Scientific paper

Alkylation of Amines with Alcohols and Carboxylate Esters: the Origin of *N*-Methylpyridinium Cations in the Synthesis of Pyridine-Molybdate(V) Complexes

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Dedicated to the memory of professor Ljubo Golič

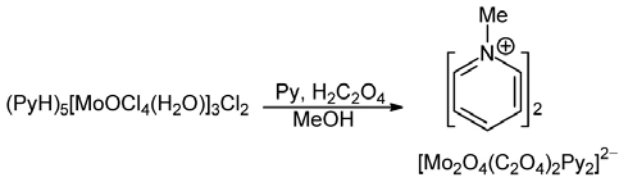
Abstract

The formation of *N*-methylpyridinium salts in the solvothermal synthesis of molybdenum(V) complexes with oxalate in methanol in the presence of pyridine was investigated. It was found that dimethyl oxalate is formed first, which can thereupon alkylate pyridine. Pyridine reacts with a variety of esters, forming *N*-alkylpyridinium salts. Most reactive in this respect are sulfonates, whereas among carboxylates suitable esters are trifluoroacetates and oxalates. The reactivity of esters is proportional to the *K*a of the parent acid. Primary and secondary amines attack an acyl carbon rather than alkyl one, thus forming amides. Sulfonate esters are attacked by all types of amines exclusively at the alkyl carbon.

Keywords: Alkylation, amines, alcohols, esters, *N*-methylpyridinium

1. Introduction

A solvothermal synthesis of several molybdenum(V) complexes with oxalate starting from $(PyH)_5MoOCl_4[(H_2O)]_3Cl_2$ at approx. 100 °C in pyridine-methanol was accompanied by the formation of *N*-methylpyridinium cations.[1] A typical example:



In a related reaction with squaric acid in ethanol, the formation of the corresponding *N*-ethylpyridinium cations was observed.[2]

Direct alkylation of pyridine with methanol does not seem probable, although some examples of alkylation of aniline with alcohols are known.[3] In these cases, the reaction is most probably a redox process, taking place in the presence of Raney nickel and its mechanism is not known. Hydroxy group of an alcohol is a very poor leaving group and nucleophillic substitution at an adjacent carbon atom is rarely feasible. Transformation of hydroxy group to a suitable derivative or activation by acid catalysis is generally necessary.[4] The unusual formation of *N*-methylpyridinium cations stimulated us to carry out a more detailed investigation of this reaction.

2. Results and Discussion

At first, a catalytic role of molybdenum was assumed, but it was later disproved as the reaction took place also in mixtures containing no molybdenum. On the contrary, the role of the acid was crucial. After heating mixtures of pyridine, methanol and acid for 5 days at 105 °C in sealed ampoules, the following results were obtained (Table 1).

Besides methanol, other alcohols were observed to alkylate pyridine. In the pyridine-alcohol mixtures in the presence of trifluoroacetic acid, *N*-alkylpyridinium salts are also obtained with other primary aliphatic alcohols (EtOH, PrOH), although in somewhat lower yields. Pro-

Table 1. Yields of *N*-Methylpyridinium Salts in Methanol-Pyridine in the Presence of an Acid[a]

Acid	Yield of *N*-MePy$^+$/%[b]
none	0
oxalic dihydrate	88
methanesulfonic	22
tetrafluoroboric	0
trifluoroacetic	100

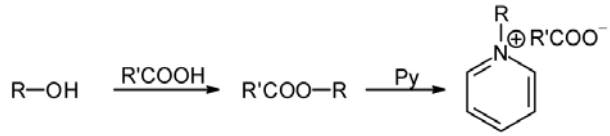
[a] 0.67 mL of a mixture of methanol and pyridine (1:1 v/v) and 2.0 mmol of an acid was kept 5 days at 105 °C in a sealed ampoule. [b] Yield based on the starting amount of the acid. Determined by ^{1}H NMR.

pan-2-ol reacts with pyridine with very low conversion and with *tert*-butanol no reaction takes place at all. The reactivity of benzyl alcohol and particularly 4-methoxybenzyl alcohol is higher and comparable to that of methanol. The reaction takes place in various solvents, particularly well in polar aprotic ones, such as DMSO, DMF and acetonitrile.

Measurements of the rates of alkylation of pyridine with 4-methoxybenzyl alcohol in the presence of methanesulfonic acid in DMSO-d_6 at 110 °C exhibit complex kinetics, thus indicating a complex, most probably multistep reaction. An interesting fact, emerging from these measurements, is that the rate increases with the concentration of the acid even in the case it exceeds the concentration of pyridine. At first it seems strange that pyridine would be a reactive species in a medium containing an excess of a strong acid. Considering the ionization constants of sulfonic acids and pyridine in aprotic solvents such as DMSO (p*K*a in DMSO at 25°C: $MeSO_3H$ ~1.6; TsOH ~1; PyH^+ ~3.5)[5] it becomes clear, that the mixture of pyridine and methanesulfonic or toluenesulfonic acid in DMSO or similar solvent is only partially ionized, particularly at elevated temperatures. On the other hand, triethylamine does not react with alcohols under similar conditions. Triethylamine (p*K*a(Et_3NH^+) = 9.0 in DMSO at 25 °C) is a stronger base and virtually completely protonated.[5] The probable candidate for the reacting species thus remains pyridine.

A measurement of the substituent effect for the reaction of substituted benzyl alcohols with pyridine in the presence of trifluoroacetic acid exhibited a fairly good Hammett correlation ($r^2 = 0.98$) with $\rho = -2.7$. A negative ρ would point to the appearance of a positive charge on benzylic C atom in the transition state, i.e. an S_N1 mechanism. If this were true, tertiary alcohols are expected to be more reactive than primary, but this is not the case. Direct displacement of the OH group in the alcohol by the amine in an S_N2 process would exhibit a positive value of ρ. The negative sign of the Hammett ρ, as well as a non-single order kinetics are most probably a result of a complex, multistep reaction, most likely the ester formation in the first step which subsequently reacts with pyridine.[6]

When 1.0 mmol of oxalic acid was heated in methanol under reflux for 6 h it was completely transformed into dimethyl oxalate. To this ester 2 mmol of pyridine and 2 mL of acetonitrile were added and the mixture was heated under reflux for several hours. After evaporation of the solvent, NMR showed a substantial amount of *N*-methylpyridinium cation in the reaction mixture. Obviously, the transformation of alcohol to *N*-alkylpyridinium salt proceeds via ester, followed by its reaction with pyridine.



The reaction of amines with esters is well known. It is usually a slow reaction in which amine preferentially attacks the acyl carbon in the molecule of the ester, forming an amide.[7] The attack on the alkyl carbon is known for esters of strong acids (e.g. sulfuric, various sulfonic acids and especially trifluoromethanesulfonic), which are widely used as alkylating agents for amines and other nucleophiles.[8] Carboxylate esters are less reactive and simple carboxylates are apparently not used for this purpose. The exceptions, which are reactive enough to make this reaction synthetically useful, are trifluoroacetates and oxalates. Esters of these types react with aliphatic amines yielding the corresponding amides in few minutes or hours at room temperature or under reflux.[9]

To establish the reactivity of various sulfonates and carboxylates toward pyridine, we have measured the reactivity of some esters in competition kinetics experiments (Table 2, Figure 1). Most reactive are sulfonates, particularly triflate, which gave with pyridine in mixture with benzyl trifluoroacetate, exclusively *N*-methylpyridinium

Table 2: Relative Reactivity of Esters in the Reaction with Pyridine in MeCN[a]

Ester	Relative reactivity	pKa[b]
MeOTf[c]	>10^3	2.6
MeOTs	52	8.0
EtOTs	1.8	
i-PrOTs	0.35	
$MeOSO_2Me$	15	10.0
BnOTFA[d]	1	12.7
MeOTFA	0.46	
Me_2Ox[e]	0.086f	14.5
Me_2Mal[g]	0.0026	15.3
MeOAc	– [h]	22.3

[a] 0.5 mmol of pyridine, 0.5 mmol of each of ester, 1 mL MeCN, reflux or ampoule at 80 °C. [b] pKa of the corresponding acid in acetonitrile.[4] [c] Triflate. [d] Trifluoroacetate. [e] Oxalate. [f] DMSO-d_6, 60 °C. [g] Malonate. [h] Immeasurably low conversion compared to BnOTFA.

cations (no traces of *N*-benzylpyridinium could be detected in the reaction mixture). Among carboxylates, the highest reactivity was exhibited by trifluoroacetates, followed by oxalates and malonates. It can be concluded from the results presented in Table 2 and Figure 1 that the reactivity of esters is proportional to the acidity of the parent acid. The expected rate for simple carboxylates (e.g. acetate) is too low to allow a measurement in a competitive kinetic experiment with methyl or benzyl trifluoroacetate and the experimental result confirms the expectation.

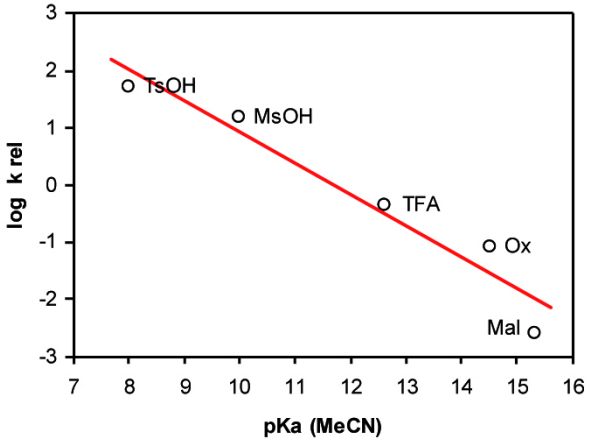
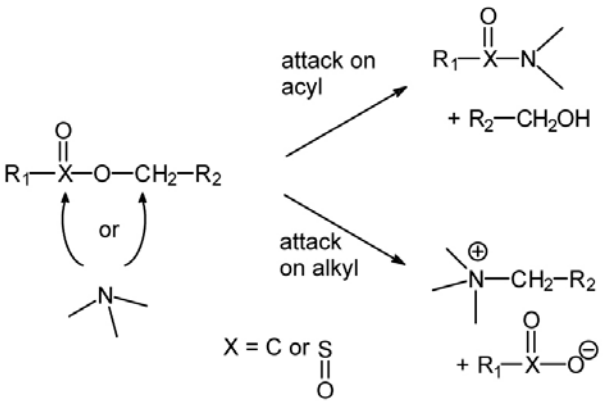
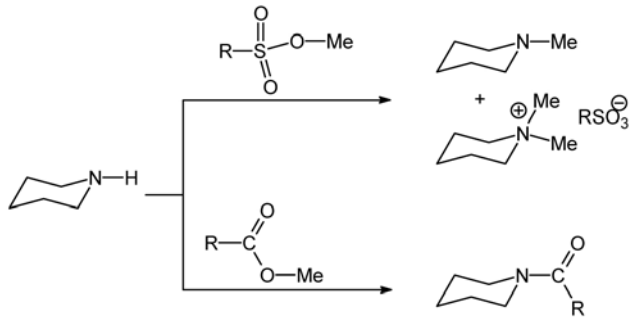


Figure 1. Plot of log relative reactivity of methyl esters versus the p*K*a of the parent acid for the reaction of esters with pyridine in acetonitrile.

In a molecule of an ester there are two reactive sites, namely acyl carbon (or other atom, e.g. sulfur) and alkyl carbon atom. Attack of an amine on one of these two sites leads to two different products. Intuitively, one would expect the attack of the amine on the acyl moiety to be favored, at least in the case of primary and secondary amines. Tertiary amines yield an unstable cationic derivative with quaternized nitrogen. Pyridine, being a tertiary amine, hence yields a stable product only upon attack on alkyl carbon. The result is an exclusive alkylation of pyridine. The question appears what kind of products would be obtained by the reaction of primary and secondary amines with different esters.



Piperidine reacts with methyl methanesulfonate yielding a mixture of *N*-methylpiperidine and *N*,*N*-dimethylpiperidinium salt. No products of the attack on the sulfur atom were detected. On the other hand, with methyl trifluoroacetate and dimethyl oxalate, the exclusive products were *N*-acylpiperidines.



Thermochemical calculations for the reaction of dimethylamine with methyl acetate, based on enthalpies of formation of reactants and products in liquid phase, are also in agreement with the experiment.[10] The reaction enthalpy for the attack of amine at acyl carbon is by 9.4 kJ mol^{-1} more exothermic than that for the attack at the alkyl carbon. Thermochemical data for the corresponding sulfonates are unfortunately not available.

In a preparative experiment, in which methanol and pyridine with an excess trifluoroacetic acid were heated 5 days at 100 °C in a sealed tube, pure *N*-methylpyridinium trifluoroacetate was formed in a quantitative yield. The reaction might find a practical application, since the alkylation is performed with the use of an alcohol rather than less-readily available or more expensive ester or other derivative. The reaction indeed requires higher temperatures, however in industrial production higher temperatures and/or pressures do not represent a major obstacle. The product of the above mentioned reaction is an ionic liquid, whose properties and applicability are still to be explored.

3. Conclusions

Tertiary amines can be alkylated by some carboxylic esters. The reactivity of esters is proportional to the acidity of the parent acid and the esters; most appropriate for this purpose are trifluoroacetates and oxalates. The nature of the alkyl carbon is also important; most reactive are esters of primary alcohols, especially methyl and benzyl.

Alcohols, e.g. methanol or benzyl alcohol in the presence of a suitable acid, such as oxalic, trifluoroacetic or sulfonic acids, can also be used for the alkylation of pyridine, although the reaction is rather slow. In such a case, the ester is formed first which, in turn, reacts with the amine. With the choice of a suitable alcohol and acid this reaction could be also used preparatively.

Tertiary amines exclusively attack alkyl carbon in the carboxylate ester molecule. Primary and secondary amines attack acyl carbon, forming amides. With sulfonates, the products of the attack at the alkyl carbon are formed exclusively, regardless of the type of the amine.

4. Experimental Section

Chemicals were used as purchased, NMR spectra were measured on 300 MHz instrument, Bruker Avance 300 DPX, chemical shifts (ppm) are reported relative to tetramethylsilane standard. Benzyl trifluoroacetate[11] and isopropyl *para*-toluenesulfonate[12] were synthesized by literature procedures.

Measurement of relative rates for the reaction of pyridine with substituted benzyl alcohols. 1.00 mL of a solution of methanol (1.00 mol L^{-1}), trifluoroacetic acid (0.50 mol L^{-1}) and pyridine (0.50 mol L^{-1}) in DMSO was placed in an ampoule and 1.00 mmol of a substituted benzyl alcohol (H, 4-MeO, 4-Me, 4-F, 4-Cl, 3-Cl) was added. Ampoules were sealed and heated for 48 h at 105 °C. Reaction mixtures were diluted with DMSO-d_6 and analyzed by ^{1}H NMR and the relative rates calculated from the ratio of integrals of methyl and benzyl protons in the *N*-alkylpyridinium cations, assuming 2nd order kinetics.

Measurement of relative rates for the reaction of pyridine with esters. In a typical experiment, 135.3 mg (0.662 mmol) of benzyl trifluoroacetate, 78.7 mg (0.661 mmol) of dimethyl oxalate and 54.1 mg (0.68 mmol) of pyridine was dissolved in 2 mL of acetonitrile and heated for 6 h under reflux. The reaction mixture was evaporated under reduced pressure and analyzed by ^{1}H NMR. Relative rates were calculated from the ratio of integrals of methyl and benzyl protons in the *N*-alkylpyridinium cations, assuming 2nd order kinetics. In cases of volatile esters (e.g. methyl trifluoroacetate), the reaction mixtures were heated under similar conditions in sealed ampoules and the composition of the reaction mixtures measured by ^{1}H NMR without evaporation of the solvent.

Reaction of methyl *para*-toluenesulfonate with pyridine. A mixture of 186 mg (1.0 mmol) of methyl *para*-toluenesulfonate, 87 mg (1.1 mmol) of pyridine and 1 mL of acetonitrile was heated for 3 h under reflux. Reaction mixture was cooled and diluted with a few mL of diethyl ether. The precipitated white crystalline *N*-methylpyridinium *para*-toluenesulfonate was filtered with suction, yield 246 mg (93%), mp. 132–137 °C (lit.[13] 138–139 °C). ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 4.35 (s, 3H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 8.11 (t, *J* = 7.0 Hz, 2H), 8.56 (t, *J* = 7.8 Hz, 1H), 8.98 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 47.9 (CH_3), 125.4 (CH), 127.6 (CH), 128.0 (CH), 137.6 (C), 145.0 (CH), 145.5 (CH), 145.7 (C).

Reaction of methyl trifluoroacetate with piperidine. Into a conical-bottom vial, 86 mg (1.0 mmol) of piperidine, 1.0 mL of hexane and 140 mg (1.1 mmol) of methyl trifluoroacetate was placed at r.t. After 1 h, the solvent was evaporated under reduced pressure and 174 mg of colorless liquid remained. GC-MS and NMR analyses showed a formation of *N*-trifluoroacetylpiperidine[14] as an oil in 96% yield. ^{1}H NMR ($CDCl_3$) δ 1.60–1.74 (m, 6H), 3.53 (m, 2H), 3.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 25.5 (CH_2), 26.4 (CH_2), 44.7 (CH_2), 46.9 (q, *J* = 3.5 Hz, CH_2), 116.8 (q, *J* = 288.0 Hz), 155.4 (q, *J* = 35.2 Hz). MS *m/z* (%) 181 (70), 166 (18), 152 (17), 140 (23), 112 (60), 84 (15), 69 (100), 56 (34), 41 (52).

Reaction of dimethyl oxalate with piperidine. A mixture of 118 mg (1.0 mmol) of dimethyl oxalate, 94 mg (1.1 mmol) of piperidine and 1 mL of acetonitrile was left for 24 h at r.t. The solvent was evaporated under reduced pressure and 166 mg (97%) of colorless oil was isolated, which was shown by NMR to be almost pure *N*-(methoxyoxalyl)piperidine.[15]

Reaction of methyl methanesulfonate with piperidine. 110 mg (1.0 mmol) of methyl methanesulfonate and 85 mg (1.0 mmol) of piperidine was disolved in 1.0 mL of acetonitrile in a conical-bottom vial. The mixture was allowed to stand overnight at r.t. and analyzed in the following manner: (a) 0.1 mL of the mixture was dissolved in diethyl ether and treated with aqueous sodium hydroxide. The ether layer was analyzed by GC, which showed *N*-methylpiperidine as the only product, together with traces of unreacted ester. (b) 0.1 mL of the reaction mixture was evaporated under reduced pressure, the solid residue dissolved in DMSO-d_6 and analyzed by NMR. (c) To the 0.1 mL of the reaction mixture 10 mg of sodium hydroxide, dissolved in a minute amount of water, was added. The mixture was evaporated under reduced pressure and the residue analyzed by NMR.

The ^{1}H NMR spectrum (DMSO-d_6) of the sample (c) exhibited one singlet with δ 3.05 (6H, NMe_2), along with a triplet at 3.30 (4H, H-2, H-6) and multiplets (6H, H-3–H-5) for piperidine protons as well as a singlet at 2.36 ($MeSO_3^-$).[16] The evaporated sample (c) thus contained only the *N*,*N*-dimethylpiperidinium methanesulfonate. The spectrum of the sample (b) contained an additional set of signals corresponding to *N*-methylpiperidinium cation: 2.74 (s, 3H, Me), 3.01 (m, 4H, H-2, H-6) and multiplets for H-3–H-5. The ratio NMe/NMe_2 calculated from the spectra was 0.69 : 1.

Reaction of pyridine with methanol in the presence of trifluoroacetic acid. A mixture of 0.395 g (5.0 mmol) of pyridine and 0.855 g (7.5 mmol) of trifluoroace-

tic acid in 5 mL of methanol was heated in a sealed ampule at 100 °C.[17] After 5 days, the solvent and excess acid were evaporated under reduced pressure and 1.12 g (100%, calcd as a monohydrate) of a colorless oil was obtained, which was shown by NMR to be pure *N*-methylpyridinium trifluoroacetate,[18] containing probably 1 equivalent of water. ^{1}H NMR (D_2O) δ 4.38 (s, 3H, Me), 8.03 (m, 2H, H-3, H-5), 8.52 (t, *J* = 7.9 Hz, 1H, H-4), 8.76 (d, *J* = 5.9 Hz, 2H, H-2, H-6). ^{13}C NMR (D_2O) δ 48.7 (Me), 116.9 (q, $^1J_{C\text{-}F}$ = 291.7 Hz, CF_3), 128.6 (C-3, C-5), 145.6 (C-2, C-6), 145.9 (C-4), 163.3 (CO). IR cm^{-1} 3424 (br), 1689. Elemental analysis: Calcd for $C_8H_8F_3NO_2 \cdot H_2O$: C, 42.67; H, 4.48; N, 6.22. Found: C, 42.53; H, 4.52; N, 6.15.

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Povzetek

Raziskali smo nastanek *N*-metilpiridinijevih soli, nastalih pri solvotermalni sintezi molibdenovih(V) kompleksov z oksalatom v metanolu v prisotnosti piridina. Ugotovili smo, da najprej nastane dimetil oksalat, ki potem reagira s piridinom. Piridin lahko reagira z različnimi estri, pri čemer nastanejo *N*-alkilpiridinijeve soli. Najbolj reaktivni so različni sulfonati, med karboksilati pa trifluoroacetati in oksalati. Reaktivnost estrov je sorazmerna s *K*a kisline, iz katere je ester nastal. Primarni in sekundarni amini pri reakciji z estri napadejo acilni ogljikov atom, kar daje ustrezne amide. Sulfonati pa reagirajo z vsemi vrstami aminov na alkilnem ogljikovem atomu.