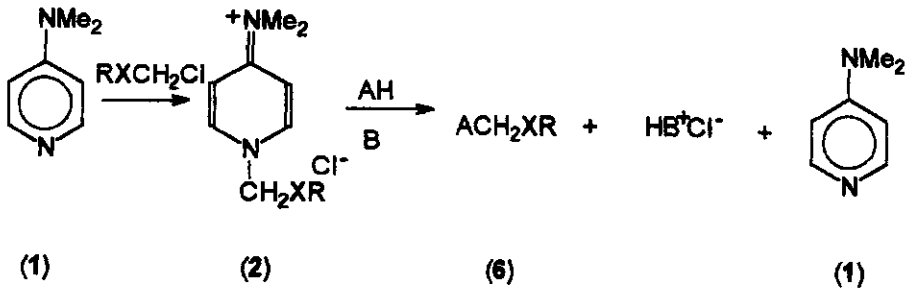
[a]Chemical shift (δ) in ppm and coupling constants (*J*) in Hz, solution in $CDCl_3$. [b]Solution in Me_2SO-d_6.

Table VI ^{13}C Nmr data[a] for *N*-alkoxymethylated azoles

Compound	Aromatic-C	$N-CH_2$	Substituent-C
6a	136.6(C-2)129.4(C-4)118.4(C-5)	47.6	32.7;21.9;13.1
6b	128.32;128.22;128.17;127.94;127.88 127.77;127.3;124.8;121.1	75.2	63.8;14.4
6c	128.88;128.6;128.17;128.12;125.5 123.1;121.4	76.0	70.7;22.7;10.6
6d	128.88;128.71;128.43;128.38; 128.29;128.1;125.54;122.42;121.	75.9	68.6;31.3;19.2;13.7
6e[b]	145.3(C-3a)119.0(C-4)124.1(C-5) 127.7(C-6)110.5(C-7)132.4(C-7a)	76.4	68.4;30.7;18.5;13.4
6f	145.9;119.5;123.4;127.3;109.6;132.3	76.9	69.2;29.2;29.0;28.9 25.6;22.4;13.8
6g	146.7;119.5;124.1;127.6;109.9;132.1	77.7	70.9;31.5;26.3
6h	146.2;119.7;124.1;127.6;109.8;132.5	77.4	71.4;40.7;23.1;10.8
6i	142.6(C-2)119.7(C-4)122.2(C-5) 123.1(C-6)110.0(C-7)	74.4	70.2;22.3;10.2
6j	142.55;119.1;122.8;123.4;110.4	75.0	70.8;40.6;22.9;10.7

[a]In $CDCl_3$ with 77.0 ppm as reference [b]In Me_2SO-d_6 with 39.5 ppm as reference

DMAP initially reacted with $RXCH_2Cl$ to give the intermediate chloride (2) which then reacted with azoles in the presence of a strong base (Scheme 3).



(1) (2) (6) (1)

Scheme 3

EXPERIMENTAL

Melting points were determined using a hot-stage microscope and are uncorrected. ^1H Nmr spectra were recorded with a Varian Model XL 300 spectrometer at 300 MHz with TMS as standard. ^{13}C Nmr spectra were recorded on the same instrument at 75 MHz. Elemental analyses were performed at the University of Poznań. Chloromethylalkyl ethers and sulfides were prepared by using general procedure and have been reported elsewhere.[24]

General procedure for the preparation of 1-alkoxymethyl-4-dimethylaminopyridinium chlorides (2a-d): A chloromethylalkyl ether (5.5 mmol) was added to DMAP (5 mmol) in anhydrous $CHCl_3$ (50 ml), and the mixture was stirred and heated under reflux for 5 h. The solvent was removed under reduced pressure. The residue was extracted with hexane using a Soxhlet apparatus and recrystallized from toluene.

General procedure for the preparation of 1-alkylthiomethyl-4-dimethylaminopyridinium chlorides (2e-g): These products were obtained by the above procedure with chloromethylalkyl sulfides. They were isolated from the crude mixture by column chromatography on silica gel using ethanol as the eluent.

General procedure for the preparation of 1-alkoxymethyl-4-pyridones (3): Aqueous NaOH (1 M,10 ml) was added to the chlorids (2) (5 mmol),which was then heated on a waterbath. After 1 h the solution was cooled and acidified with HCl to pH 6.5. The product was extracted with chloroform, dried over Na_2SO_4 and the solvent was evaporated. An analytical sample was prepared by recrystallization from acetone.

4-Hydroxy-1-undecyloxymethylpyridinium chloride (4): 1-Undecyloxymethyl-4-pyridone (3 mmol) was dissolved in 4% aqueous hydrochloric acid (10 ml) at 70°C. The mixture was cooled to 0°C and extracted with chloroform. The chloroform layer was separated and dried over $MgSO_4$.Rotoevaporation of the solvent gave a solid which after recrystallization from acetone gave 4.

General procedure for preparation of *N*-substituted azoles (6): Azole (0.02 mol), chloromethylalkyl ether or sulfide (0.21 mol), DMAP (0.86 mmol, 0.11g) an triethylamine (0.05 mol, 7 ml) were dissolved in CH_2Cl_2 (40 ml). The mixture was allowed to stand at room temperatuer for 24 h. Water and then 10 % aqueous sodium carbonate were successively added to the reaction mixture until evolution of carbon dioxide ceased, and the aqueous layer was made alkaline (litmus). The organic layer was extracted with chloroform, dried over Na_2SO_4 and the solvent was removed to give a colourless oil which extracted with hexane and recrystallized from methanol.

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