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A Novel Electrophilic Methoxylation (with a Little Help from F_2)

Shlomo Rozen,* Eyal Mishani, and Moshe Kol

Contribution from the School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel. *Received September 30, 1991*

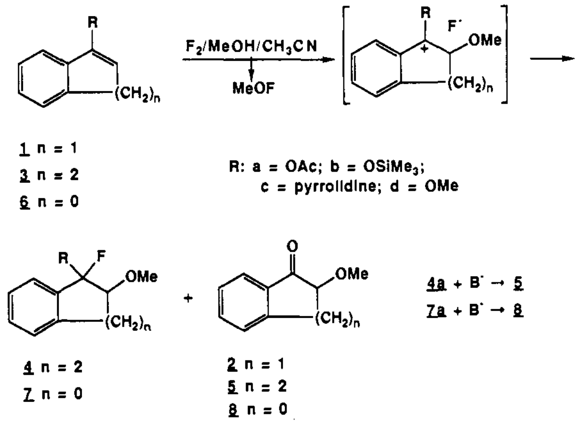
Abstract: Methyl hypofluorite, MeOF, easily made from MeOH and F_2, proved to be an excellent source for the novel electrophilic methoxylium ion "MeO^+". MeOF was reacted with the enol forms of carbonyls, producing in good to excellent yields the corresponding α-methoxy carbonyl derivatives. It was found that the methoxylation is best carried out on methyl enol ethers. Silyl enol ethers and enol acetates were also tested but with limited success. The reaction proceeds through an addition elimination mechanism.

As with halides, the methoxide anion is one of the most frequently used tools in organic chemistry, but unlike the various electrophilic halonium species, the electrophilic methoxylium, "MeO^+",[1] has never been described in the literature. This is despite the synthetic and theoretical potential such a moiety could have. The obvious reason for this situation is that, apart from fluorine, nothing is more electronegative than oxygen, and until recently the only available form of fluorine in the minds of most chemists was the fluoride anion. Dealing with electrophilic fluorinating reagents for more than a decade has taught us that F_2 can be a surprisingly versatile agent for both fluorination purposes[2] and difficult organic transformations leading eventually to fluorine-free derivatives.[3] Some time ago we developed the $HOF{\cdot}CH_3CN$ reagent in which the reactive part was the hydroxylium moiety ("$HO^{\delta+}$") responsible for unprecedentedly fast epoxidations and hydroxylations.[4] The unique role of the acetonitrile in stabilizing HOF enabled us to prepare what was at the time the smallest unknown organic molecule, MeOF,[5] which is the only possible source for the electrophilic methoxylium.

α-Methoxy ketones are known but usually obtained by multistep synthesis, frequently in low overall yields. The determining step is a nucleophilic displacement of an appropriately placed leaving group by the methoxide anion.[6] The electrophilic methoxylium moiety in MeOF offers a different approach based on its attraction to the electron-rich end of the π region of the carbonyl's enol form.

When the enol acetate of 1-indanone (**1**) was reacted with the oxidizing MeOF, obtained by the reaction of fluorine and methanol in acetonitrile, 2-methoxy-1-indanone (**2**) was obtained in 70% yield.[6c] At this point, proof was needed that the MeO moiety originates from the MeOF itself and not from some secondary reaction with the methanol present in the reaction mixture. For this purpose, the gaseous MeOF was transferred with a stream of nitrogen to a secondary reactor containing only the substrate **1** in pure acetonitrile solution. The results were identical. Another question concerned the reaction mechanism. As with most electrophiles the addition elimination pathway seemed quite plausible.[7] It was indeed and was fully supported by the reaction of tetralone enol acetate (**3a**) with MeOF where the carbocationic intermediate is less stable than in the indan system. Consequently a faster collapse of the tight ion pair occurs resulting in adduct **4** in 65% yield. As with indanone, however, some of the fluoride anion does diffuse out of the cage, forcing the benzylic carbocation to collapse internally to form 2-methoxy-3,4-dihydronaphthalenone (**5**).[8] It should be noted that **4**, either in its pure form or when in the crude reaction mixture, can be quantitatively transformed into **5** under a short basic treatment. Enol acetates such as the one of acetophenone (**6a**) could still be reacted, but only the adduct 1-acetoxy-1-fluoro-1-phenyl-2-methoxyethane (**7**) was obtained in 20% yield. The low yield reflects the relatively low nucleophilicity of the terminal double bond, while the lower stability of the intermediate carbocation, when compared with the system in the previous case is responsible for the formation of the adduct only. Here again a short basic treatment hydrolyzed the adduct **7** quantitatively to α-methoxyacetophenone (**8**).[6d] Enol acetates, other than benzylic, are usually even less suitable and tend to produce either tars or very low yields of the desired α-methoxy ketones (Scheme I).

Scheme I



Silyl enol ethers proved to be somewhat more promising. Tetralone silyl enol ether (**3b**) reacted rapidly with MeOF to give **5** in higher than 85% yield. The electron density of the double bond in acetophenone silyl enol ether (**6b**) is higher than that of the corresponding enol acetate **6a**, increasing the yield of **8** to higher than 85%. Pinacolone silyl enol either (**9b**) also gave

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(1) It should be clear that, as with the various electrophilic species such as "Cl^+" or "F^+", "MeO^+" indicates only that in the transition state the molecule is polarized in such a way that the methoxylium pole acts as an electrophile. This feature is enhanced by the counterpole being a good leaving group. For a more detailed discussion on the subject, see: Lerman, O.; Tor, Y.; Hebel, D.; Rozen, S. *J. Org Chem.* **1984**, *49*, 806 (ref 12).

(2) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307.

(3) See, for example: Rozen, S.; Brand, M.; Lidor, R. *J. Org. Chem.* **1988**, *53*, 5545. Rosen, S.; Hebel, D. *Heterocycles* **1989**, *28*, 249. Rozen, S.; Zamir, D. *J. Org. Chem.* **1990**, *55*, 3552.

(4) Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325. Rozen, S.; Kol, M. *J. Org. Chem.* **1990**, *55*, 5155.

(5) The existence of MeOF was first reported during the 1990 ACS meeting: Rozen, S.; Hebel, D.; Kol, M. *Abstracts of Papers* 199th National Meeting of the American Chemical Society, Boston, MA, April 1990, American Chemical Society: Washington, DC, 1990; FLUO-17. (see also *Chem. Eng. News* **1990** (May 7), 62.) Lately we have isolated and fully characterized this molecule: Kol, M.; Rozen, S.; Appelman, E. *J. Am. Chem. Soc.* **1991**, *113*, 2648.

(6) (a) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687. (b) Catacuzene, D.; Tordeux, M. *Can. J. Chem.* **1976**, *54*, 2759. (c) De Jongh, D. C.; Van Fossen, R. Y. *Tetrahedron* **1972**, *28*, 3603. (d) Sawaki, Y.; Inome, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1133. (e) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Musallam, H. A. *J. Org. Chem.* **1987**, *52*, 150.

(7) It has been shown that CF_3OF reacts with enols through an addition elimination mechanism; see: Barton, D. H. R.; Godhino, L. S.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1968**, 804. A similar mechanism was also found with electrophilic aromatic fluorination by AcOF; ref 1.

(8) Arnould, J. C.; Pete, J. P. *Tetrahedron* **1975**, *31*, 815.

(9) Vyplel, H. *Chimia* **1985**, *39*, 305.

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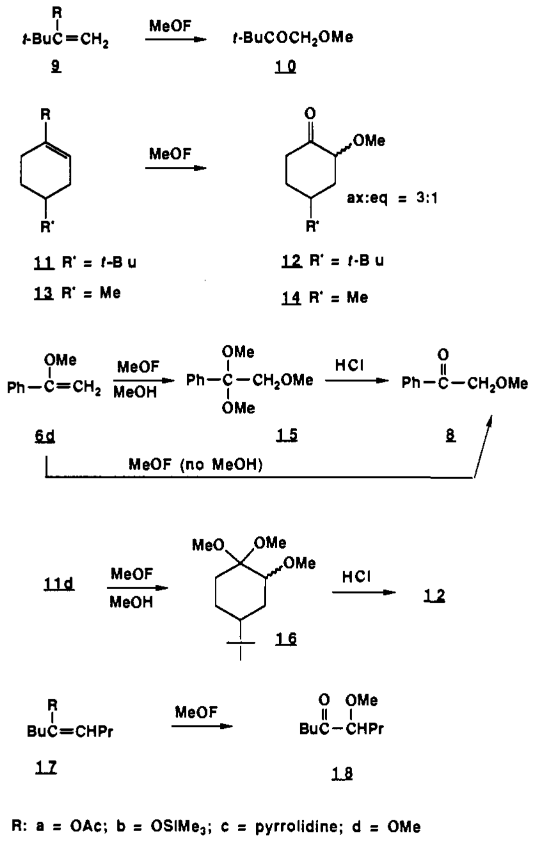
Scheme II



excellent results with MeOF producing 3,3-dimethyl-1-methoxy-2-butanone (**10**) in 90% yield.[6e] When however, the silyl enol ether of 4-*tert*-butylcyclohexanone (**11b**) was reacted the yield of 2-methoxy-4-*tert*-butylcyclohexanone (**12**)[6a] was less impressive and did not exceed 30%. With other aliphatic silyl enol ethers the results were even less encouraging. Similar results were obtained with the enamine **11c** and the enamine of 4-methylcyclohexanone **13c**, which formed **12** and 2-methoxy-4-methylcyclohexanone (**14**), respectively. In these cases the parent ketones were also obtained in considerable amounts due to the sensitivity of enamines toward hydrolysis. One of the reasons for the relatively low yields for these enol derivatives may be the abundance of fluoride ions present in the reaction mixture since the production of MeOF is associated with formation of HF. Addition of HF scavengers such as NaF or transfer of the methyl hypofluorite with a stream of nitrogen improved the yields only marginally with both silyl enol ethers and enamines. Thus, while generally better than enol acetates, the reactions were still not very satisfactory.

The best results so far were obtained with enols captured as methyl enol ethers. There was little room for improvement in the case of the tetralone enol ether **3d** which was converted directly to the desired **5** in 85% yield. With the methyl enol ether of acetophenone (**6d**), the only isolated compound proved to be 1-phenyl-1,1,2-trimethoxyethane (**15**) in 87% yield, which could be quantitatively hydrolyzed to the desired α-methoxyacetophenone (**8**). The formation of the adduct **15** in contrast to **7a**, resulting from the enol acetate, could be explained by the greater stability of the intermediate α-methoxy carbocation compared to the α-acetoxy one. This facilitates the fluoride diffusion out of the ion pair cage, and recombination with MeOH present in the solvent forms **15**. When the MeOF was transferred to a methanol-free environment, the reaction with **6d** directly produced **8** in 85% yield (Scheme II).

Considerable improvement compared to all other enol derivatives was noticed with the cyclic **11d**. Analogous to the previous case, a trimethoxy derivative **16** was formed in 60% yield and could be easily and quantitatively hydrolyzed with dilute HCl to give the desired **12**. It should be noted that, similar to the reactions of **11b** and **11c**, the methoxy ketone **12** was a mixture of two stereoisomers in a ratio of 3:1 (ax:eq methoxy), reflecting the steric and electronic factors which favor such a distribution.[6a] A straight chain methyl enol ether such as di-*n*-butyl ketone (**17d**) gave the unknown 4-methoxy-5-nonanone (**18**) in higher than 65% yield. This compound and other straight chain α-methoxy ketones could not be obtained from the corresponding enol acetates, enamines, or silyl enol ethers.

In conclusion, it should be stressed that, although fluorine is not incorporated in the final product, its role is indispensable in creating a new moiety, the electrophilic methoxylium ion, whose full potential synthetic value has yet to be unveiled.

Experimental Section

^1H NMR spectra were recorded with a Bruker AM-360 WB spectrometer at 360 MHz with $CDCl_3$ as solvent and Me_4Si as internal standard. The ^{19}F NMR spectra were measured at 338.8 MHz and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded at 90.5 MHz, and only the C–F couplings were observed. Here too $CDCl_3$ served as a solvent and TMS as internal standard. Mass spectra were measured with a Du Pont 21-491B instrument, and IR spectra were recorded on a Perkin-Elmer 177 spectrometer.

General Fluorination Procedure. Fluorine is of course a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. This line is equipped with secondary containers of a known volume made also from copper or monel. Pressure gauges constructed especially for work with fluorine (Matheson or Air Products) are attached to the line. All possible outlets of the system, including the one connected to the oil pump, are guarded by soda-lime traps so that no fluorine escapes to the atmosphere. Variations of such vacuum lines are illustrated in Matheson Report No. G-115B or in Vyplel's review.[9] The secondary cylinders are first evacuated and then charged with nitrogen to a positive pressure of about 5 psi. The nitrogen flow is stopped, and F_2 is allowed to pressurize the system to the desired final concentration. The system is then charged again with N_2 up to 60–90 psi. The main fluorine and nitrogen cylinders are then completely disconnected. If so wished, this mixture can be passed through an NaF trap (Matheson) in order to absorb part of the HF always found in some quantity in technical commercial fluorine. Prediluted mixtures of fluorine in inert gases are also commercially available. The reactions themselves can be carried out in glass or Teflon vessels whose outlets are connected to soda-lime traps. A simple gas bubbler fitted at the end of this trap can give a fair idea of the bubbling rate of the gas through the reaction mixture, although this can be accurately measured if needed. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no accidents with it in the last 18 years.

Preparation of MeOF and Its Reactions with Enol Derivatives. A mixture of 15% F_2 in N_2 was bubbled into a cold (−40 °C) solution of 5 mL of MeOH in 115 mL of CH_3CN placed in a Teflon vessel. The amount of the MeOF thus obtained can be easily determined by reacting aliquots of the reaction mixture with aqueous KI solution and titrating the liberated iodine. After the desired concentration of MeOF was achieved, usually around 0.1–0.15 M, a cold (−40 °C) solution of the enol derivative in $CHCl_3$ was added and the mixture allowed to warm to room temperature. The reactions were usually carried out on scales of 10–15 mmol using 1.5–2-fold excess of MeOF, with conversions usually higher than 90%. If needed, a stream of nitrogen could be employed for transferring the gaseous MeOF to a secondary reactor containing only cold (−40 or −78 °C, respectively) aceto- or propionitrile. By employing this procedure about 25% of the MeOF decomposed, but the oxidizing solution in the secondary reactor was HF free. The reactions were usually monitored by GC, TLC, or NMR and in most cases were complete within 5–15 min. The reaction was terminated by pouring it into 500 mL of $NaHCO_3$ solution, extracting with $CHCl_3$, washing with water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The crude reaction mixture was usually subjected to vacuum flash chromatography using silica gel 60-H (Merck) with mixtures of EtOAc in petroleum ether serving as eluent. All compounds described here are oils. The adducts were obtained in purities of at least 90%, but some could not be analytically purified since they tend to readily convert to the corresponding methoxy ketones. The known methoxy ketones are referenced throughout the paper (where the yields can also be found), while the physical data of the new compounds are given below.

Synthesis of the Enol Derivatives. The enol acetates, silyl enol ethers, and enamines are known and were prepared from the corresponding ketones by standard procedures (e.g., with isopropenyl acetate, pyrrolidine, and trimethylsilyl triflate for the Si). The methyl enol ethers were prepared by mixing the appropriate ketone (1 mol equiv), trimethyl orthoformate (1.1 equiv), and *p*-toluenesulfonic acid (0.005 equiv) at room temperature for 24 h. The methyl formate and the methanol formed were distilled slowly for at least 4 h until no more methanol was formed. The methyl enol ethers were then distilled under reduced pressure.

Physical Properties of the New Compounds. A. 1-Acetoxy-1-fluoro-2-methoxy-3,4-dihydronaphthalene (**4**): IR 1745 cm^{-1}; ^{1}H NMR 7.8–7.2 (4 H, m), 4.72 (1 H, m), 3.43 (3 H, s), 3.0 (1 H, m), 2.65 (1 H, m), 2.30 (1 H, m), 2.17 (3 H, s), 2.08 (1 H, m); ^{19}F NMR −91.64 ppm (s); ^{13}C NMR 129.8, 128.5, 127.3, 126.5 (C_{arom}), 109.4 (d, $^1J_{CF}$ = 227 Hz), 74.7 (d, $^2J_{CF}$ = 32 Hz), 57.2, 23.10, 22.6, 22.5 ppm; MS *m/z* 178 [(M − AcOH)$^+$].

B. 1-Acetoxy-1-fluoro-1-phenyl-2-methoxyethane (**7**): ^{1}H NMR 7.45–7.24 (5 H, m), 3.79 (2 H, d, J = 15 Hz), 3.39 (3 H, s), 2.12 (3 H, s); ^{19}F NMR −122 ppm (t, J = 15 Hz); ^{13}C NMR 167.3 (CO), 130–120 (C_{arom}), 111 (d, $^1J_{CF}$ = 233 Hz), 76 (d, $^2J_{CF}$ = 30 Hz), 59.9, 21.67 ppm. Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.13. Found: C, 62.10; H, 6.25.

C. 1-Phenyl-1,1,2-trimethoxyethane (**15**): ^{1}H NMR 7.98–7.26 (5 H, m), 3.64 (2 H, s), 3.23 (6 H, s), 3.2 (3 H, s); MS *m/z* 165 [(M − OMe)$^+$], 151 [(M − CH_2OMe)$^+$].

D. 1,1,2-Trimethoxy-4-*tert*-butylcyclohexane (**16**): ^{1}H NMR 3.44–3.38 (1 H, m), 3.35 (3 H, s), 3.2 (3 H, s), 3.17 (3 H, s), 2.2–1.8 (2 H, m), 1.6–1.2 (5 H, m), 0.9 (9 H, s); ^{13}C NMR 100.05, 76.31, 55.75, 47.37, 46.93, 39.9, 31.6, 27.35, 27.62, 25.5, 22.5 ppm; MS *m/z* 199 [(M − OMe)$^+$], 173 [(M − *t*-Bu)$^+$], 57 [(*t*-Bu)$^+$].

E. 4-Methoxy-5-nonanone (**18**): IR 1710 cm^{-1}; ^{1}H NMR 3.58 (1 H, t, J = 6.2 Hz), 3.37 (3 H, s), 2.52 (2 H, t, J = 7.2 Hz); MS *m/z* 87 [PrCHOMe]$^+$, 85 [BuCO]$^+$, 57 [Bu]$^+$. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.76; H, 11.6. Found: C, 69.53; H, 11.2.

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Synthesis and Study of New α-Haloacid Ferroelectric Liquid Crystal Derivatives. MM2 Approach to the Molecular Structure–Ferroelectric Activity Relationship

T. Sierra,[†] J. L. Serrano,[*,†] M. B. Ros,[†] A. Ezcurra,[‡] and J. Zubía[§]

Contribution from the Química Orgânica, Facultad de Ciencias, Instituto de Ciencia de Materiales de Aragôn, Universidad de Zaragoza-C.S.I.C., 50009-Zaragoza, Spain, Departamento de Física Aplicada II, Facultad de Ciencias, Universidad del País Vasco, Aptdo 644, 48080-Bilbao, Spain, and Departamento de Automâtica, Elêctronica y Telecomunicaciones, Escuela Têcnica Superior de Ingenieros Industriales y de Telecomunicaciôn, Universidad del País Vasco, Alameda de Urquijo s/n, 48013-Bilbao, Spain.

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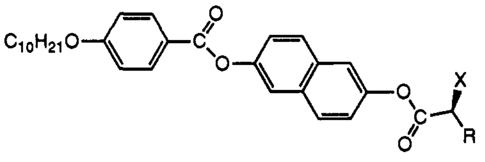
Abstract: In order to understand the structural factors that influence ferroelectric properties, three new series (**F**, **Cl**, and **Br**) of chiral naphthalene-ring derived compounds were synthesized, and their ferroelectric properties [spontaneous polarization (Ps) and response time (τ)] were evaluated in the pure compound. The chiral tails are α-halo acids derived from L-α-amino acids: L-α-alanine (**1**), L-leucine (**2**), L-isoleucine (**3**), and L-valine (**4**), with a fluorine, chlorine, or bromine atom in the chiral center. The highest Ps values were obtained for compounds containing a fluorine or chlorine atom in their asymmetric center and with chiral tail derived from L-isoleucine (**3**) (**F-3**, 102 nC/cm^2; **Cl-3**, 100 nC/cm^2). The steric requirements of the halogen atom and the bulky alkyl group in the asymmetric center determine the most stable conformations of these chiral tails, which have been studied by molecular mechanic empirical calculations, MM2. MM2 calculations prove to be a successful tool for understanding how the structure of the lateral chiral tail affects molecular arrangement and, as a consequence, the ferroelectric properties of the materials.

Introduction

Since the discovery, in 1975, of the first ferroelectric liquid crystal, DOBAMBC,[1] considerable efforts have been made to design and synthesize new organic molecules with structures that will give rise to SmC* arrangement and good ferroelectric properties.[2,3] The study of the relationship between molecular structure and ferroelectric activity has been one of the most interesting subjects,[2-4] and, as a consequence, the challenge of finding a model which reflects this relationship has been the aim of many researchers. In 1986, Walba et al.[5] proposed a model, the "Boulder Model", for the molecular origins of the spontaneous polarization, which has been successfully applied to the design of new FLC materials with high Ps values.[6] In 1990, Koden et al.[7] published a model, based on the "zigzag" model for the smectic C phase, which has been used to investigate the spontaneous polarization of some chiral compounds possessing cis and trans isomers.[8] Both models are mainly based on the disposition of the chiral tail in the SmC* phase.

Chart I



-R

1 $-CH_3$

2 $-CH_2CH(CH_3)_2$

3 $-{}^*CH(CH_3)CH_2CH_3$

4 $-CH(CH_3)_2$

X = F, Cl, Br

In this paper, we have tried to approach this subject from a different viewpoint: molecular mechanic empirical calculations[9]

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[*] Corresponding author.

[†] University of Zaragoza.

[‡] F.C., Universidad del País Vasco.

[§] E.T.S.I.I.T., Universidad del País Vasco.

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