

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*-Alkoxy methylation 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.

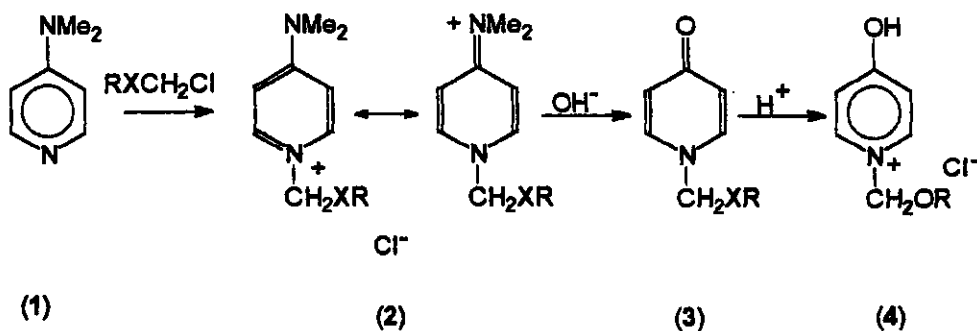
Quaternary pyridinium salts are prepared usually by an electrophilic attack by an alkyl halide at a pyridine nitrogen. Quaternization of pyridine is an example of the Menshutkin reaction. Alkylation of 4-dimethylaminopyridine (DMAP) gives ring alkylation products. DMAP, so-called "a super nucleophile" 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 $\text{S}_{\text{N}}1$ mechanism.^{9,10} Compounds with the group $-\text{CHR}^1-\text{OR}^2$ 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 , ROCOC , Ph_2CHCl , PhCOCH_2Cl , $\text{PhCH}(\text{COPh})\text{Cl}$ and $4\text{-ClC}_6\text{H}_4\text{COCH=CHCl}$.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 hydrolysed.

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.



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 ₂ H ₅ O	92	212-4	55.38	8.02	12.81	C ₁₀ H ₁₇ N ₂ OCl	55.42	7.91	12.93
2b	C ₃ H ₇ O	79		57.32	8.15	12.29	C ₁₁ H ₁₉ N ₂ OCl	57.26	8.30	12.14
2c	C ₄ H ₉ O	97	167-9	59.01	8.83	11.59	C ₁₂ H ₂₁ N ₂ OCl	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 ₂ OCl	67.29	10.45	7.85
2e	C ₄ H ₉ S	81	153-5	55.03	7.96	10.83	C ₁₂ H ₂₁ N ₂ SCl	55.26	8.12	10.74
2f	C ₆ H ₁₃ S	75	162-4	58.05	8.56	9.70	C ₁₄ H ₂₅ N ₂ SCl	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 ₂ SCl	67.29	10.45	7.85
3a	C ₄ H ₉ O	88	oil				C ₁₀ H ₁₅ NO ₂			
3b	C ₉ H 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 ₄ H ₉ S	86	oil				C ₁₀ H ₁₅ NOS			
3e	C ₆ H ₅ CH ₂ S	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 ₂ Cl	64.64	9.57	4.43

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

Compound	Aromatic-H	$\text{N}^+\text{-CH}_2$	$\text{N}(\text{CH}_3)_2$	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)

^aChemical shift (δ) in ppm and coupling constants (J) in Hz. ^bSolutions in $\text{Me}_2\text{SO}-d_6$. ^cSolution in CDCl_3 .

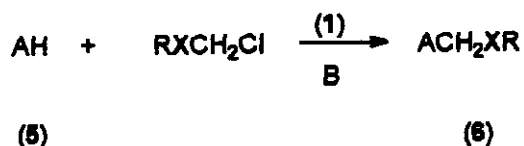
Table III ^{13}C Nmr data^a for preparation of pyridinium chlorides and 4-pyridones

Compound	Pyridine ring					Substituent-C
	C-4	C-2,6	C-3,5	N^+-CH_2	$\text{N}(\text{CH}_3)_2$	
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

^aIn $\text{Me}_2\text{SO}-d_6$ with 39.5 ppm as reference ^bIn 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-CH₂-SR and N-CH₂-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



Scheme 2

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

Table IV Perparation of N-alkoxymethylated azoles

Azole (6)	Compound	RX	Yield [%]	mp [°C]
Imidazole	6a	C ₃ H ₇ S	85	oil
2-phenyl- imidazole	6b	C ₂ H ₅ O	71	oil
	6c	C ₃ H ₇ O	75	oil
	6d	C ₄ H ₉ O	69	oil
Benzotriazole	6e	C ₄ H ₉ O	67	oil
	6f	C ₁₀ H ₂₁ O	66	oil
	6g	(CH ₃) ₃ CCH ₂ O	71	124-6
	6h	(C ₂ H ₅) ₂ CHCH ₂ O	77	oil
Benzimidazole	6i	C ₃ H ₇ O	76	oil
	6j	(C ₂ H ₅) ₂ CHCH ₂ O	75	oil

Table V ^1H 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)	5.27(2H,s)	3.50(2H,t,J 7)1.59(2H,m)1.39(2H,m)
	7.15(1H,s)7.02(1H,s)		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)	6.12(2H,s)	3.49(2H,t,J 7)1.43(2H,m)1.23(2H,m)
	7.49(1H,t,J 8)		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)	5.98(2H,s)	3.48(2H,t,J 7)1.51(2H,m)1.27(14H,m)
	7.39(1H,t,J 8)		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)	6.00(2H,s)	3.13(2H,s)0.79(9H,s)
	7.42(1H,t,J 8)		
6h	8.06(1H,d,J 8)7.69(1H,d,J 8)7.50(1H,t,J 8)	5.92(2H,s)	3.37(2H,d,J 6)1.39(1H,m)1.26(4H,m)
	7.38(1H,t,J 8)		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)

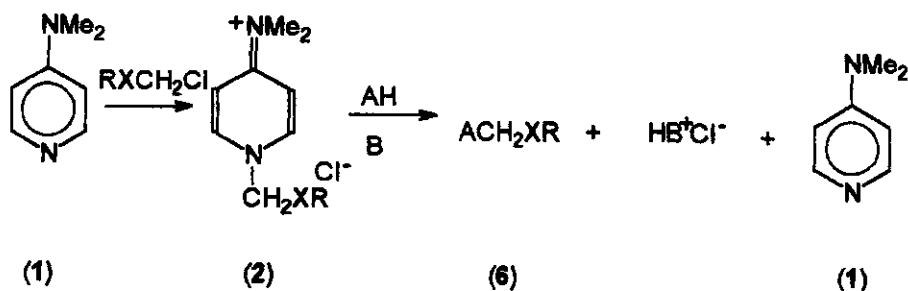
^aChemical shift (δ) in ppm and coupling constants (*J*) in Hz, solution in CDCl_3 . ^bSolution in $\text{Me}_2\text{SO}-d_6$.

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

^aIn CDCl_3 with 77.0 ppm as reference ^bIn $\text{Me}_2\text{SO}-d_6$ 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).



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) and triethylamine (0.05 mol, 7 ml) were dissolved in CH_2Cl_2 (40 ml). The mixture was allowed to stand at room temperature 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 was extracted with hexane and recrystallized from methanol.

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