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Methylation of Protomeric Ambident Nucleophiles with Methyl Fluorosulfonate: A Regiospecific Reaction

Peter Beak,* Jae-keun Lee, and B. Gary McKinnie

Roger Adams Laboratory, University of Illinois at Urbana-Champaign, Urbana Illinois 61801

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Methylation of 15 protomeric ambident nucleophiles with methyl fluorosulfonate has been found to occur regiospecifically at the heteroatom remote from the mobile proton. In most cases the fluorosulfonate salts thus obtained can be isolated, identified by ^{1}H NMR spectroscopy, and converted to the neutral methylated derivatives by aqueous base. The compounds studied include five of the nine possible systems X=YZH ⇄ HXY=Z, in which Y is carbon and X and Z are oxygen, nitrogen, and/or sulfur. In 12 cases the reaction is synthetically useful, although it is sometimes necessary to remove the excess methyl fluorosulfonate prior to treatment with base. Three cases give mixtures of methylated products, a result established for the case of 2-pyridone to be due to proton transfer from the initial regiospecifically formed salt.

The alkylation of protomeric tautomers is of interest in a wide variety of chemical and biochemical studies.[1,2] More detailed understanding and better control of such reactions would be useful.

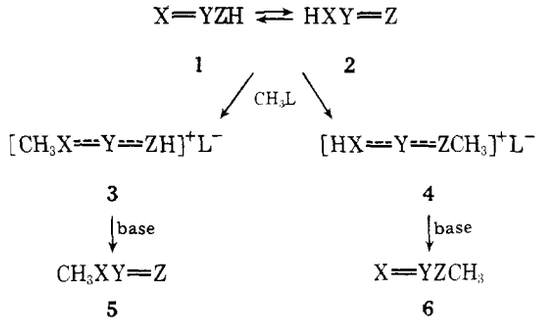
A generalized case is shown in Scheme I for methylation of the ambident protomeric nucleophiles **1** and **2** to give the salts **3** and **4**. Reaction of **3** and **4** with a base would provide the methylated isomers **5** and **6**. It is well-recognized that there is not necessarily any correspondence between the relative amounts of the protomeric reactants, **1** and **2**, and the isomeric products, **3** and **4** or **5** and **6**. Recent analyses of such reactions have been appropriately cautious.[1,3-6]

If X and Z are heteroatoms, proton transfer would be expected to be several orders of magnitude more rapid than methylation, and the relative rates of formation of **3** and **4** would then be determined solely by the relative transition-state energies leading to these cations.[7,8] If **3** and **4** are stable under the conditions of their formation, subsequent deprotonation would provide **5** and **6** in a ratio which has been determined by the relative transition-state energies leading to **3** and **4**. Reaction profiles showing product control under the Curtin–Hammett principle[7] in which the ratios of **3** and **4** could be greater or less than one are illustrated in Figure 1.

Nonetheless, the possibility does exist that there might be a circumstantial relationship between the ground-state energies of **1** and **2** and the transition states for their alkylation. For example, the bonding features which make **1** of lower energy than **2** could persist in the respective transition states (Figure 1a). In that case, cation **3** would be predominant and the subsequent isomer **5**, in which the alkyl group is attached to the heteroatom remote from the mobile proton in the major tautomer, would be produced after proton removal by a base. While this guide would be at best a *qualitative* indication of the position of alkylation, it is interesting that if the transition-state energy difference were >2 kcal/mol (at 25 °C) an effectively regiospecific alkylation of the tautomeric system would result. Formally the proton would appear to be a directing group if the profile of Figure 1a were followed. In fact, a number of cases exist which follow such a qualitative course.[1,3,5,9]

It should be emphasized that quantitative correlation of the

Scheme I



tautomeric ratio and the ratio of alkylated products is neither expected[6,7] nor observed, as careful studies of 5-nitroimidazole by Ridd[3] and of 3-hydroxyisothiazole by Crow[4] have shown. Moreover, our above suggestion of possible qualitative generality for the reaction path of Figure 1a might well be considered naive by the following argument. If isomers **1** and **2** undergo protonation to give a common product, the difference in the ground-state energies of **1** and **2** can be considered to reflect the difference in basicity of the atoms X and Z. If that basicity difference reflects a parallel difference in the nucleophilicity of these atoms in the respective transition states for alkylation, the suggested regiospecificity would not be observed.[3,10] On a practical level, the assumptions that the salts **3** and **4** will be stable and that the neutral tautomers will be reactive nucleophiles might not be valid.

In order to explore the possibility that the pathway of Figure 1a could be followed for more than a few cases, we have investigated the reactions of 15 protomeric ambident nucleophiles and methyl fluorosulfonate.[11] This highly reactive readily soluble methylating agent was chosen to maximize the possibilities that transition states would reflect the ground-state energies of the tautomers and that the reaction could be driven, and the initially formed salts stabilized, by precipitation from a nonpolar solution. In general, the regiospecific course suggested by Figure 1a is followed, although synthetic complications arise due to the instabilities of the initially formed salts to the reaction conditions for three cases.[12-14]

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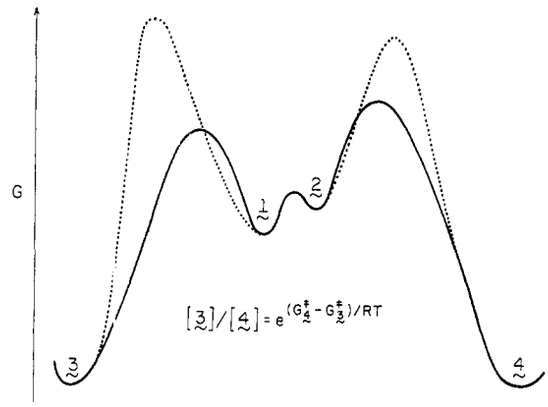


Figure 1. Illustrative reaction profiles for Scheme I. (a) Solid line: the transition-state energy difference is of the same sign as the ground-state energy difference; [3]/[4] > 1. (b) Dotted line: the transition-state energy difference is of opposite sign to the ground-state energy difference; [3]/[4] < 1.

Results and Discussion

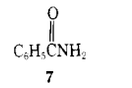
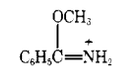
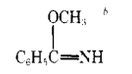
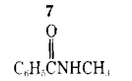
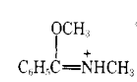
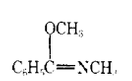
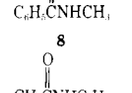
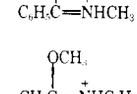
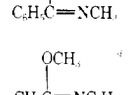
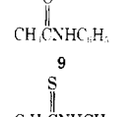
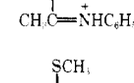
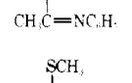
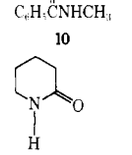
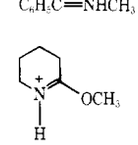
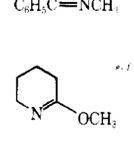
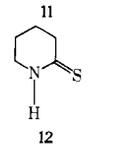
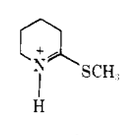
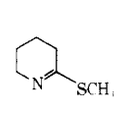
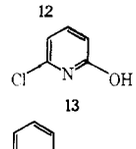
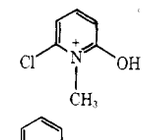
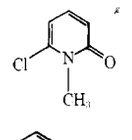
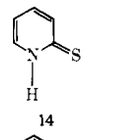
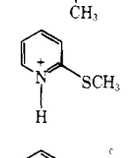
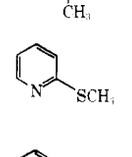
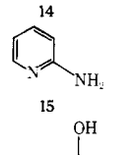
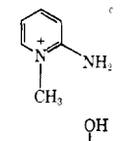
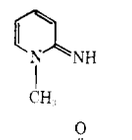
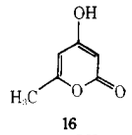
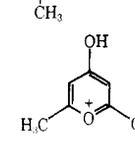
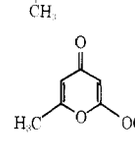
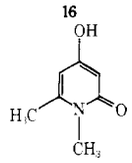
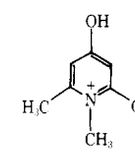
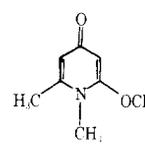
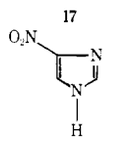
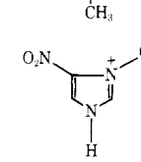
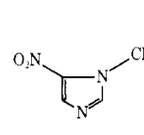
If the major product of reaction of a series of ambident protomeric tautomers with methyl fluorosulfonate is the isomer in which the methyl group is bonded to the heteroatom remote from the mobile proton in the major tautomer, then the process of Figure 1a is followed qualitatively. In effect, for the conversion shown in Scheme I, the more stable tautomer **1** would be converted to **5** via **3**; such a regiospecific conversion could be synthetically valuable. The nucleophiles **7–18** shown in Table I follow the prescribed course for reactions at ambient temperature in <2 h. These compounds cover five of the nine possible cases representable by **1** and **2** in which X and Z are oxygen, nitrogen, and/or sulfur and Y is carbon. A second-order rate constant for the disappearance of **8** and the appearance of the corresponding fluorosulfonate of 2.9 (±0.8) $\times 10^{-4}$ M^{-1} s^{-1} was measured by ^1H NMR. The intermediate salts can be isolated and were spectroscopically characterized (Table IV) for seven of the cases in Table I. None of the isomers which would result from methylation at the heteroatom which bears the proton in the major tautomer is detected in these cases. The yields of alkylated products (Table I) are usually high and generally superior to those of alternative procedures. The fact that the less stable, and therefore prospectively more reactive, isomer of **5** ⇆ **6** is produced readily and in high yield suggests that these reactions may be useful for sequences in which further conversions are important.

The conversions of the amides and thioamides **7–12** and **14** to the corresponding imidates by reactive alkylating agents are well precedented.[9] In fact Julia and Ryan have reported such conversions with methyl fluorosulfonate.[9i] The reactions of 2-aminopyridine (**15**) and 5-nitroimidazole (**18**) also follow previously known courses. Comparison of **13, 14,** and **15** suggests that the presence of a pyridine ring does not affect the outcome of the reaction.[15] Precipitation of the intermediate salt occurs in 6 of the 12 cases shown in Table I so that driving force does not appear to be required for successful reaction.

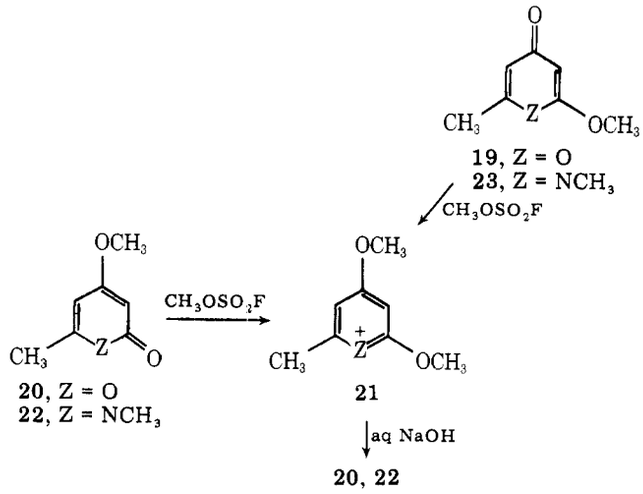
The conversion of 4-hydroxy-6-methyl-2-pyrone (**16**) to 2-methoxy-6-methyl-4-pyrone (**19**) in 98% yield provides our best example of the value of this procedure in convenience and yields. Alternative conversions, which involve reaction of **16** with diazomethane followed by separation of **19** from **20**[16] or blocking of the hydroxyl function of **16** with the trimethylsilyl group followed by methylation,[17] provide **19** in ~20% yield.

The possibility that the reactions of **16** and 4-hydroxy-1,6-dimethyl-2-pyridone (**17**) proceeded by formation of the polymethylated salts **21** was discounted in two ways. In the first place, the precipitated salts can be isolated and characterized by ^1H NMR as monomethylated species (Table IV). Secondly, formation of the dialkylated salts **21** from the respective isomeric pairs **19** ⇆ **20** and **22** ⇆ **23** followed by basic hydrolysis gives the products **20** and **22**, respectively.

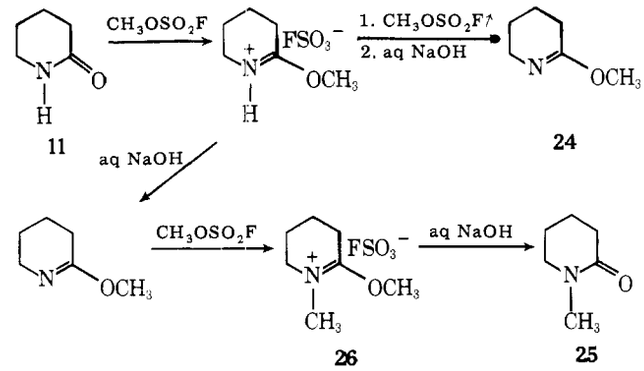
Table I. Reactions of Protomeric Tautomers with Methyl Fluorosulfonate Which Provide Products of Methylation at the Heteroatom Remote from the Mobile Proton

Reactant	Registry no.	Intermediate cation	Product[a]
 **7**	55-21-9		
 **8**	613-93-4		
 **9**	103-84-4		
 **10**	5310-14-5		
 **11**	675-20-7		
 **12**	13070-01-4		
 **13**	16879-02-0		
 **14**	2637-34-5		
 **15**	504-29-0		
 **16**	675-10-5		
 **17**	6052-75-1		
 **18**	2075-46-9		

[a] Yields are 98–100% unless otherwise indicated. [b] The yield estimated by NMR is 85% and the isolated yield is 41%. [c] The fluorosulfonate salt precipitates during reaction. [d] The yield estimated by NMR is 80% and the isolated yield is 37%. [e] The isolated yield is 78%. [f] The same product could be produced in 82% by reaction with 1 equiv of trimethyloxonium fluoroborate in methylene chloride followed by treatment of that solution with aqueous base. [g] The yield is 78%. [h] The isolated yield is 71%.

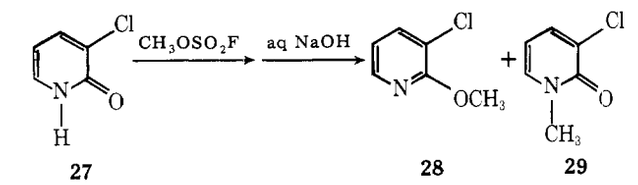


The manner in which the reaction is quenched can be critical. For example, although reaction of 11 with methyl fluorosulfonate followed by removal of the excess methylating agent and treatment with aqueous base provides **24** in 78%



yield, if the reaction is quenched with aqueous base without removal of the excess methylating agent only the amide **25** is observed (Table II). Since the expected oxygen-methylated fluorosulfonate salt is formed in the first step (Table IV), base and excess methylating agent must convert this salt to the dimethylated salt **26**, which undergoes hydrolysis to **25**. Such a sequence is precedented by similar observations of Lüssi[18] with dimethyl sulfate.

A similar, potentially misleading result was observed with 3-chloro-2-pyridone (**27**). In this case reaction was unusually



slow and a mixture of products **28** and **29** with **28** predominant was obtained in moderate yield (Table III).[19] However, if the reaction was quenched without removal of excess methylating agent, **28** and **29** were produced in high yields with **29** the predominant isomer (Table III). The apparent explanation of these results is that in the presence of excess base and methylating agent unreacted **27** is methylated through the corresponding anion. Hence, both the rate and product distribution are very different from the reactions of the neutral species. This possibility was confirmed by the finding that addition of **27** to a mixture of methylene chloride, aqueous base, and excess methyl fluorosulfonate gave **28** and **29** in 92% yield in a ratio of 5:95 (Table III).

If the regiospecificity of the alkylations of protomeric ambident nucleophiles by methyl fluorosulfonate could be controlled by removal of excess methylating agent, the process might be of broad synthetic value. However, additional complications were revealed in our investigations of 2-pyridone and 4-pyridone (Table II). Reaction of 2-pyridone (**30**) with methyl fluorosulfonate followed by removal of excess reagent in vacuo gives <50% total yield of 2-methoxypyridine (**31**) and 1-methyl-2-pyridone (**32**) in a ratio which varies in

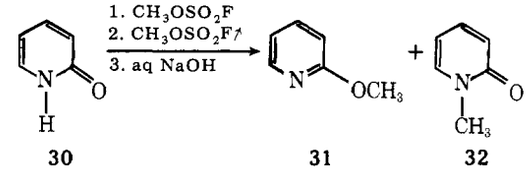
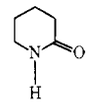
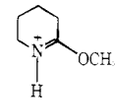
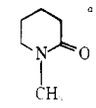
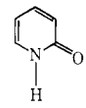
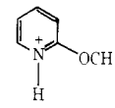
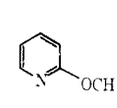
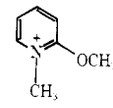
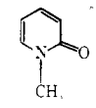
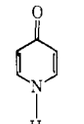
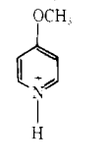
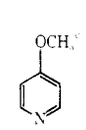
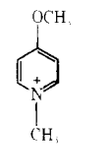
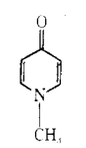


Table II. Methylations of Protomeric Tautomers with Methyl Fluorosulfonate Which Do Not Fit the Hypothesis

Reactant	Registry no.	Intermediate cation(s)	Product
 11			 [a]
 30	142-08-5		
			
 33	108-96-3		
			

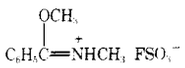
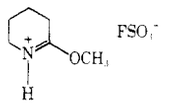
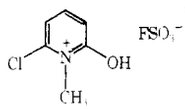
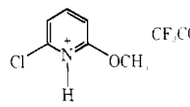
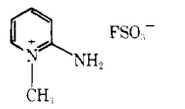
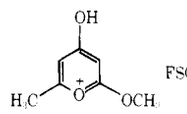
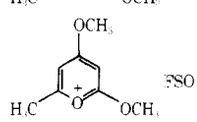
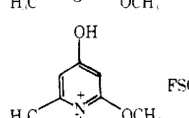
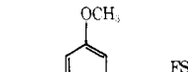
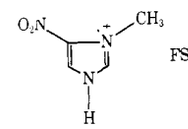
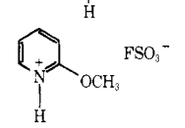
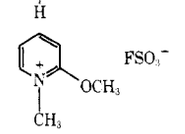
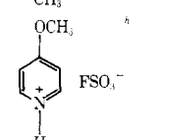
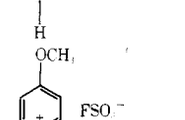
[a] The amide is the only product observed by NMR of the neutral products if the excess solvent and methyl fluorosulfonate are not removed prior to quenching with 1 N sodium hydroxide. [b] 2-Methoxypyridine and 1-methyl-2-pyridone are produced in 12 and 28% yields, respectively. [c] The reaction was carried out in neat methyl fluorosulfonate and quenched with aqueous base as soon as all the 4-pyridone had dissolved to give 4-methoxypyridine and 1-methyl-4-pyridone in 20 and 10% yields, respectively.

Table III. Methylation of 3-Chloro-2-pyridone with Methyl Fluorosulfonate in Methylene Chloride to Give 3-Chloro-2-methoxypyridine (28) and 3-Chloro-1-methyl-2-pyridone (29)

Reaction time, h	Excess methyl fluorosulfonate	Product, **28/29**
3	Removed in vacuo	80/20
21[a]	Removed in vacuo	84/16
5	Not removed	46/54
0.1	Not removed	8/92
b	Not removed	5/95

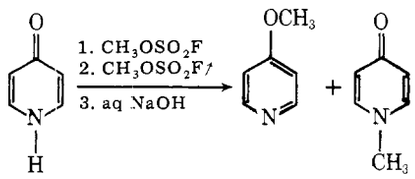
[a] Solvent was 5:3 benzene/methylene chloride; yield is 51%. [b] Reaction was carried out in the presence of 1 N aqueous KOH; yield was 92%.

Table IV. Proton Magnetic Resonance Spectra of Fluorosulfonate Salts

Compd	Registry no.	Chemical shifts,[a] δ
	65103-51-7	[b] 3.20 (d, NCH_3), 4.15 (OCH_3), 7.70 (C_6H_5)
	65103-52-8	2.70 (m, H_3 and H_6), 3.65 (m, H_4 and H_5), 4.16 (OCH_3)
	65103-54-9	8.00 (H_4), 7.25–7.50 (H_3 and H_5), 4.19 (NCH_3)
	65103-55-1	8.50 (H_4), 7.25–7.70 (H_3 and H_5), 4.26 (OCH_3)
	65103-56-2	[b] 7.00 and 7.80 (m, ArH), 3.75 (NCH_3)
	65103-58-4	[b] 6.86 (H_5), 6.55 (H_3), 4.23 (OCH_3), 2.59 (CCH_3)
	52911-90-7	[b] 6.96, 6.62 (H_3 and H_5), 4.17, 4.32 (OCH_3), 2.57 (CCH_3)
	65103-60-8	[b] 6.65, 6.72 (H_3 and H_5), 4.08 (OCH_3), 3.65 (NCH_3), 2.52 (CCH_3)
	65103-61-9	[b] 6.90, 6.72 (H_3 and H_5), 4.20, 4.05 (OCH_3), 3.70 (NCH_3), 2.40 (CCH_3)
	65103-63-1	8.75, 8.35 (H_2 and H_5), 4.35 (NCH_3)
	65103-64-2	8.1–7.3 (ArH), 4.30 (OCH_3)
	52911-95-2	8.1–7.3 (ArH), 4.38 (OCH_3), 4.09 (NCH_3)
	65103-65-3	8.30 (H_2 and H_6), 7.33 (H_3 and H_5), 4.25 (OCH_3)
	65103-66-4	8.50 (H_2 and H_6), 7.45 (H_3 and H_5), 4.20, 4.17 (OCH_3 and NCH_3)

[a] Relative to DDS in trifluoroacetic acid unless otherwise specified. [b] Relative to Me_4S; in acetonitrile-d_3. [c] Independently prepared by the reactions of 4-methoxy-6-methyl-2-pyrone and 2-methoxy-6-methyl-4-pyrone with methyl fluorosulfonate.[i] [d] Mp 126–128 °C. Anal. ($C_8H_{12}FNO_5S$) C, H, N. [e] Independently prepared by the reactions of 4-methoxy-1,6-dimethyl-2-pyridone and 2-methoxy-1,6-dimethyl-4-pyridone with methyl fluorosulfonate. [f] Essentially the same spectrum is obtained for 6-chloro-1-methyl-2-pyridone in trifluoroacetic acid. [g] The spectrum of 6-chloro-2-methoxypyridine in trifluoroacetic acid. [h] The same spectrum is obtained for 4-methoxypyridine in trifluoroacetic acid. [i] Prepared from 4-methoxypyridine and methyl fluorosulfonate.

favor of **32** at longer reaction times. Similar reaction of 4-pyridone (**33**) gives a mixture of 4-methoxypyridine (**34**) and 1-methyl-4-pyridone (**35**) in low yield.

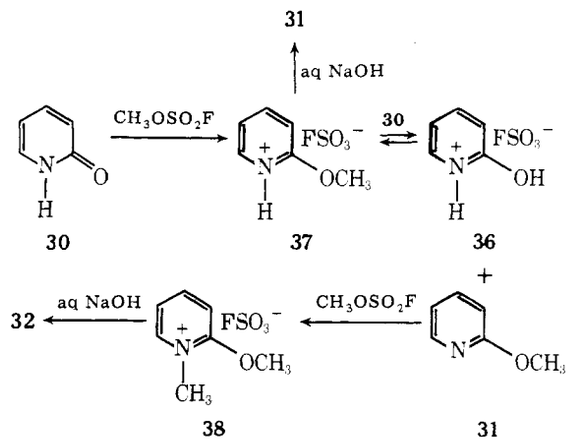


33 **34** **35**

The reaction of **30** has been investigated in detail. If the reaction is allowed to proceed overnight, a white solid precipitates which is 2-hydroxypyridinium fluorosulfonate (**36**). At shorter reaction times, the material obtained by evaporation of the excess methylfluorosulfonate is shown by proton magnetic resonance spectroscopy to be a mixture of 2-methoxypyridinium fluorosulfonate (**37**) and 2-methoxy-1-methylpyridinium fluorosulfonate (**38**). When the independently prepared fluorosulfonate salt **38** is treated with aqueous sodium hydroxide the only product is the pyridone **32**.[20]

These results can be accommodated by the process shown in Scheme II. It is proposed that after initial reaction of 2-pyridone (**30**) to give the expected salt **37** proton transfer to **30** occurs against an unfavorable equilibrium constant pro-

Scheme II



viding **36** and 2-methoxypyridine. The pyridine **31** then reacts with the methylating agent to give **38**, which gives 1-methyl-2-pyridone (**32**) on hydrolysis. The removal of **31** by methylation drives the reaction toward **36**, which eventually precipitates from the reaction medium. The formation of **36** explains the <50% yields. A decrease in **37** as a function of time would explain the variable ratio of **31** and **32**. The fact that 4-methoxypyridinium fluorosulfonate and 4-methoxy-1-

methylpyridinium fluorosulfonate can be isolated from the reaction of **33** with methyl fluorosulfonate suggests a similar course for that reaction. A large number of attempts to induce the reaction of 2-pyridone to yield only **37** by changes in solvent and methylating agent were not successful.[20]

The case of 2-pyridone shows that even though an initial reaction may follow the course prescribed by Figure 1a, that does not ensure synthetic success. In this case the site of initial methylation is obscured by subsequent events. The reaction of 2-pyridone suggests it may be difficult to achieve the synthetically prescribed regiospecific alkylation with protomeric ambident nucleophiles which are basic.

In an effort to extend the scope of these methylations, the reactions of thio acids, imides, β-hydroxy-α,β-unsaturated ketones, and β-amino crotonates with methyl fluorosulfonate were explored. In all cases mixtures of unidentified products were obtained. The cause of these difficulties was not determined, but the use of more reactive methylating agents should be explored.[12,21]

The present results raise interesting questions about the mechanism of alkylations of ambident protomeric nucleophiles. Questions about the nature of the actual nucleophile, the possible effects of association,[10] the possibility of proton or alkyl transfers of the salts,[22] and the relative transition-state energies for alkylation should be investigated.

In summary, the reaction profile of Figure 1a appears to be frequently observed for the reaction of protomeric ambident nucleophiles with methyl fluorosulfonate. For cases in which the initially formed salt is stable, it appears that isolation of the salt followed by treatment with base provides a regiospecific methylation in which the methyl group is bonded to the heteroatom remote from the proton in the major tautomer. On the other hand, complications with some cases suggest further efforts to stabilize the initially formed salts or to find more reactive alkylating agents would be useful.

Experimental Section

Caution: Methyl fluorosulfonate has been reported to be highly toxic; it should be used only with proper precautions.[23] Methyl fluorosulfonate (Aldrich) was purified by distillation from calcium hydride (bp 91–93 °C) and stored under nitrogen, over calcium hydride, at −15 °C prior to use.

2-Pyridone and 4-pyridone were purified by repetitive sublimations.[24] 2-Thiopyridone,[25] 4-thiopyridone,[25] 3-chloro-2-pyridone,[26] 4-hydroxy-6-methyl-2-pyridone,[27] 1,6-dimethyl-4-hydroxy-2-pyridone,[28] and *N*-methylthiobenzamide[29] were prepared by established methods and identified by their physical and spectral properties. All other reactants and solvents were commercially available and used without further purification.

General Procedure for Methylation. A five-to tenfold excess of methyl fluorosulfonate was added to the neat nucleophile or to a methylene chloride solution of the nucleophile. After being allowed to stir for 1–2 h at ambient temperature, any solid which formed was collected by filtration and the solution was heated in vacuo to remove solvent and excess methyl fluorosulfonate. The solid residue was examined by NMR spectroscopy in trifluoroacetic acid of acetonitrile-d_3 (Table IV).

Without further purification, the residue was treated with 1 N aqueous sodium hydroxide. The basic solution was extracted with either diethyl ether or chloroform and dried (Na_2SO_4), and the product isolated and purified by conventional methods. Products were identified by comparison of physical and spectral properties with established values: methylbenzimidic acid,[30] *N*-methyl methylbenzimidate,[31] *N*-phenyl methylacetimidate,[32] *N*-methyl methylbenzthioimidate,[33] *O*-methylvalerolactim,[22a] 2-methylthio-3,4,5,6-tetrahydropyridine,[9e] 6-chloro-1-methyl-2-pyridone,[34,35] 2-methylthiopyridine,[9e] 1-methyl-2-imidopyridone,[36] 2-methoxy-6-methyl-4-pyrone,[17] 4-methoxy-6-methyl-2-pyrone,[17] 2-methoxy-1,6-dimethyl-4-pyridone,[35] 4-methoxy-1,6-dimethyl-2-pyridone,[35] 1-methyl-5-nitroimidazole,[3] *N*-methylvalerolactam,[22a] 2-methoxypyridine,[22a] 1-methyl-2-pyridone,[22a] 4-methoxypyridine,[22a] 1-methyl-4-pyridone,[22a] 3-chloro-2-methoxypyridone,[26] 3-chloro-1-methyl-2-pyridone.[26]

The results of the methylations are presented in Tables I, II, and III.

Reaction of 2-Pyridone with Methyl Fluorosulfonate. To 2 mL of methyl fluorosulfonate was added 400 mg (4.2 mmol) of 2-pyridone. After being allowed to stir at ambient temperature for 5 min, the excess methylating agent was removed in vacuo and the residual solid was shown by comparison of its NMR spectrum (CF_3CO_2D) with that of authentic materials to be a mixture of 2-methoxypyridinium fluorosulfonate, 1-methyl-2-methoxypyridinium fluorosulfonate, and 2-hydroxypyridinium fluorosulfonate in a ratio of 24:30:36.

Separate treatment of the residue with 1 N aqueous sodium hydroxide followed by extractive separation of the products with chloroform and preparative thin-layer chromatography provided 2-methoxypyridine and 1-methyl-2-pyridone in 12 and 28% yields. Alternatively, if the hydrolysis of salts was carried out with neutral water followed by extraction with diethyl ether, 2-methoxypyridine free from 1-methyl-2-pyridine can be obtained in low yield.

2-Hydroxypyridinium Fluorosulfonate. Isolation on Methylation of 2-Pyridone. To 500 mg (5.2 mmol) of 2-pyridone suspended in 3 mL of methylene chloride was added 900 mg (10 mmol) of methyl fluorosulfonate. After being allowed to stir overnight, the white crystals collected by filtration were found to be a 10% yield of 2-hydroxypyridinium fluorosulfonate: mp 137–139 °C; NMR (CF_3CO_2D) δ 8.6–8.1 (m, 2 H), 7.6–7.3 (m, 2 H). Anal. ($C_5H_6FNO_4S$) C, H, N, S.

Reactions of 3-Chloro-2-pyridone with Methyl Fluorosulfonate. The reactions of 3-chloro-2-pyridone were carried out at ambient temperature with a four- to fivefold excess of methyl fluorosulfonate in methylene chloride for the time and with the disposition of excess methyl fluorosulfonate indicated in Table III. The reactions were worked up extractively. In an additional experiment, 0.3 mL (3.7 mmol) of methyl fluorosulfonate was added to 55 mg (0.44 mmol) of 3-chloro-2-pyridone in a mixture of 5 mL of methylene chloride and 7 mL of 1 N potassium hydroxide. After being allowed to stir for 21 h, extractive workup gave 60 mg of an oily product shown by NMR to be a 5:95 mixture of 3-chloro-2-methoxypyridine and 3-chloro-1-methyl-2-pyridone. 3-Chloro-2-methoxypyridine: δ 4.00 (s, 3 H), 6.81 (d of d, 1 H), 7.64 (d of d, 1 H), 8.09 (d of d, 1 H). 3-Chloro-1-methyl-2-pyridone: δ 3.60 (s, 3 H), 6.11 (t, 1 H), 7.29 (d of d, 1 H), 7.52 (d of d, 1 H).

Rate of Reaction of *N*-Methylbenzamide with Methyl Fluorosulfonate in Deuteriochloroform. The disappearance of the *N*-methyl signal of *N*-methylbenzamide and the appearance of the *O*-methyl signal of *O*-methyl-*N*-methylbenzamidic fluorosulfonate were followed in the NMR probe at ~38 °C. From two runs a second-order rate constant of 2.9 (±0.08) × 10^{-4} M^{-1} s^{-1} was obtained.

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Registry No.—Methyl fluorosulfonate, 421-20-5; 3-chloro-2-pyridone, 13466-35-8; 4-methoxy-6-methyl-2-pyrone, 672-89-9; 2-methoxy-6-methyl-4-pyrone, 4225-42-7; 4-methoxy-1,6-dimethyl-2-pyridone, 40334-97-2; 2-methoxy-1,6-dimethyl-4-pyridone, 40334-98-3; 6-chloro-1-methyl-2-pyridone, 17228-63-6; 6-chloro-2-methoxypyridine, 17228-64-7; 4-methoxypyridine, 620-08-6; 2-hydroxypyridinium fluorosulfonate, 65103-67-5; 3-chloro-2-methoxypyridine, 13472-84-9.

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Nucleophilic Aromatic Substitution on *o*-(Methoxy)aryloxazolines. A Convenient Synthesis of *o*-Alkyl-, *o*-Alkylidene-, and *o*-Arylbenzoic Acids

A. I. Meyers,* Richard Gabel, and Edward D. Mihelich

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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Reaction of *o*-(methoxy)aryloxazolines **1** with organolithium or Grignard reagents results in methoxy displacement to the *o*-(alkyl)-, *o*-(aryl)-, and *o*-(vinyl)aryloxazolines **3**. A variety of organometallics were employed and only those considered to be delocalized anions failed to displace the methoxy group. Various poly(methoxy)aryloxazolines (**1a–e**) were investigated, and the reactions proceeded with general success, the yields dropping off in the 2,6-(dimethoxy)aryloxazoline **1d** due to steric factors. The method describes a facile synthesis of unsymmetrically substituted biphenyls and terphenyls by merely choosing the appropriate aryl metallic and methoxyaryloxazolines. Hydrolysis of the *o*-(substituted)aryloxazoline gave the corresponding benzoic acid derivatives **4** in good yield. In the case of 2,6-(disubstituted)aryloxazolines, hydrolysis to the benzoic acid proved difficult and led only to partially hydrolyzed amides.

Nucleophilic aromatic substitution has long been recognized as an important synthetic process, but has been limited to aromatic substrates with so-called "activating groups".[1] In recent years a number of elegant synthetic techniques have evolved which do not require the traditional activating groups and nucleophiles for substitution. Among these are the nickel-catalyzed reaction of aryl halides with Grignard reagents,[2] arene chromium derivatives reacting with carbanions,[3] the nickel-catalyzed reaction of enolates and aryl halides,[4] displacement on aryl halides[5] by alkoxide in powerful ion-solvating media, the copper-catalyzed substitution of *o*-bromobenzoic acids with enolates,[6] and the [2,3]sigmatropic rearrangements of sulfur ylides to ortho-substituted anilines.[7] The extensive studies by Bunnett,[8] which provided a variety of substituted benzenes, involve radical and radical ion intermediates and electron-transfer processes ($S_{RN}1$ mechanism). In effect, the overall transformation is that of nucleophilic substitution on aryl halides with traditional carbanions (enolates, thiolates, amide ions, etc.).

This report describes an aromatic substitution process which involves an activating group, but not in the traditional sense since it "activates" only toward nucleophilic reagents that are possessed of metal ions capable of chelation and transfer of the nucleophile from a tight ion pair to the electrophilic site.

In 1975, a preliminary report appeared[9] which described the overall process (eq 1) as a nucleophilic displacement of the *o*-methoxy group by several organometallics. This report will provide, in greater detail, the scope and limitations of this useful transformation and offer some evidence that the reaction is most probably occurring by an addition–elimination sequence and not by a free-radical mechanism.

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