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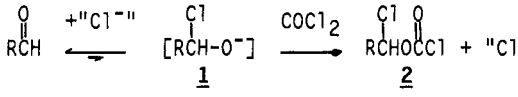
New, useful reactions of novel haloformates and related reagents

Roy A. Olofson

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, U.S.A.

Abstract - Uses of the α-chloroalkyl chloroformates **2** obtained by the Cl^- catalyzed addition of phosgene to aldehydes are reported. The best known compound of this type, α-chloroethyl chloroformate (ACE-Cl), is a mild reagent for the selective N-dealkylation of tertiary amines with commercial value. Both ACE-Cl and its congener from chloral are protecting groups for alcohols The derived carbonates are efficient precursors to fluoroformates including the important t-butyl fluoroformate. Applications in which fluoroformates are superior to chloroformates are outlined. The elimination of HCl from the carbamates/carbonates easily formed from **2** is described. (From the surprising carbonate elimination mechanism, a simple synthesis of aldehyde enolates under preparatively useful conditions has been discovered.) The product vinylic carbamates and carbonates are monomer precursors to vinyl polymers with urethan and carbonate branches. 2,2-Dihalovinyl chloroformates also have been made and converted to carbamate and carbonate monomers. Finally, 3- and 4-carbon synthons available by extensions of the above chemistry are introduced.

Some years ago, together with Senet and coworkers at le Bouchet Research Center of SNPE in France, we reported that aldehydes are readily converted to α-chloroalkyl chloroformates **2** when treated with phosgene in the presence of a "naked Cl^-" catalyst (ref. 1). In the key step of the process, the adduct **1** is acylated by the phosgene, thus regenerating the "Cl^-". The reaction occurs cleanly with almost all aldehydes but not with most ketones. On a laboratory scale the favored catalyst is $[PhCH_2N(nBu)_3]^+ Cl^-$ (BTBAC). Traces of HCl (moisture) inhibit the reaction but can be scavenged by including a little toluene diisocyanate in the mixture. The most important reagent, α-chloroethyl chloroformate (ACE-Cl) typically is isolated in 96% yield just by stirring acetaldehyde with phosgene (1.1 equiv) neat for an hour in the presence of 5 mol % BTBAC. After vacuum distillation of the ACE-Cl (bp 77 °C at 180 mm), the reaction flask may be stoppered and the residue reused as the catalyst in the next run without loss of yield. Considering the low cost of acetaldehyde and phosgene along with the simplicity of the procedure, ACE-Cl is potentially less expensive than some important solvents. Several of the known compounds **2** are listed below.

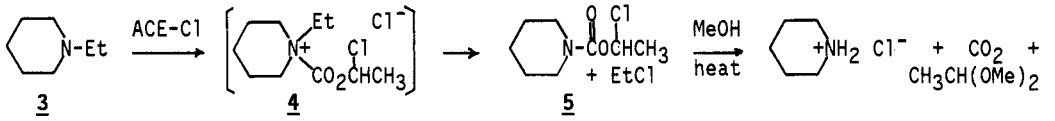


R ▫ Me (ACE-Cl), Et, nBu, iBu, iPr, cyHex, 3-cyHexen, 2-Cl-Et, Vinyl, H (ref. 2), Ph, other Aryl, Cl_3C-, Br_3C-.

When distilled at atmospheric pressure, the simple alkyl products **2** decompose to the dichlorides ($RCHCl_2$). Most of the benzylic chloroformates decompose below 60 °C by the same pathway. In contrast, the chloroformates from chloral and bromal revert to the respective aldehydes and phosgene when heated (caution, catalyzed by "Cl^-").

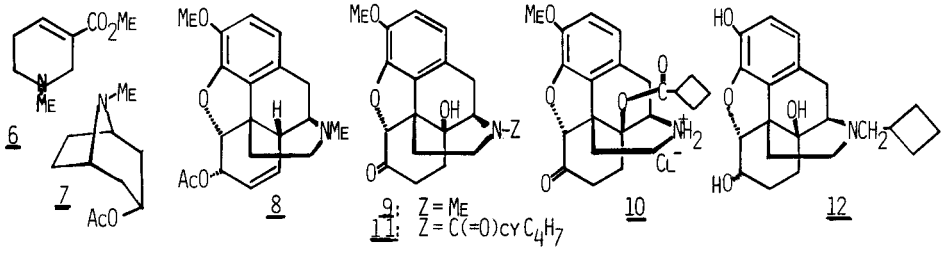
When ACE-Cl was synthesized, part of its value immediately was recognized, because ACE-OEt (from ACE-Cl + ethanol) already was sold as an alkylating agent to mask carboxyls in penicillins and cephalosporins. The prodrugs so formed are orally active. Previously, ACE-OEt only was available from the mixture obtained by photochlorination of diethyl carbonate. Since the present work made carbonates ($RCHClOCO_2R'$) from **2** readily accessible, many patents have issued in which these reagents are used to make prodrugs of, for example: antibiotics, analgesics, antiinflammatories, antihypertensives, and antiepileptics (ref. 3).

Since the initial discoveries, the interaction between the groups at SNPE and at Penn State has prospered with advances in each laboratory serving as the foundation for new research in the other. In one of these earlier collaborations, ACE-Cl was introduced as a reagent for the selective N-dealkylation of tertiary amines (ref. 4,5). The process is illustrated by the specific N-deethylation of N-ethylpiperidine (**3**) to give piperidine·HCl in 99% yield. In this reaction, the ACE-Cl is added to **3** in 1,2-dichloroethane and then the mixture is refluxed. The intermediate ACE-piperidine (**5**) can be isolated but usually is deACE-ylated directly by evaporating the reaction mixture in vacuo and then heating the residue in methanol for 30-60 min. High yield N-dealkylation with ACE-Cl is surprising since other alkyl chloroformates (ROCOCl, R = Et, $PhCH_2$, Cl_3CCH_2) almost exclusively fragment to RCl + CO_2 in the presence of **3** (ref. 6). Here the 1-chloroethyl portion of the intermediate **4** seems too hindered to undergo competitive S_N2 attack by Cl^- and the related cation is too unstable to permit S_N1 substitution. In its reactivity, ACE-Cl parallels vinyl chloroformate (VOC-Cl), the best previous chloroformate type N-dealkylation reagent (ref. 6). But ACE-Cl has the advantage that the conditions required for ACE removal are much milder, thus expanding the list of functionalities allowed in the amine to be dealkylated.



3 **4** **5**

Alkaloids which have been N-demethylated to the N-desmethyl hydrochlorides include arecoline (**6**, 95% yield), O-acetyltropine (**7**, 97% recryst. yield), and 6-acetylcodeine (**8**, 97% recryst. yield) (ref. 5). Neither the product from **8** nor its free base were isolated previously - strong testimony to the mildness of the reaction conditions. In other reaction sequences, oxycodone (**9**) has been converted to the narcotic antagonist, naltrexone, and the analgesic, nalbuphine (**12**) (ref. 5). In the synthesis of **12**, **9** is treated consecutively with cyclobutanecarboxylic anhydride, ACE-Cl, and methanol to give **10**. The rearrangement, **10** to **11**, which is based on the strategy of Olofson and Pepe (ref. 7), is instantaneous on neutralization with bicarbonate (96% overall yield for **9** to **11**). Reaction of **11**, first with borane in THF and then with BBr_3, completes the synthesis of **12**. In other work, Bachelet and Caubere have dealkylated aromatic amines with ACE-Cl (ref. 8). In a recent paper, this method also has been applied to benzodiazepines (ref. 9).

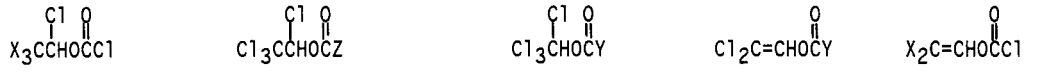


6 **7** **8** **9**: Z = Me; **11**: Z = C(=O)cyC_4H_7 **10** **12**

With ACE-Cl, N-dealkylation selectivities follow the order: benzyl, allyl, tert-alkyl >> sec-alkyl ≥ methyl > prim-alkyl >> piperidino ring scission. The inertness of the piperidine ring under the dealkylation conditions has prompted Olofson and Abbott to propose the use of piperidino as a long term masking group for primary alkyl halides in complex synthesis. As the free base, the group is stable to strong bases, nucleophiles, and reduction; and as the acid salt, it is stable to electrophiles and oxidation. The presence of a piperidine unit would also simplify the isolation and crystallization of intermediates. In tests of this hypothesis, a series of N-alkylpiperidines were converted to their respective primary alkyl chlorides in 90-97% yield with ACE-Cl (ref. 10). The potential significance of this process in drug congener preparation also has been outlined (ref. 10) and at SNPE this scheme has been applied to the efficient synthesis of the pesticide, Barban (ref. 11).

More recently at Penn State, the potential value of ACE-Cl for the protection of alcohols has been explored. A model carbonate ACE-OCH_2CMe_3 is stable: at 170 °C in nitrobenzene, in CD_3CO_2D at 60 °C for 12 hours, in 1 M anh. HCl in EtOH for 24 hours at r.t., and in MeOH for a day at r.t. However, only neopentyl alcohol is found after a day in MeOH at reflux, and at 25 °C in one day, the carbonate is 60% destroyed in CD_3CO_2D at 80 °C and 20% gone in 2/1 MeOH/water. The ACE group is easily removed with mild base (ref. 12).

In most published alcohol masking schemes, the blocking groups are stable to base and cleaved in acid. The ACE moiety is removed easily enough with base to be complementary to this literature methodology. However, it is not inert enough in acid or high-dielectric, hydroxylic solvents to have more than limited short term applications, In polar solvents, the rate determining step in ACE-scission is S_N1 ionization of the chloride ion (ref. 12). Thus, if the stability of the carbocation counterion were reduced, satisfactory protection should be achieved. This might be accomplished by replacing the electron-releasing methyl of ACE by an electron withdrawing trichloromethyl unit. 1,2,2,2-Tetrachloroethyl chloroformate (**13a**), from addition of chloral to phosgene as already described, was converted to the carbonate **14a** in 95% yield. This model reactant is stable: (1) neat at 165 °C for 22 hours, (2) in CD_3CO_2D at 80 °C for 12 hours, (3) **in neat trifluoroacetic acid at 50 °C for 16 hours**, (4) in 2:1 MeOH/H_2O at r.t. for a day, and (5) in refluxing MeOH for 20 hours. Only when refluxed in 4:1 MeOH/H_2O for 19 hours did degradation take place, and even then 70% of the original **14a** remained. In another test, standard acylation of cholesterol with **13a** using pyridine as the acid scavenger quantitatively yielded the carbonate **14b**. Moreover, when the blocking group was removed with dilute K_2CO_3 in refluxing methanol, cholesterol was recovered in 99% yield. In these and other studies (ref. 12), **13a** would seem to fit the desired criteria for inclusion in the arsenal of alcohol masking reagents.



13a: X = Cl; **13b**: X = Br

14a: Z = OCH_2CMe_3; **14b**: Z = O-Cholesteryl

15a: Y = OR; **15b**: Y = NR_2

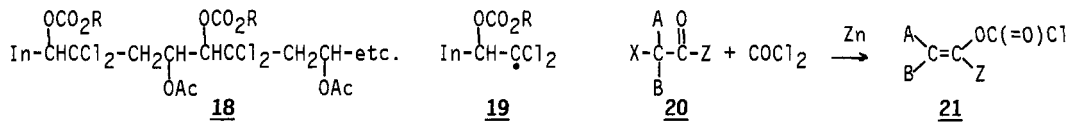
16a: Y = OR; **16b**: Y = NR_2

17a: X = Cl; **17b**: X = Br

The only apparent drawbacks to the use of **13a** in alcohol protection are the sensitivity of **13a** (*vide supra*) and the creation of a new chiral center in the products **15a** (a problem shared with many published OH masks). To circumvent these inconveniences, an effort was made to prepare and evaluate a 2,2-dichlorovinyloxycarbonyl containing reagent.

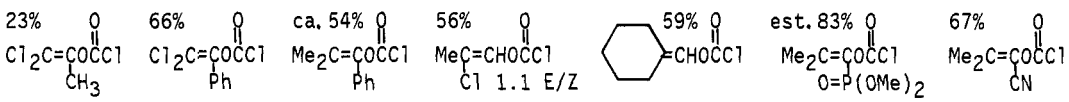
In initial tests, the carbonates/carbamates **15a,b** cleanly eliminated $ZnCl_2$ to give the vinyl products **16a** (67-90% yield) and **16b** (48-85% yield) on treatment with zinc dust either in refluxing anh. HOAc or in cold THF containing a trace of $TiCl_4$ (refs. 12, 13). This selectivity is surprising since the oxygen containing function could just as easily have been lost. Note that Favorskii first made 1,1-dichloroethylene in 1899 by the very exothermic reaction of 2,2,2-trichloroethyl acetate with zinc. Also today, zinc is widely used to unmask 2,2,2-trichloroethyl esters, phosphates, carbonates, and carbamates. Even more remarkable was the discovery that both tetrahaloethyl chloroformates **13a,b**, when reacted with zinc dust, are converted to their 2,2-dihalovinyl derivatives, **17a** (in THF, 75% distilled yield, bp 82-85 °C at 120 mm) and **17b** (in EtOAc) (refs. 12, 14). To isolate **17a,b** as stable liquids, it is important to remove zinc salts by precipitation with pentane prior to vacuum distillation. No evidence for competing attack of the acid chloride function by zinc was found. Finally, in a most astonishing process, treatment of chloral with phosgene and zinc dust in MeOAc/ether afforded dichlorovinyl chloroformate (**17a**) in 50% distilled yield (refs. 12, 14). Similar reaction of bromal gave **17b** (26% yield). Besides the side reactions already noted, another complication should have been attack of the phosgene by the zinc to give carbon monoxide and $ZnCl_2$. Acylation of **17a** with alcohols or amines gave the corresponding carbonates **16a** and carbamates **16b** in excellent yield. The carbamates **16b** often were obtained even more easily by N-dealkylation of appropriate tertiary amines. For example, heating N-ethylpiperidine with **17a** gave **16b** [$R_2 = (CH_2)_5$] in 97% yield by a simple vacuum distillation workup. Analogous procedures afforded the dibromo congeners of **16a,b** from **17b**. Considering the unexpectedly easy accessibility of the dichlorovinyl reagent **17a**, it is disappointing to report that the derived carbonates **16a** are less stable in acid and polar, protic solvents than their tetrachloroalkyl congeners **15a**. Thus, **17a** would have little value as a reagent for alcohol protection (ref. 12).

However, this side excursion had other merits. The halogenated carbonates and carbamates **15** and **16**, their bromo analogues, and mixed halo adducts from halogenation of the vinylic compounds (refs. 12, 14) are structurally related to a large variety of important pesticides (ref. 15). Indeed, some compounds **16a,b** made by circuitous routes already are known to be bioactive (ref. 16). Also, Chevalier at SNPE has found that the dichlorovinyl carbonates **16a** are too hindered to undergo self polymerization but do give an alternating 1:1 copolymer with vinyl acetate with the unusual structure **18** (ref. 17). Presumably the most stable initial radical is **19** but this is too hindered to react with more **16a**. Instead, vinyl acetate adds in its normal fashion and the cycle is repeated.



18 19 20 21

Some experiments designed to establish the scope of the remarkable reaction of chloral with zinc and phosgene to give the vinylic chloroformate **17a** were performed. The generation of zinc enolates by treatment of α-haloesters (Reformatsky reaction) and α-haloketones with zinc ranks among the most useful processes in synthetic chemistry. However, these enolates are invariably acylated and alkylated at the carbon end of the ambident anion (except possibly by TMS-Cl). In contrast, we have discovered that with certain combinations of X, A, B, and Z of **20**, the enol chloroformates **21** are obtained instead of products from C-attack. First, X may be either chlorine or bromine. Second, A and B may be either halogen or alkyl or a combination of the two **but not hydrogen**. This suggests that attack at the enolate oxygen is due to a combination of steric hindrance at carbon and the very high electrophilicity of the phosgene (alkyl chloroformates did not give O-substituted products). The requirements for Z are somewhat less stringent; **21** has been isolated with Z = H, alkyl, aryl, cyano, and dialkylphosphonato. With Z ▫ alkoxy, the normal Reformatsky reaction occurs, and with Z ▫ halo, the predicted ketene product is formed. Some of the compounds made by the process, **20** to **21**, are depicted below with % yields (refs. 12, 18):

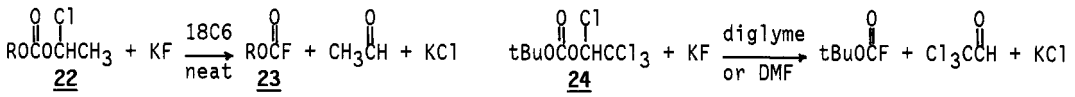


23% 66% ca. 54% 56% 59% est. 83% 67%

The ready hydrolysis of ACE-OR and its tetrachloro analogue in mild base suggests that the nucleofugacities of these chloroethoxide anions are high enough to permit their replacement by other nucleophiles. An important situation is which this property could prove valuable was recognized.

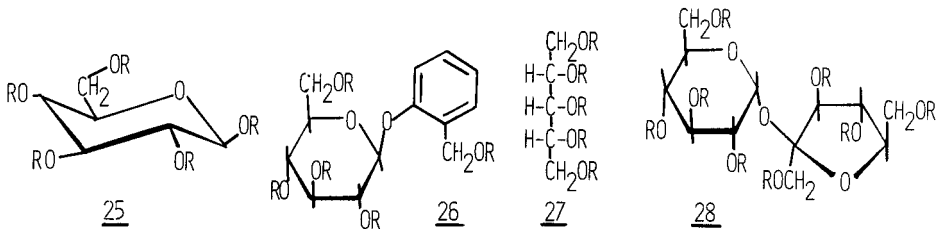
The t-butyloxycarbonyl (BOC) group introduced over 30 years ago by Carpino is now the most broadly used amino protecting group in peptide chemistry and also plays a significant role in other areas of synthetic chemistry. Its major disadvantage lies in the introduction step. Because t-butyl chloroformate decomposes at -10 °C, it cannot serve as the acylating agent. Instead, BOC-N_3 was the reagent of choice for a long period but its toxicity and propensity for detonation finally led to its abandonment. Presently, $(BOC)_2O$ is the most widely used reagent despite its high MW and high cost ($400/kg, 97%, Aldrich). Almost 20 years ago Schnabel and Carpino independently reported that BOC-F is stable and also is an excellent acylating agent for amino acids by standard pH stat methodology (ref. 19). However, these investigators did not propose a practical route to the BOC-F reagent. Usually, alkyl fluoroformates are most easily and economically made from the corresponding chloroformates by halide exchange with KF/18-crown-6 (ref. 20). However, the instability of BOC-Cl eliminates this method as a source of BOC-F.

If the nucleofugacities of chloroalkoxide anions are as high as expected, it should be possible to make BOC-F by attacking ACE-OtBu and/or its tetrachloroethyl congener with activated fluoride. To test this idea, t-butyl alcohol was treated with ACE-Cl using pyridine as the acid scavenger to obtain ACE-OtBu in 90% yield (bp 58-60 °C at 10 mm). Then this carbonate was heated (70 °C oil bath) at reduced pressure with 1.5-2 equiv. of KF and 3-5 mol % of 18-crown-6 catalyst. The BOC-F and acetaldehyde were allowed to evaporate from the stirred mixture as formed and were collected in a -80 °C trap. Estimated NMR yields of BOC-F in the trap ranged up to 95%, and under optimum conditions, the yield of pure distilled BOC-F was 84%. When other carbonates **22** were prepared and reacted similarly, the yields of product fluoroformates **23** again were excellent. Some examples of **23** with distilled or crystallized yields are: R = t-amyl (83%), 1-adamantyl (76%), benzyl (60%), n-octyl (86%), and 3-cholesteryl (82%). In this process, it is critical to remove at least one of the products as formed (vide infra) (refs. 21, 22). In a related experiment, the carbonate **24** was obtained in 99% yield as a stable solid (mp 68-70 °C). When **24** was heated with KF **but no added catalyst** in diglyme or DMF at 50 °C at reduced pressure, BOC-F distilled over (ca 80% yield after purification, ref. 21). However, the reagent is not as stable thermally as promised by Schnabel and Carpino: BOC-F decomposes irreproducibly at 50 °C and thus cannot be shipped safely. Still, with recent improvements BOC-F now is made commercially at substantially lower molar cost than $(BOC)_2O$. Much experience manufacturing and reacting BOC-F on site has been accumulated by SNPE and a subsidiary, Propeptide.



At SNPE, the activated carbonate **24** has been used directly as the acylating agent in the formation of BOC-amino acids (ref. 23). Similar reagents have been developed for the introduction of other amine masking groups (ref. 23). In related chemistry, N-protected amino acids have been converted to active esters for subsequent peptide coupling by treatment with the tetrachloroethyl carbonates of N-hydroxysuccinimide, 2,4,5-trichlorophenol, and pentafluorophenol (ref. 24). The process is illustrated by the isolation of the N-succinimidyl ester of Z-(S-benzyl)cysteine in 92% yield from activation of Z-(Bzl)Cys with 1,2,2,2-tetrachloroethyl N-succinimidyl carbonate. In the further generalization of these concepts, Barcelo, Senet, and Sennyey at SNPE have utilized several different chloroalkyl chloroformates **2** as selective precursors to carbamates, thiocarbamates, and unsymmetrical ureas. Applications include practical syntheses of N-nitrosourea antitumor agents (ref. 25) and the pesticides, Aldicarb, Carbofuran, and Molinate (ref. 26).

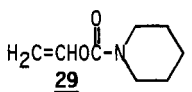
The development of a new route to fluoroformates (vide supra) was followed by our discovery that fluoroformates have important advantages over chloroformates as synthetic acylating agents in specific situations. When chloroformates are added to DMSO, the adducts generated in an explosively exothermic reaction usually rearrange immediately to Pummerer type products. Chloroformates also acylate DMF to give adduct salts which fragment to Vilsmeier reagents. In a surprising contrast, fluoroformates are inert to these solvents up to temperatures of at least 80 °C. Thus, unlike chloroformates, fluoroformates should be effective acylating agents in very polar aprotic solvents like DMF and DMSO. Important representatives of compounds insoluble in less polar aprotic media include amino acids, carbohydrates, nucleotides, and certain organic salts. It often is desirable to carboalkoxylate such compounds either to modify their properties as materials or as part of a synthetic scheme (e.g., attachment of blocking groups). Attempts to perform such reactions in polar protic solvents with added base generally results in at least partial decomposition of both reactants. To study the proposed fluoroformate in DMSO acylation methodology, some experiments were performed using carbohydrates and analogues as model substrates (ref. 22). With their several hydroxyls, carbohydrates would provide a stringent test of reaction efficiency and expose any cyclic carbonate forming side reactions. In the first test, when triethylamine was added to β-D-glucose and excess FCO_2Et in DMSO, the known pentacarbonate **25** was isolated in 82% yield. Similar treatment of the analgesic salicin with FCO_2iPr afforded the crystalline pentacarbonate **26** in 80% yield. With KF (to give KHF_2) instead of Et_3N as the added base, the yield of **25** was 89% (60 °C for 10 hours) and with adonitol and KF in DMSO, the yield of **27** was 91%. Finally acylation of sucrose in DMSO (Et_3N) with FCO_2Et and FCO_2n-octyl afforded the octacarbonates **28** in 82% and 83% yields, respectively. In a parallel reaction in DMF, the yield was higher but the product was not as pure. The new process was not satisfactory for the carboalkoxylation of cellulose to a high degree of substitution. However, treatment of polyvinyl alcohol of average MW 14,000 in DMSO with FCO_2Et and Et_3N yielded a yellow rubber-like material with 85% of the OH's acylated and no detectable cyclic carbonate by NMR analysis (ref. 22). As this investigation was being completed, Lang and Shreeve (ref. 27) noted that DMSO is unreactive with acetyl or benzoyl fluoride but they did not mention any consequences of their observation in synthetic chemistry.



If a simple method for the β-elimination of HCl could be devised, the ready availability and low cost of α-chloroalkyl carbonates and carbamates would seem to make these compounds attractive precursors to their O-1-alkenyl derivatives. Vinyl polymerization of such monomers would yield polyurethan and polycarbonate polymers with polyvinyl backbones. These materials should have both similarities to and differences from today's widely used

polyurethan and polycarbonate carbonate polymers in which the urethan and carbonate functions are part of the polymer backbone. A few poly(vinyl carbamates) and poly(vinyl carbonates) have been made (ref. 28). However, since the initial reagent is the expensive vinyl chloroformate (VOC-Cl), little incentive to develop commercial products has existed. The monomer also can be made from enol silanes (ref. 29) but this route is even more costly. From what little is known, the side chain structure is important, but usually the polymers are hard but not brittle, clear thermoplastics with very high decomposition temperatures and excellent chemical resistance (ref. 28). In other words, if O-vinyl carbamates and carbonates could be made at little cost, investigations of the use of these monomers to prepare useful new materials should be quite rewarding.

In fact, thermal elimination of HCl from ACE-NR_2 is a relatively simple process. Wooden made VOC-piperidine (**29**) in 91% distilled yield just by refluxing ACE-piperidine for 3 hr in o-dichlorobenzene containing recyclable collidine (C) as an acid scavenger (ref. 30). The reaction is much slower without C, but anyone patient enough to heat ACE-piperidine neat for 6 days at 0.3 mm can isolate **29** in 78% yield. In the same reaction of the morpholide and C, the yield of **30a** is 88% (2 hr at reflux). When the methyl of the ACE group is substituted by alkyls, the elimination is easier. For example, refluxing tetrachloroethylene (24 hr) is favored in the preparation of **30b** (E/Z ▫ 0.6, 84% yield). In this latter reaction, 0.05 equiv. of the salt, $(nBu)_4N^+ Br^-$ (TBAB), is included to catalyze the E_1 process. In another comparison, the yields of **31a** and **31b** are 90% (in refluxing bromobenzene + C, 2 hr) and 99% (in refluxing tetrachloroethylene + C + TBAB, 2 hr). Products from double eliminations also have been obtained in moderate yields: **32** (35% yield), **33** (40%), and **34** (93%). Many extra functionalities are tolerated. For example, the ACE-normethyl derivatives of **6-8** all have been converted to the VOC-products. Similarly, **35** (E/Z = 3/4) and **36** (E/Z = 3/5) have been made in 94% and 56% yields, respectively. Some moieties even catalyze the elimination by increasing salt concentration: the yield of **37** is 85% when the precursor is heated neat (no C, but note salt formation from tert-amine) at 1 mm for 3 h and the yield of **38** is 97% when the reactant is merely refluxed in 1,2-dichloroethane (no C, 4 hr) (ref. 30).



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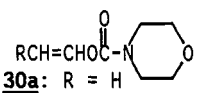
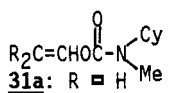
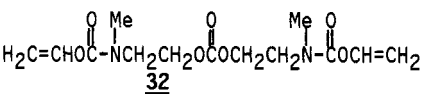


30a: R = H
30b: R = Me



31a: R ▫ H
31b: R = Me



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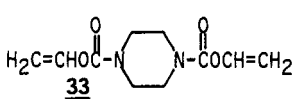

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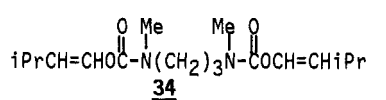

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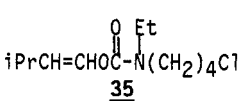

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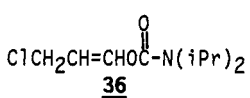

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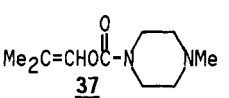

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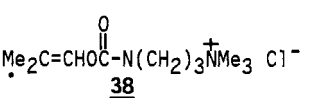

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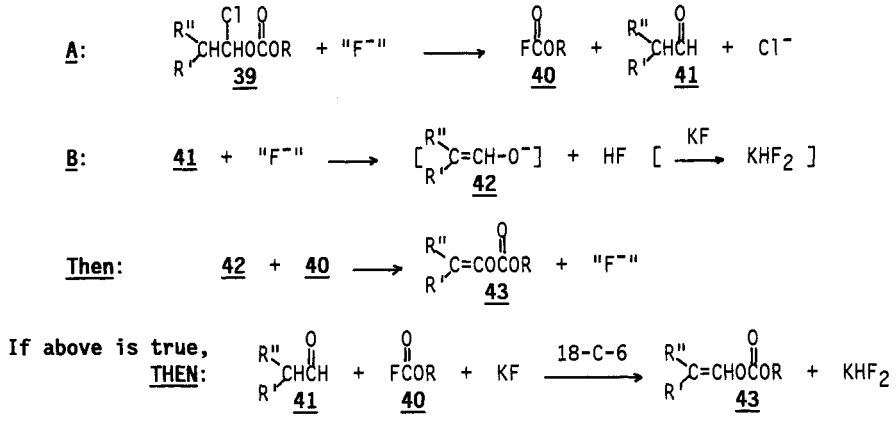
In contrast to the carbamate chemistry, thermal loss of HCl from the analogous carbonates requires much higher temperature and is accompanied by major yield destructive side reactions (ref. 12). For example, after 20 hr at 200 °C, the bis-ACE carbonate of hexanediol still contains 1.2 ACE units per VOC group and the major product is the alkyl chloride (3.6 units). By reducing HCl concentration with an Argon flow, the amount of alkyl chloride is lowered but the ratio of ACE to VOC to RCl still is 0.8:1:0.2. Even worse, the bis-ACE carbonate of diethylene glycol at 200 °C under a 30 mm vacuum contains only 20% VOC groups after 4 hr. After 20 hr, the major product is bis-2-chloroethyl ether. The failure to obtain a good yield of the bis-vinyl carbonate of diethylene glycol is especially unfortunate. The analogous bis-allyl carbonate is the monomer for the CR-39 polymer used in high quality plastic safety prescription glasses and it has long been known that the vinyl congener is much easier to polymerize. However, development of the vinyl monomer has not been feasible before because of its very high cost.

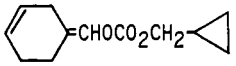
The key to an economical route to alkenyl carbonates was discovered by Dang (ref. 22). When he heated ACE-OCH_2CMe_3 with KF(18-C-6) in benzonitrile at atmospheric pressure (**no vacuum**), the products after 2½ hr were $FCO_2CH_2CMe_3$ in 79% yield and unexpectably VOC-OCH_2CMe_3 in 19% yield. Also, amazingly after 10 hr, no fluoroformate remained and the yield of VOC-product was 68%.

Since the carbonate **39** is first converted to the fluoroformate **40** and the aldehyde **41** (*vide supra*), this result must mean that "F^-" is a strong enough base to form the aldehyde enolate **42**, which then is immediately acylated by **40** to give the alkenyl carbonate product **43**. If this conclusion is correct, it follows that **enolizable aldehydes** will react with KF/18-crown-6 in the presence of fluoroformates to give the **elusive carbonates 43** and that excess KF neutralizes the HF which is liberated in the reaction as KHF_2.



Before examining this heretical proposal further, some additional examples of the formal β-elimination of HCl from **39** to give **43** are worthy of discussion. Note that the reaction stoichiometry requires 2 equiv. of KF. Under optimum conditions, some excess KF is used along with 4-7 mol % of 18-crown-6. The preferred solvents are PhCN and $PhNO_2$ for low boiling carbonates and acetonitrile for the higher boiling products. When the reaction is performed neat, the 1-fluoroethyl carbonate is a major side product. Otherwise this difficult to separate contaminant rarely is found. If the intermediate aldehyde is volatile, some is lost thus lowering the yield unless the reaction flask is topped by a dry-ice acetone condenser. To further increase the yield in such situations, it is advantageous to include some extra aldehyde in the reaction medium. Reaction temperature and time vary widely with reactant structure and other conditions but usually are 55-80 °C for 8 hr to a day. Some results are given in Table 1 (refs. 22, 31).

TABLE 1. Direct Conversion of **39** to **43**.

Product	Solvent	Ald +eq	Yield (%)
$H_2C{=}CHOCO_2CH_2CMe_3$	PhCN	--	68
$Me_2C{=}CHOCO_2CH_2CMe_3$	Neat	--	71[a]
$H_2C{=}CHOCO_2Et$	$PhNO_2$	0.3	74
$H_2C{=}CHOCO_2tBu$	MeCN	0.2	77
$H_2C{=}CHOCO_2nOctyl$	MeCN	0.2	83
$Me_2C{=}CHOCO_2tBu$	MeCN	--	61
$MeCH{=}CHOCO_2iPr$	MeCN	0.3	71[b]
$Me_2CHCH{=}CHOCO_2iPr$	MeCN	--	82
$[H_2C{=}CHOCO_2(CH_2)_3]_2$	MeCN	0.2	93
$(H_2C{=}CHOCO_2CH_2CH_2)_2O$	MeCN	1.0	99[c]
	MeCN	--	80

[a]Also MeCHF- 18%; [b]E/Z=0.4; [c]With 5% MeCHF-

TABLE 2. Conversion of **41** and Haloformate (X = Cl[a] or F) with KF/18-crown-6 to **43**.

Product	X=	Solvent	Yield (%)([b])
$Me_2C{=}CHOCO_2CH_2CMe_3$	Cl	MeCN	85(8)
$H_2C{=}CHOCO_2Et$	F	$PhNO_2$	83
"	Cl	MeCN	76(4)
$H_2C{=}CHOCO_2Me$	F	MeCN	62(11)
$H_2C{=}CHOCO_2CH_2CF_3$	F	MeCN	76(12)
$H_2C{=}CHOCO_2CH_2Ph$	F	MeCN	89
$H_2C{=}CHOCO_2tBu$	F	MeCN	89
$H_2C{=}CHOCO_2CH_2CH{=}CH_2$	Cl	MeCN	74(10)
$H_2C{=}CHOCO_2Ph$	F	MeCN	15[c]

[a]Extra equiv of KF included; [b]Amount MeCHF-contaminant; [c]Get 28% $(PhO)_2C{=}O$.

Ketones are readily deprotonated to their respective enolates with appropriate bases under synthetically useful conditions. As a consequence, an enormous wealth of publications involving the selective chemistry of ketone enolates may be found in the literature. The opposite is true with aldehydes. When attempts are made to deprotonate enolizable aldehydes, the enolate thus generated immediately reacts as a donor with another molecule of

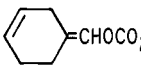
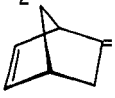
aldehyde as acceptor in an aldol or Michael condensation. The chemistry is dominated by the powerful acceptor properties of aldehydes. Even TMS enol ethers generally fail as satisfactory aldehyde enolate precursors. To generate the enolate of acetaldehyde in a synthetically useful form, the RLi-induced ring-cleavage of THF has been favored - hardly a very cheap or straightforward reaction.

In the present chemistry, however, the aldehyde enolates must be cleanly generated and rapidly and efficiently trapped. The yield increase from including extra aldehyde in the reaction medium has been noted and with substantial concentrations of aldehyde in an enolate forming system, it is puzzling that there are no complications from competing aldol condensations. Such processes would not only lower the yield of the product **43** but even more importantly should deactivate the F^- by H-bonding. The chemistry of fluoride both as a strong nucleophile and as a base is amply documented. Both of these reactivities are in demand and are enhanced when the F^- is activated, most notably by 18-crown-6 in an aprotic solvent (ref. 32). Still, it is surprising that this F^- could so easily yield such a selective naked aldehyde enolate.

Some of the data which prove the fact are summarized in Table 2 (refs. 22, 31). In the preparation of alkenyl carbonates **43** from aldehydes (excess with acetaldehyde), either fluoroformates or chloroformates may be the other reagent. The latter will rapidly undergo halide exchange in the reaction medium (ref. 20, easily compensated with another equiv. of KF). In acetonitrile, 1.5-2 equiv of KF (per **40**) and 7-10 mol % 18-crown-6 are optimum, with temperature and time ranges of 35-70 °C and ca 4 hr to a day. Workup consists of dilution with dichloromethane, extraction with water, and vacuum distillation. The good yields of the -Me and $-CH_2CF_3$ carbonates are pleasing because both have been proposed as useful monomers in fiber optics applications (ref. 33). The 89% yield of the benzyl carbonate also is noteworthy because complications from a benzyl fluoride forming side reaction were not encountered. The same is true for the allyl product. The significant amount of fluoroalkyl side product in some of the Table 2 reactions is surprising.

The lack of a greater variety of products in Table 2, despite good yields, is an incidental byproduct of the invention of a valuable modification of the Table 2 process. Our discovery of the compatibility of fluoroformates with DMSO already has been presented along with some useful consequences. Since the polar aprotic solvent DMSO would also activate F^- (ref. 32), alkenyl carbonate formation might occur in the absence of 18-crown-6. Experiments defining the success of this variation are presented in Table 3 (refs. 22, 31).

TABLE 3. Preparation of Alkenyl Carbonates **43** from Fluoroformates and Aldehydes in DMSO.

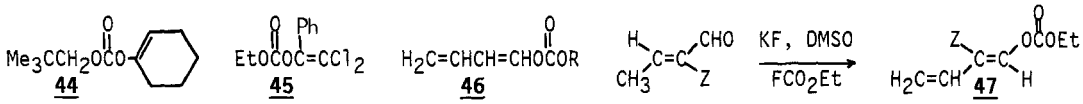
Product	RCHO/FCO_2R/KF	%Yield	Product	RCHO/FCO_2R/KF	%Yield
$H_2C{=}CHOCO_2CH_2CMe_3$	1.5/1/2.8	72	$[H_2C{=}CHOCO_2(CH_2)_3]_2$	1.5/1/1.5[a]	92
$H_2C{=}CHOCO_2Et$	1.5/1/2	73	$(H_2C{=}CHOCO_2CH_2CH_2)_2O$	1.5/1/2[a]	80[b]
$H_2C{=}CHOCO_2iPr$	1.8/1/2.3	86	$MeCH{=}CHOCO_2Et$	1.5/1/2.2	71[c]
$H_2C{=}CHOCO_2$(1-Adamantyl)	1.8/1/2.5	84	$MeCH{=}CHOCO_2C(Me){=}CH_2$	1.1/1/2	82[d]
$Me_2C{=}CHOCO_2Et$	1.4/1/2	74	$H_2C{=}CHOCO_2CH_2Ph$	1.4/1/2.4	80
	1/1/3	80		0.8/1/2.6	85

[a]per OC(=O)F unit; [b]Plus 3% CH_3CHF-; [c]E/Z=0.3; [d]E/Z=0.33.

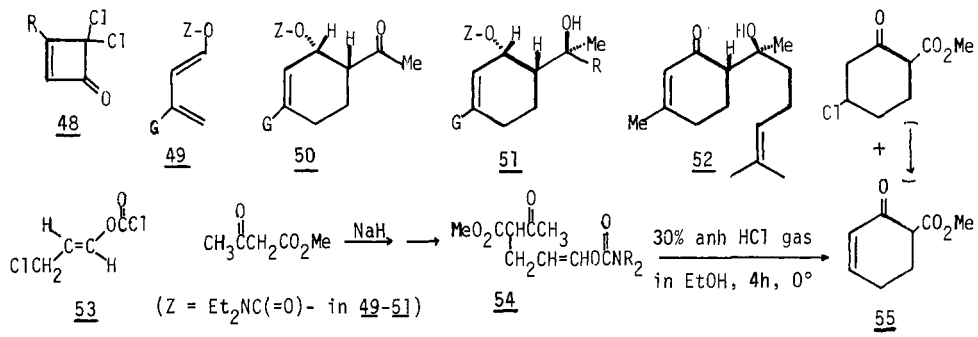
From Table 3, it is evident that little is lost by the DMSO method although all of these reactions were substantially slower (10-24 hr at 60-90 °C) than the related KF/18-C-6/MeCN processes. Again workup is simple. The mixture is diluted with dichloromethane, washed with water, concentrated and vacuum distilled. No fluoroethyl impurity was found in any reaction except for the 3% in the synthesis of the bis-VOC derivative of diethylene glycol.

Enol carbonate formation also occurs with a few acidic ketones, although in general the reaction is much slower. For example, cyclohexanone is converted to the enol carbonate **44** in 77% yield after 8 days at reflux in acetonitrile with 1.3 equiv of chloroformate and 4.3 equiv KF and 19 mol % 18-crown-6. Based on this result, aldehydes must be significantly

more acidic than simple ketones. Literature experimental data pertaining to this point is effectively nonexistent. More acidic ketones do react under reasonable conditions: the dichlorovinyl carbonate **45** (83% yield) is obtained from α,α-dichloroacetophenone in DMSO after 12 hr at r.t. (ref. 31, 34) In another extension of scope, trans-crotonaldehyde is even more reactive than simple aldehydes. With KF/18-C-6/MeCN, **46** (R = Et, E/Z=8.4) is obtained in 78% yield and even with sulfolane as the solvent (120 °C, no 18-C-6), **46** (R = CH_2tBu) is isolated in 86% yield. These mimics of 1-acetoxybutadiene monomer are similarly reactive. By the DMSO method, the isoprene and chloroprene congeners **47**, (Z ▫ Me, 79% yield; Z ▫ Cl, 57%) are formed stereospecifically (ref. 35).



Alkenyl carbonates are not limited to roles as monomers and bioactive materials. They add HBr to give α-bromo adducts which are better alkylating agents than α-chloroalkyl carbonates (vide supra) (ref. 36). [The Br-compounds also are available by Cl/Br exchange (ref. 37). Other substitutions have been performed by Caubere and SNPE (ref. 38).] Cycloaddition of alkenyl carbonates with $Cl_2C=C=O$ directly forming the cyclobutenone **48** (R=H, 50% yield, new) and its homologue **48** (R ▫ Me) have been achieved. The latter previously was made only from propyne. This and related cyclobutenones have given Danheiser and others entry into several important ring systems (ref. 39). Much present chemistry at Penn State focuses on the use of our products as synthons and intermediates. For example, **49** reacts both regio- and sterospecifically with methyl vinyl ketone to give **50** (G ▫ H, 92% yield; G = Me, 89% yield), which in turn adds RMgX(RLi) regio- and stereospecifically to form **51** (ref. 35). In one example, the product after LAH reduction and oxidation was ±-Hernandulcin **52**. Analogs of this terpenoid sweetener, said to be over 1000 times sweeter than sucrose (ref. 40), also have been made (ref. 35). In other work, the acrolein-phosgene adduct readily rearranges to **53** (78% yield, E/Z=17, $ZnCl_2$ catalyst). Reaction of the corresponding carbamate as an alkylating agent with acetoacetic ester gives **54** (86% yield) which is easily cyclized to **55** (98% yield) (ref. 41).



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