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A REGIOSPECIFIC AND STEREOSPECIFIC ROUTE TO ENOL CARBONATES AND CARBAMATES: CLOSER LOOK AT A "NAKED ANION"

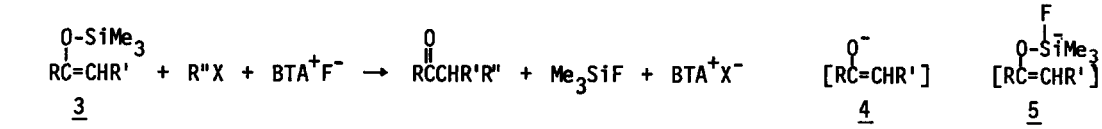
R. A. Olofson* and John Cuomo

Chemistry Department, The Pennsylvania State University
University Park, Pennsylvania 16802

Summary. A fluoride ion catalyzed reaction which affords the title compounds in good yield from enol silyl ethers is described.

Several communications from this laboratory have illustrated the exceptional reactivity differences between enol carbonates, $R_2C{=}CROCO_2R$ (1), and carbamates, $R_2C{=}CROCONR_2$ (2), and have shown how these differences can be utilized to synthetic advantage.[1,2] However, this work has been limited by the inaccessibility of many structural variations encompassed by formulas (1 and 2),[3] a problem exemplified by the competitive C-acylation which occurs when O-acylation of the ambident lithium enolates with acid halide type reagents is attempted.[4] Recently however, we described an efficient synthesis of 1 from ketones and chloroformates in which C-acylation is avoided by generating the enolates with the H^+arpoon base, lithium 2,2,6,6-tetramethylpiperidide,[5] and then reacting them in HMPT.[6] We now report a second, more general process, also based on a "naked enolate" approach, which has further advantages in that the regiochemistry and stereochemistry induced in an enol surrogate precursor are retained in the reaction.

In 1975, Kuwajima and Nakamura[7] described the C-alkylation of enol silyl ethers (3) in the presence of excess $PhCH_2\overset{+}{N}Me_3\ F^-$ (BTAF). Later an analogous aldol-type condensation was reported.[8]

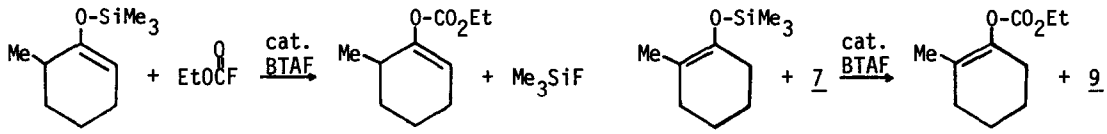


3 4 5

In these processes, the authors favored the equilibrium intervention of a trace of the enolate (4) but they also suggested the pentavalent silicon anion (5) as an alternative intermediate which could be attacked by the electrophilic carbon reactant.[7,8] The fact that fluorosilicate anions and dianions are known provides attractive support for this latter hypothesis (or its

variant involving an even more nucleophilic hexacoordinate Si$^{=}$: K_2PhSiF_5 has even been isolated).[9] These pathways are potentially distinguishable: The anion (5) with Si attached to five large groups (or the more hindered dianion) will react at carbon with both weak and strong electrophiles. However, electrophiles active enough to be strongly influenced by (i.e., "to see") the ground state charge distribution in the "naked anion" (4) should yield products from O-attack. The first reaction affording such products and thus requiring the intermediacy of 4 is described here.

When the enol silane (6, from the kinetic enolate of 2-methylcyclohexanone[10]) was treated with a THF solution of ethyl fluoroformate (7,[11] 1.3 eq) containing 0.07 eq BTAF, the enol carbonate (8, bp 67-69° at 2 torr[12]) was isolated in 90% yield after filtration and distillation of the reaction mixture. Similarly, the isomeric enol carbonate (11, bp 100-102° at 5 torr) was isolated

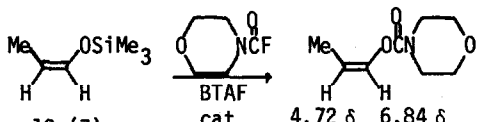


6 7 8 (90%) 9 10 11 (91%)

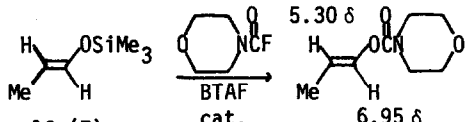
in 91% yield after stirring the enol silane (10, from the thermodynamic enolate[10]) with 7 and BTAF (0.06 eq) in THF for two hours at room temperature. In both of these processes, none of the regioisomeric product was obtained (e.g., 8 from 10). Note that only a catalytic amount of BTAF is required because F^- is regenerated during the O-acylation step.

The versatility of this new enol carbonate synthesis is illustrated in reactions A-H of Table I. Note that the silyl ether may be derived from an aldehyde or from an aliphatic, aromatic, or conjugated ketone and that the fluoroformate may be either aliphatic or aromatic. The enol silane reactants are readily available from carbonyl precursors, often by regio- and/or stereoselective and -specific processes,[10,13] and chloroformates are conveniently converted to fluoroformates in high yield by halide exchange with KF/18-crown-6.[11] Since the yields in Table I are also good to excellent, the practicality of the new methodology is also evident. The reaction does not work with a chloroformate in place of ROCOF, and ROCOCl in the ROCOF also impedes the reaction. However, this latter problem is easily remedied by using more BTAF. Thus, the reaction conditions given in Table I often are a better indication of the amount of ROCOCl impurity in the ROCOF (varies up to 6% in C) than of intrinsic reactivity (reaction time always was determined by periodic gc assay). The synthesis also may be performed by halide exchange on the ROCOCl and then adding the enol silane to the mixture without prior isolation of the ROCOF. However, this process is less efficient (56% in A; KF/18-crown-6 is the preferred F^- source for both steps in this situation).

The extension of the new methodology to the useful preparation of enol carbamates from carbamoyl fluorides[11] also is exemplified in Table I (rxns I, J; 12% Me_2NCOCl impurity in I). This system also was used to test the stereospecificity of the synthesis. As anticipated, when the Z-

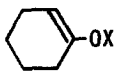
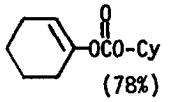
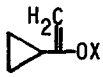
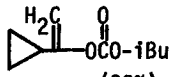
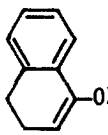
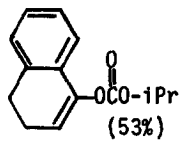
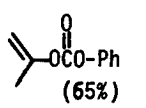
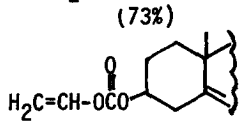
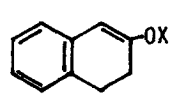
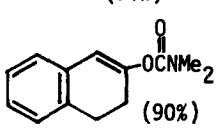


12 (Z)



13 (E)

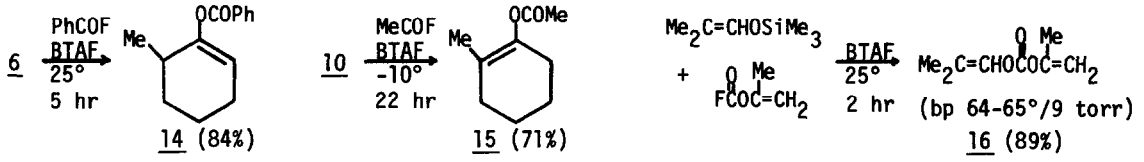
Table I. Enol Carbonates and Carbamates: Synthesis and Properties[a]

Rxn	Enol Ether (X=-SiMe$_3$) RCOF (R=)	Product[b] (Yield)	BP (°C) (torr)	Reaction Cond. Time and Temp. BTAF Conc.	IR Stretch (μ in CCl_4) C=O	C=C	NMR: Vinyl H δ in $CDCl_3$ (J in Hz)
A	 (R=-O-Cyclohexyl)	 (78%)	104-106 (0.6)	9 hr 25° 7 mol %	5.72	5.90	5.3-5.5 (m)
B	 (R=-O-Isobutyl)	 (93%)	74-75 (2)	0.5 hr 25° 4 mol %	5.67	6.01	4.55-4.65 (m) 4.7-4.8 (m)
C	 (R=O-Isopropyl)	 (53%)	128-130 (3)	1 hr 25° 11 mol %	5.66	6.23	5.65-5.9 (m)
D	 (R=-O-Phenyl)	 (65%)	92-93 (4)	23 hr 65° 12 mol %	5.64	5.96	4.71 (d, 1.5) 4.89 (d, 1.5) 5.0 (broad s [2])
E	H_2C=CH-C(=CH_2)-OX (R=-O-Cyclohexyl)	H_2C=CH-C(=CH_2)-OCO-Cy (79%)	84-85 (1)	0.5 hr 25° 5 mol %	5.68	6.06 6.27	5.17 (d of d, 12, 2) 5.40 (d of d, 18, 2) 6.32 (d of d, 18, 12)
F	Me_2C=CH-OX (R=-O-nButyl)	Me_2C=CH-OCO-nBu (73%)	88-89 (13)	0.3 hr 25° 6 mol %	5.71	5.93	6.8 (broad s) 4.57 (d of d, 6, 2)
G	H_2C=CH-OX (R=-O-Cholesteryl)	 (97%)	90-92 (mp)	0.3 hr 25° 17 mol %	5.68	6.06	4.88 (d of d, 14, 2) 5.2-5.5 (m) 7.12 (d of d, 14, 6)
H	H_2C=CH-OX (R=-O-Isobutyl)	H_2C=CH-OCO-iBu (71%)	82-85 (63)	3 hr 0° 4 mol %	5.67	6.07	4.60 (d of d, 7, 1.5) 4.92 (d of d, 14,1.5) 7.17 (d of d, 14, 7)
I	 (R=-NMe_2)	 (90%)	76.5-77 (mp)	20 hr 50° 16 mol %	5.81	6.00	6.23 (s) 5.0 (broad s [2])
J	H_2C=CH-C(=CH_2)-OX (R=-N-Morpholino)	H_2C=CH-C(=CH_2)-OC-N(CH$_2$CH$_2$)$_2$O (52%)	97-100 (0.2)	51 hr 25° 2.4 mol %	5.76	6.07 6.26	5.16 (d of d, 10, 2) 5.28 (d of d, 17, 2) 6.34 (d of d, 17, 10)

[a]Prepared as described in text with reaction condition variations indicated in Table. [b]All products are new except those from rxns B,[6] D,[6] and G[1c] which were compared with authentic samples. For procedures used in determining structure and purity of new compounds, see footnote 12.

and E-enolsilanes (12 and 13) were converted to their respective morpholinyl carbamates in separate experiments, the products were obtained uncontaminated by their geometrical isomers (gc, NMR).

In other generalizations, reaction of 6 with benzoyl fluoride[11] regiospecifically afforded the enol benzoate (14, 84% yield) and 10 similarly was transformed to the enol acetate (15, 71% yield) on treatment with acetyl fluoride.[11] Finally, reaction of isobutenyloxytrimethylsilane



with isopropenyl fluoroformate[11] (bp 58-59°) and BTAF (0.02 eq) gave the mixed bis-enol carbonate (16) in 89% distilled yield (IR: 5.68, 5.90, 5.98μ; NMR: vinyl H's at 4.7-4.8, 4.8-4.9, 6.77δ). Because competitive processes are available, this route to simple enol esters (e.g., 14, 15) probably will find value only in sensitive systems. However, the last reaction (→16) illustrates a particularly useful synthesis of mixed bis-enol carbonates, species with potentially significant preparative applications.[6] Only one such compound is known previously.[6]

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References and Footnotes

1) (a) R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, Tetrahedron Lett., 1563 (1977); (b) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, ibid., 1567 (1977); (c) R. A. Olofson and R. C. Schnur, ibid., 1571 (1977); (d) R. A. Olofson and J. P. Pepe, ibid., 1575 (1977).

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3) E.g., H_2C=CHOCOCl is the only readily available enol chloroformate; ref. 2 and refs. therein.

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12) New compound (indicated by inclusion of physical or spectral data); IR, NMR, and high resolution mass spectra were obtained for all new cpds. and are in accord with proposed structures.

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