Synthesis of Enol Chloroformates

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In a recent series of communications from this laboratory, vinyl chloroformate (VOC-Cl) was introduced as a useful reagent for the selective N-dealkylation of tertiary amines[1-3] and for the masking of amino[4] and hydroxyl[3] groups in synthesis. N-Dealkylation with VOC-Cl has already permitted the development of much improved preparative routes to the important narcotic antagonists, naloxone and naltrexone, as well as the potent mixed agonist–antagonist analgesics, *N*-cyclobutylmethylnoroxymorphone and nalbuphine.[1,2,5] An efficient process for the construction if the heptapeptide sequence H-Ser-Phe-Leu-Pro-Val-Asn-Leu-OH (all L) has been used to show the utility of VOC-Cl in amino protection.[4,5] To illustrate the advantages of VOC-Cl in hydroxyl protection, a facile synthesis of the classic narcotic antagonist, nalorphine, has been reported.[3] The scope and limitations of other uses of VOC-Cl as a reagent and precursor are presently under investigation.[5]

The demonstrated value of VOC-Cl and VOC groups in synthetic chemistry has provided substantial incentive for initiating a comparative study of the utility of other enol chloroformates in similar applications. Can more effective reagents be developed by appropriate substitution of the vinyl unit? Certainly an α-alkyl-VOC moiety (**1**) should be more reactive than VOC toward electrophilic cleavage due to the increased stability of the intermediate cation (**2**).

$$\underset{\mathbf{1}}{CH_2{=}C(R')OC(O)XR} \xrightarrow{E^+} \underset{\mathbf{2}}{[ECH_2{-}C^+(R')OC(O)XR]}$$

XR is OR, SR, NR_2

Inductive and steric factors should reduce the sensitivity of **1** (vs. VOC-XR) toward base hydrolysis, another potentially attractive feature. Similar and other variations in the vinyl substitution pattern could induce greater crystallinity and, thus, more facile isolation of the modified VOC compounds.

The literature records only two enol chloroformate syntheses. VOC-Cl itself is made[6] by the gas-phase pyrolysis of the bis(chloroformate) **3**.

$$HOCH_2CH_2OH + COCl_2 \rightarrow \underset{\mathbf{3}}{ClC(O)OCH_2CH_2OC(O)Cl} \xrightarrow{480\ ^\circ C} \underset{\text{VOC-Cl}}{H_2C{=}CHOC(O)Cl}$$

(35% overall)

In the other publication, the combination of acetone with phosgene is claimed to yield isopropenyl chloroformate.[7] However, this work could not be reproduced and has since been disproved.[8] Thus, since substituted enol cholorformates are previously unknown and obviously not accessible by the pyrolytic route to VOC-Cl, the development of a general synthesis would be required before their merits could be appraised.

Acylation of enolates with phosgene would seem a simple and direct route to enol chloroformates. However, complications caused by the ambident nature of enolates would be anticipated as would problems caused by reaction of the enolate-forming base and its conjugate acid with phosgene and the product chloroformate. Still several potential schemes of this kind are tested. Enolate-forming bases used included NaH, $NaNH_2$ (with NH_3 removal prior to $COCl_2$ addition), lithium 2,2,6,6-tetramethylpiperidide,[9] and hexamethylphosphoric triamide radical anion[10] (as Li^+ salt). Processes involving other potential enolate-forming reactions such as the *n*-BuLi initiated fragmentation of THF[11] and the oxygenation of alkenyllithiums[12] were also examined. All of these schemes failed entirely; no enol chloroformate was found.

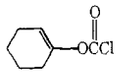
Success was finally achieved by using bis(keto)mercurials as the enolate equivalents. Motivation for testing this approach was provided by reports[13,14] that treatment of α-mercuri ketones with simple acyl halides yields only the *O*-acyl products.

The enol chloroformates which have been prepared are listed in Table I along with IR and NMR data of structural importance. Most thoroughly studied was the synthesis of isopropenyl chloroformate (**4**), which was best made by adding diacetonylmercury[15] to excess phosgene in CH_2Cl_2 (86% distilled yield).

$$(MeCOCH_2)_2Hg + COCl_2 \rightarrow \underset{\mathbf{4}}{H_2C{=}C(Me)OC(O)Cl} + \underset{\mathbf{5}}{MeCOCH_2HgCl}$$

Though there is some evidence that **5** can also serve as a source of **4** (see Experimental Section), chloromercuri ketones are generally so insoluble in reaction-compatible solvents that they are not usable precursors.[16] In the syntheses of the enol chloroformates of cyclohexanone, acetophenone, and pinacolone (38–64% yield), the product distillation fractions were contaminated by starting ketone (15–30%). Since this impurity is only an inert diluent in the uses contemplated for these chloroformates, its removal by high efficiency fractionation or chromatography was not attempted. However, as a further structure proof, all chloroformates were analyzed as the crystalline anilides or cyclohexylamides. Though the expected chloroformate is obtained from cyclopropyl methyl ketone,

Table I. Enol Chloroformates: Selected Spectral Data

Registry no.	Chloroformate	IR stretch (CCl_4), μm		NMR (CCl_4), δ[b] vinyl H
		C=O	C=C[a]	
57933-83-2	$H_2C{=}C(CH_3)OC(O)Cl$	5.60	6.03	4.7–5.0 (m)
64294-76-4	$H_2C{=}C(Ph)OC(O)Cl$	5.58	6.09	5.12 (d, 3.5) 5.40 (d, 3.5)
64294-77-5	$H_2C{=}C(t\text{-}Bu)OC(O)Cl$	5.59	6.03	4.91 (s)
64294-78-6	$H_2C{=}C(c\text{-}C_3H_5)OC(O)Cl$	5.61	6.01	4.5–5.0 (m)
64294-79-7		5.59	6.08	5.1–6.0 (m)
5130-24-5	$H_2C{=}CHOC(O)Cl$	5.60	6.07	4.79 (q, 2.5, 6) 5.09 (q, 2.5, 14) 7.11 (q, 6, 14)

[a] Carbonyl stretch band much stronger than C=C stretch. [b] Coupling constants in hertz, multiplet = m, quartet = q, etc.

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the process was not practical because of difficulties in isolating pure the volatile $(C_3H_5COCH_2)_2Hg$. Volatility problems also hampered the isolation of VOC-Cl from treatment of $(HCOCH_2)_2Hg$ with phosgene.

From preliminary tests involving **4**, it is already apparent that enol chloroformates from ketones could have substantial impact as synthetic reagents.[5,17] However, for some of the processes envisioned to be practical, the synthesis outlined here must first be superceded by a more economical route.

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer, NMR spectra on a Varian A60-A spectrometer, and mass spectra on an AEI MS-902 spectrometer.

Isopropenyl Chloroformate. (Hood!) A 250-mL three-neck flask equipped with a magnetic stirrer was fitted with a pressure-equalizing dropping funnel topped by a rubber septum, a dry-ice-jacketed volume-calibrated pressure-equalizing dropping funnel topped by a dry ice–acetone condenser connected to phosgene and N_2 tanks, and a dry ice–acetone condenser connected to a series of four traps (empty, concentrated H_2SO_4, empty, concentrated NH_4OH) and vented to hood exhaust. The system was flushed with N_2 to remove trace moisture. The reaction vessel was charged with anhydrous CH_2Cl_2 (25 mL) and cooled in an ice bath. Phosgene (Matheson; 10 mL, 0.14 mol) was condensed in the jacketed funnel and then added to the CH_2Cl_2. Then diacetonylmercury (13.1 g, 0.042 mol; from ethyl isopropenyl ether in 99% yield, mp 67–69 °C, lit.[15] 68 °C) in 15 mL of CH_2Cl_2 was added (15 min) to the stirred mixture, which was kept at 0 °C for another 2 h and then at 25 °C for 2 h while a white solid precipitated. Next the dropping funnels were replaced by stoppers and a take-off valve, connected to a hood aspirator via a dry ice–acetone trap, was inserted in the third neck of the reaction flask. Volatiles were evaporated at reduced pressure and collected in the trap. This condensate was warmed to 25 °C and fractionally distilled through a 10-cm Vigreux column (hood). The first fraction of bp ≤47 °C was collected in another trap and this CH_2Cl_2 solution of phosgene and other volatiles was disposed of. Simple distillation of the remaining liquid afforded 4.37 g (86% or 43% if two available isopropenyl units) of isopropenyl chloroformate, bp 74–75 °C.

Anal. Calcd for $C_4H_5ClO_2$: C, 39.9; H, 4.2; Cl, 29.4. Found: C, 39.9; H, 3.9; Cl, 29.6.

When this reaction was repeated in THF (distilled from $LiAlH_4$), the yield was 104% (or 52%, NMR analysis). Because the product and solvent were not readily separable, the THF solution was used in subsequent synthetic chemistry. The yield did not change if the reaction was left for 24 h prior to workup.

With THF as the reaction solvent, 1-*tert*-butylvinyl chloroformate was similarly synthesized from mercury bispinacolone (see below) and phosgene. Fractional distillation of the material contained in the trap afforded a fraction, bp 73 –75 °C (65 mm), which analyzed (NMR) as a mixture of the desired chloroformate (38% yield) and pinacolone in a ratio of 6:1.

Vinyl chloroformate was similarly prepared by reaction of mercury bisacetaldehyde[15] in diglyme (distilled over sodium) with phosgene in anhydrous ether. The product codistilled with the ether, but was identified by NMR comparison with an authentic sample and by derivative preparation (see below).

1-Cyclohexenyl Chloroformate. Using the apparatus design already described, mercury biscyclohexanone[13] (28.0 g, 0.071 mol) in 200 mL of $CHCl_3$ (distilled from P_2O_5) was added (3 h) to the stirred, cooled solution of phosgene (11 mL, 0.15 mol) in $CHCl_3$ (50 mL). Stirring was continued overnight and much of the excess phosgene then was blown out of the system with N_2. Next the desired solution was separated from solid by-products using a filter stick (sealed system) connected to a filter flask which in turn was connected to a hood aspirator via a trap and $CaCl_2$ drying tube. The filtrate was distilled first at atmospheric pressure (H_2SO_4–NH_4OH traps) and later at reduced pressure. The fraction bp 79–85 °C (22 mm) contained the product chloroformate and cyclohexanone in a ratio of 7:3 (NMR analysis, chloroformate yield 64%).

The similar reaction of mercury bisacetophenone (mp 170–171.5 °C, lit.[13] 171–172.5 °C) with phosgene afforded a distillation fraction of bp 64–66 °C (0.9 mm) which contained 1-phenylvinyl chloroformate (45% yield) and acetophenone in a ratio of 6:1.

The analogous reaction of impure $(C_3H_5COCH_2)_2Hg$ (see below) afforded a small amount of distillation fraction containing 1-cyclopropylvinyl chloroformate and $C_3H_5COCH_3$ in a ratio of 3:2, bp 73–77 °C (60 mm).

Enol Carbamate Derivatives. Isopropenyl chloroformate (3.5 g, 0.029 mol) in anhydrous 1,2-dichloroethane was added to a stirred solution (0 °C) of cyclohexylamine (5.75 g, 0.058 mol) in the same solvent. The next day precipitated amine hydrochloride was filtered off and the filtrate was concentrated. Isopropenyl *N*-cyclohexylcarbamate was isolated from the residue by vacuum sublimation [57 °C (0.1 mm)]: yield 5.21 g (98%); mp 95.5–96.5 °C; NMR ($CDCl_3$) δ 0.9–2.1 (13 H, br m with s at 1.95), 3.2–3.8 (1 H, br m), 4.52–4.64 (1 H, m), 4.68 (1 H, s) 4.8–5.2 (1 H, m); IR ($CHCl_3$) 2.93, 5.78, 5.99 μm; mass spectrum *m/e* (rel intensity) 183 (2), 126 (7), 125 (10), 83 (57), 58 (100).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.4; N. 7.6. Found: C, 65.8; H, 9.3; N, 7.8.

The following enol carbamates were similarly prepared from the appropriate chloroformates and amines.

Vinyl *N*-cyclohexylcarbamate: sublimed at 50 °C (1 mm), mp 83–84 °C; NMR ($CDCl_3$) δ 0.8–2.3 (10 H, m), 3.1–3.9 (1 H, m), 4.34 (1 H, q, J = 1, 6 Hz), 4.66 (1 H, q, J = 1, 14 Hz), 4.9–5.4 (1 H, m), 7.14 (1 H, q, J = 6, 14 Hz); IR ($CHCl_3$) 2.93, 5.78, 6.06 μm; mass spectrum *m/e* (rel intensity) 169 (0.5), 126 (35), 83 (94), 55 (100).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3. Found: C, 64.0; H, 8.9; N, 8.2.

1-Cyclohexenyl *N*-phenylcarbamate: triturated with pentane, mp 119.5–120 °C; NMR ($CDCl_3$) δ 1.3–2.4 (8 H, m), 5.3–5.6 (1 H, m), 6.8–7.5 (6 H, m); IR ($CHCl_3$) 2.90, 5.79, 6.03 μm; mass spectrum *m/e* (real intensity) 217 (1), 119 (100), 98 (41), 91 (39).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 71.9; H, 7.2; N, 6.3.

1 Phenylvinyl *N*-cyclohexylcarbamate: triturated with pentane, mp 104–105 °C; NMR ($CDCl_3$) δ 0.8–2.3 (10 H, m), 3.1–3.9 (1 H, m), 5.04 (1 H, d, J = 2 Hz), 5.40 (1 H, d, J = 2 Hz), 4.9–5.4 (1 H, m), 7.0–7.7 (5 H, m); IR ($CHCl_3$) 2.90, 5.79, 6.05 μm; mass spectrum *m/e* (rel intensity) 245 (1), 120 (85), 105 (100), 77 (69).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.1; H, 8.1; N, 5.6.

1-Cyclopropylvinyl *N*-phenylcarbamate: crystallized from pentane, mp 104–105 °C; NMR ($CDCl_3$) δ 0.6–0.9 (4 H, m), 1.3–1.9 (1 H, m), 4.76 (2 H, s), 6.8–7.6 (6 H, m); IR ($CHCl_3$) 2.90, 5.76, 6.03 μm; mass spectrum *m/e* (rel intensity) 203 (1), 119 (100), 91 (42), 84 (32), 69 (58).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9. Found: C, 70.9; H, 6.3; N, 6.7.

1-*tert*-Butylvinyl *N*-cyclohexylcarbamate: sublimed at 85 °C (0.1 mm), mp 79–80 °C; NMR ($CDCl_3$) δ 1.05 (9 H, s), 1.1–2.2 (10 H, m), 3.2–3.8 (1 H, m), 4.68 (1 H, d, J = 2 Hz), 4.79 (1 H, d, J = 2 Hz), 4.7–5.3 (1 H, m); IR ($CHCl_3$) 2.93, 5.78, 6.04 μm; mass spectrum *m/e* (rel intensity) 225 (10), 126 (15), 125 (31), 124 (10), 100 (100).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.3; H, 10.3; N, 6.2. Found: C, 69.1; H, 10.5; N, 6.1.

Mercury Bispinacolone: This was made by the general method of House[13] from the trimethylsilyl enol ether of pinacolone (bp 140–143 °C) and yellow HgO with $Hg(OAc)_2$ as catalyst, and crystallized from benzene–hexane (94% yield): mp 102–103 °C; NMR ($CDCl_3$) δ 1.33 (9 H, s), 2.62 (2 H, s); IR ($CHCl_3$) 6.09 μm.

The analogous reaction of 1-cyclopropyl-1-trimethylsilyoxyethylene [bp 83–84 °C (95 mm)] afforded a product too volatile to separate from the reaction solvent by vacuum evaporation. However, material collected in the evaporation trap could be partly purified by dissolution in EtOH, filtration to remove a gray flocculence, and slow evaporation at 25 °C. Several crops of precipitated powder were collected and the $(C_3H_5COCH_2)_2Hg$ was crystallized from CH_2Cl_2–pentane: mp 106–108 °C; NMR ($CDCl_3$) δ 0.6–1.2 (m), 1.5–2.3 (m), 2.60 (s), 3.02 (s), 4.0–4.2 (m) (ratio: 6.54:1.84:2:0.46:0.15; contains cyclopropyl methyl ketone impurity); IR ($CHCl_3$) 6.08 μm.

An attempt to obtain mercury bisisobutyraldehyde from $Me_2C{=}CHOSiMe_3$(bp 97–99 °C) failed. The product was too volatile to separate from the reaction solvent.

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Registry No.—Phosgene, 75-44-5; diacetonylmercury, 6704-33-2; mercury bispinacolone, 16004-47-0; mercury bisacetaldehyde, 4387-13-7; mercury biscyclohexanone, 37160-46-6; mercury bisacetophenone, 37160-45-5; $(C_3H_5COCH_2)_2Hg$, 64294-80-0; cyclohexylamine, 108-91-8; isopropenyl *N*-cyclohexylcarbamate 64294-81-1; vinyl *N*-cyclohexylcarbamate, 64294-82-2; 1-cyclohexenyl *N*-phenylcarbamate, 64294-83-3; benzamine, 62-53-3; 1-phenylvinyl *N*-cy-

clohexylcarbamate, 64294-84-4; 1-cyclopropylvinyl *N*-phenylcarbamate, 64294-85-5; 1-*tert*-butylvinyl *N*-cyclohexenylcarbamate, 64294-86-6; pinacolone trimethylsilyl enol ether, 17510-46-2; 1-cyclopropyl-1-trimethylsilyloxyethylene, 42161-96-6.

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(16) Note, however, that recovered α-chloromercuri ketones are easily symmetrized to the bis(keto)mercurials: O. A. Reutov and L. Ching-chu, *J. Gen. Chem. USSR*, **184**, 1177 (1959).
(17) However, the methodology to be developed should complement and not parallel chemistry with VOC-Cl because the derivatives (**1**, R′ = Me) are so different in reactivity vs. VOC amides and VOC esters. For example, titration of VOC-NR_2 with Br_2 yields $BrCH_2CHBrOCONR_2$, while the same reaction of $H_2C{=}CMeOCONR_2$ gives $BrCONR_2$.[5]

Synthesis of 4-Amino-3-hydroxy-6-methylheptanoic Acid by a Modified Reformatsky Reaction

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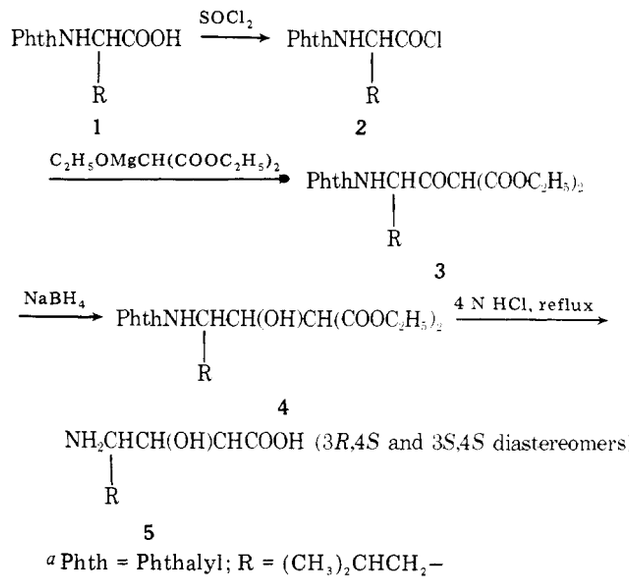
Pepstatin is a naturally occurring low-molecular-weight peptide that is a potent inhibitor of acid proteases.[1] The natural pentapeptide contains two residues of (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA), although a tripeptide containing only one residue of AHMHA at the C terminus retains its potency as an inhibitor of pepsin.[1] Since pepstatin is an effective inhibitor of renin, pepsin, and tissue cathepsin D's, there is a need for synthesis of analogues and derivatives that might be selective among these enzymes. The only derivatives reported have been prepared from AHMHA isolated from acid hydrolysates of pepstatin. AHMHA is unstable under conditions of acid hydrolysis, so it is not a good method for obtaining this amino acid. Synthesis of the 3*S*,4*S* and 3*R*,4*S* diastereomers (**5**) has been reported.[2] No yields or experimental details were given, but the yields were undoubtedly low (vide infra). All four of the possible stereoisomers have been synthesized by a method unsuitable for preparative work.[3] We report below the preparation of AHMHA in greatly improved yield via a modified Reformatsky reaction.

Results and Discussion

As a starting point, we repeated the reported[2] method for the preparation of AHMHA (Scheme I). We obtained an approximately equimolar mixture of diastereomers in 3.2% overall yield estimated by amino acid analysis of the crude

Scheme I[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

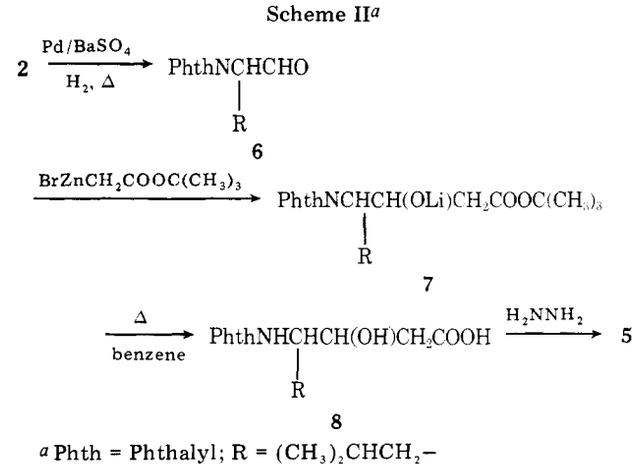
product. The intermediates **3** and **4** were obtained in good yield; their structures were confirmed by NMR analysis and by the fact that **3** is acidic and can be purified by extraction. Nearly all of **5** is lost during the hydrolysis step. The instability of **5** to acid-hydrolysis conditions was confirmed by heating a purified sample in 6 N HCl at 110 °C for 24 h which resulted in a loss of 58%. The yield of AHMHA from hydrolysis of pepstatin was about 50%.

The problem with Scheme I could have been solved by changing to *tert*-butyl ester blocking groups which could be removed by anhydrous acid, allowing removal of the phthalyl blocking group by hydrazinolysis. However, the Reformatsky reaction sequence in Scheme II was appealing in view of the reported success in obtaining β-hydroxy acids using the zinc enolate of *tert*-butyl acetate.[4]

The acid chloride **2** was obtained in quantitative yield as an oil that was used without further purification. Reduction gave the aldehyde **6** in 85% yield after removal of unreacted **2** by stirring the mixture with aqueous sodium bicarbonate and was used without further purification. Performing the Reformatsky reaction in the usual manner gave **8** in only 20% yield, due primarily to reaction of the enolate at the phthalyl carbonyl groups. The yield of **8** was improved to 40% with no side reaction at the blocking group by preparing the enolate separately and adding it to a cooled solution of the aldehyde. Hydrazinolysis proceeded in quantitative yield, giving a 55:45 mixture of **5** (3*S*,4*S*:3*R*,4*S*).

Although separation of the diastereomers **5** was reported

Scheme II[a]



[a] Phth = Phthalyl; R = $(CH_3)_2CHCH_2$–

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