Acetylenic Esters. Preparation and Characterization of Alkynyl Carboxylates via Polyvalent Iodonium Species†

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Abstract: The first synthesis of acetylenic carboxylates is reported. Reaction of $PhI(OCOR')_2$ with lithium acetylides, or anion exchange of alkynylphenyliodonium tosylates, gives alkynylphenyliodonium carboxylates that readily decompose to the desired acetylenic carboxylates and iodobenzene. The new acetylenic carboxylates are characterized by spectral means and show unique IR and C-13 absorptions. The scope and limitations of this methodology as well as mechanistic possibilities are discussed.

Carboxylate esters as well as acetylenes are important and valuable functional groups in organic chemistry.[2] They both serve as useful synthons,[3] they have been extensively employed in mechanistic studies,[4] and they play a significant role in biochemistry.[5]

A wide variety of individual acetylenes as well as carboxylate esters are of course well known, as are triple bond containing carboxylate esters. Despite the ubiquitous nature and importance of esters and the diversity of functionalized acetylenes[6] including esters of propiolic acids, **1**, and alkynyl thiocarboxylates,[7] **2**, alkynyl carboxylates, **3**, are hitherto unknown.

$RC{\equiv}CCO_2R'$ (1) $RC{\equiv}CSC(O)R'$ (2) $RC{\equiv}CO_2CR'$ (3)

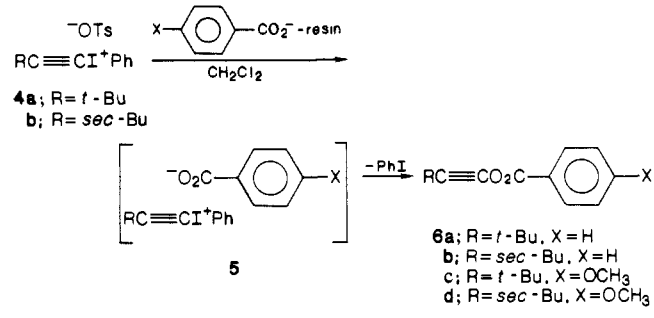
Hence, we report[8] the preparation by a general, simple procedure and the spectral characterization of a variety of alkynyl carboxylates **3**; the first examples of this novel, interesting class of compounds that combine two of the most common and simple organic functionalities into a single, unique derivative.

Results and Discussion

Carboxylate esters are most commonly prepared by interaction of a carboxylic acid or its derivative with the appropriate alcohol or in the case of vinyl esters, by reaction of an acid derivative with an enolate.[9] Since alkynols, RC≡COH, are unknown,[10] this simple, standard procedure cannot be used for the preparation of alkynyl carboxylates. On the other hand, acetylenes, including functionalized ones, are generally prepared by one of three common procedures:[6] (a) elimination processes, (b) substitutions, and (c) pyrolysis or rearrangement methods. In our hands none of these standard methods worked for the preparation of alkynyl carboxylates **3**, and this probably accounts for the hitherto unknown nature of this unique, albeit simple, class of compounds.

Recently, we reported[14] the preparation and mechanism of formation of alkynyl tosylates, the first known member of the family of alkynyl esters,[15] via tricoordinate iodonium species. Therefore, we examined the use of tricoordinate iodonium as a means to alkynyl carboxylates.

The crystal structure of phenyl(phenylethynyl)iodonium tosylate (**4**; R = Ph) shows clearly the anionic character of the tosylate moiety.[14] This structural feature was used in our first synthesis of the hitherto unknown alkynyl benzoates. Exchange of the tosylate anion in **4** with benzoate, by means of an Amberlyst ion-exchange resin, leads to the formation of the alkynyl benzoates **6**. Chromatographic workup of the eluted products indicates quantitative fragmentation to iodobenzene (isolated yields 78-98%). However, the isolated yields of the desired alkynyl benzoates **6** were only moderate (10-40%).



In contrast to the stable iodonium tosylates **4**, the corresponding iodonium benzoates **5** seem to be unstable, at least under our

† Dedicated to Professor Kurt M. Mislow on the occasion of his 65th birthday.

(1) (a) Hoechst AG Postdoctoral Fellow. (b) DFG Postdoctoral Fellow.

(2) Inter alia: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967-1986; Vol. 1-13. March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: New York, 1979; Vol. 1-6.

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(10) Alkynols, analogous to enols, are in tautomeric equilibrium with ketenes: RC≡COH ⇌ RCH=C=O. Ab initio calculations[11] indicate that ketene is 36 kcal/mol more stable than the parent hydroxyacetylene. This is considerably greater than the calculated enol-keto energy difference of 11 kcal/mol for the vinyl alcohol-acetaldehyde system, yet the barrier to interconversion of HC≡COH → H_2C=C=O is very high at 73 kcal/mol as determined by calculations.[11] Stable enols are well known.[12] Recently the parent hydroxyacetylene HC≡COH was observed by tandem mass spectrometry in the gas phase.[13]

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reaction conditions. We have to date not isolated any derivative of **5**; fragmentation to the products (PhI and **6**) is found instead.

Because of the limitations of the above reaction (availability of alkynyliodonium tosylates **4**; moderate yields), we were looking for a more comprehensive, better synthesis of **6**. Commercially available (diacetyoxyiodo)benzene (**7**) is one of the best known trivalent organoiodine compounds.[16] A large variety of phenyliodine(III) diacetates and dibenzoates can be prepared from this molecule in a double decomposition reaction, as impressively demonstrated by Pausacker[17] and later by Merkushev.[18] We have used Merkushev's method to prepare the following phenyliodine(III) dibenzoates in nearly quantitative yields.

$$\underset{\mathbf{7}}{PhI(O_2CCH_3)_2} + 2R'CO_2H \xrightarrow[\text{reduced pressure}\ -CH_3COOH]{C_6H_5Cl} \underset{\mathbf{8}}{PhI(O_2CR')_2}$$

8a, R′ = C_6H_5; **b**, R′ = *p*-$CH_3OC_6H_4$; **c**, R′ = *p*-$NO_2C_6H_4$; **d**, R′ = 3,5-$(CH_3O)_2C_6H_3$; **e**, R′ = $C(CH_3)_3$; **f**, R′ = CH_2CH_2Ph; **g**, R′ = $CHPh_2$; **h**, R′ = CCl_3

Addition of lithium acetylides **9** to the phenyliodine(III) dicarboxylates **8** in THF at low temperature leads to the formation of the alkynyl benzoates **6a** and **6e–n** in 27–57% isolated yields and to the alkynyl acetates **6o–u** in 2–25% isolated yields. To

$$\underset{\mathbf{7,8}}{PhI(O_2CR')_2} + \underset{\mathbf{9a}, R = CH_3;\ \mathbf{b}, R = i\text{-Pr};\ \mathbf{c}, R = CH_3OC(CH_3)_2;\ \mathbf{d}, R = n\text{-Bu};\ \mathbf{e}, R = t\text{-Bu};\ \mathbf{f}, R = sec\text{-Bu}}{RC{\equiv}CLi} \xrightarrow[-R'CO_2Li]{THF} \underset{\mathbf{10}}{[PhI^+C{\equiv}C\text{-}R\cdot O_2^-CR']} \xrightarrow{-PhI} \underset{\mathbf{6}}{RC{\equiv}CO_2CR'}$$

6a, R = *t*-Bu, R′ = C_6H_5; **e**, R = CH_3, R′ = C_6H_5; **f**, R = *i*-Pr, R′ = C_6H_5; **g**, R = *n*-Bu, R′ = C_6H_5; **h**, R = $CH_3OC(CH_3)_2$, R′ = C_6H_5; **i**, R = CH_3, R′ = *p*-$CH_3OC_6H_4$; **j**, R = CH_3, R′ = *p*-$NO_2C_6H_4$; **k**, R = *n*-Bu, R′ = *p*-$NO_2C_6H_4$; **l**, R = *t*-Bu, R′ = *p*-$NO_2C_6H_4$; **m**, R = *n*-Bu, R′ = 3,5-$(CH_3O)_2C_6H_3$; **n**, R = *t*-Bu, R′ = 3,5-$(CH_3OC_6H_3)_2$; **o**, R = *n*-Bu, R′ = CH_3; **p**, R = *sec*-Bu, R′ = CH_3; **q**, R = *t*-Bu, R′ = $C(CH_3)_3$; **r**, R = CH_3, R′ = CH_2CH_2Ph; **s**, R = *t*-Bu, R′ = CH_2CH_2Ph; **t**, R = CH_3, R′ = $CHPh_2$; **u**, R = *t*-Bu, R′ = $CHPh_2$

optimize the yields of isolated ester product we have tried both normal addition (i.e., acetylide **9** to phenyliodine(III) dicarboxylate **8** in the presence of *t*-BuNO, method A) and inverse addition (i.e., phenyliodine(III) dicarboxylate **8** to the acetylide **9** in the absence of *t*-BuNO, method B). As seen in Table I for **6a**, **e**,**g**,**h**, method A always gives higher yields. Moreover, in the case of method B, diacetylenes **12** were isolated as side products. These diacetylenes **12** presumably arise by coupling from phenyldialkynyliodinane **11** formed under inverse addition conditions.

$$\underset{\mathbf{9}}{LiC{\equiv}CR} + \underset{\mathbf{8}}{PhI(O_2CR')_2} \xrightarrow[THF,\ -78\ °C]{-2LiO_2CR'} \underset{\mathbf{11}}{[PhI(C{\equiv}CR)_2]} \xrightarrow{-PhI} \underset{\mathbf{12}}{RC{\equiv}CC{\equiv}CR}$$

Phenyldialkynyliodinanes **11** are to our knowledge unknown. However, one would expect that their decomposition behavior is similar to triaryliodinanes or vinyldiaryliodinanes, whose homolytic fragmentation at low temperature is well documented.[19]

In order to avoid homolytic decomposition of **8** and to allow the formation of the desired phenylalkynyliodonium carboxylates **10** (by exchange, acetylide ↔ carboxylate), *t*-BuNO was added as a radical trap. As a result no diacetylene formation was observed in method A where the acetylide was added to **8** in the presence of *t*-BuNO.

Another side reaction was observed when lithium acetylide **9d** was added to phenyliodine(III) bis(trichloroacetate) (**8h**), where ketone **13** was isolated in 12% yield.

$$\underset{\mathbf{9d}}{n\text{-}BuC{\equiv}CLi} + \underset{\mathbf{8h}}{PhI(O_2CCCl_3)_2} \xrightarrow[t\text{-BuNO}]{THF,\ -78\ °C} \underset{\mathbf{13}}{n\text{-}BuC{\equiv}CC(O)CCl_3}$$

Since phenyliodine(III) bis(trifluoroacetate) decomposes in the presence of the radical trap, no trifluoroacetates could be prepared by this procedure.

The physical and spectral properties of alkynyl carboxylates **6** are summarized in Table I. As the data indicate, a wide variety of alkynyl carboxylates may be prepared by this simple two-step procedure in moderate isolated yields. Alkynyl carboxylates **6** are reasonably stable low-melting crystalline solids or pale yellow viscous oils. The solid esters are stable for several weeks at room temperature, whereas the oils tend to be less stable, and *all* alkynyl carboxylates **6** decompose upon standing at room temperature in a few days to several weeks.

Characterization of Alkynyl Carboxylates. These new alkynyl esters were characterized by spectral and analytical means as summarized in Table I and the Experimental Section.

Specifically, all alkynyl benzoates give a molecular ion (or $M^+ - 1$) and characteristic fragmentation patterns by EI mass spectra. Appropriate high-resolution mass spectra were obtained for selected, representative compounds. In the infrared there are very typical, strong absorptions between 2255 and 2290 cm^{-1} due to the unsymmetrical carbon–carbon triple bond along with characteristic, intense carbonyl absorption between 1755 and 1770 cm^{-1}.

Molecular ions were detected for the alkynyl acetates **6r–u** by EI (or CI) mass spectroscopy. However, in the case of the simpler acetates **6o**,**p**, no molecular ion was observed. Fragmentation ($RC{\equiv}CO_2CR' \rightarrow RC{\equiv}CO^{\cdot+}$) and recombination to ketene dimers [$(RCH{=}C{=}O)_2$] seems to occur instead in the MS (see the Experimental Section and Table I). In the infrared alkynyl acetates show strong triple bond absorption between 2270 and 2280 cm^{-1}, along with intense carbonyl absorption between 1775 and 1805 cm^{-1}.

All proton NMR spectra for **6** are consistent with the proposed structures. Particularly valuable and uniquely characteristic are the ^{13}C NMR data, especially the signals due to the carbonyl carbon and the two acetylenic carbons. All esters, **6**, exhibit a carbonyl signal between 161 and 174 ppm, typical[20] of carboxylate esters. The acetylenic carbons resonate between 77 and 82 ppm for the α-carbon and between 47 and 61 ppm for the β-carbon, as expected[8,14] for these electron-rich, unsymmetrical alkynes.

Finally, acid-catalyzed hydrolyses of these esters resulted in the carboxylic acid corresponding to the alkynyl moiety, together with the appropriate liberated carboxylic acid.[21] Hence, the

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(15) The family of alkynyl esters includes, besides carboxylates, sulfonate esters $RC{\equiv}COSO_2Ar$, phosphates $RC{\equiv}COP(O)(OR')_2$ and related phosphorus species, perchlorates $RC{\equiv}COClO_3$, and nitrites $RC{\equiv}CONO$. To our knowledge, outside of our own recent reports,[8,14] none of these species are known.

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Table I. Summary of Physical and Spectral Properties of Alkynyl Carboxylates 6

alkynyl carboxylates	yield, %; mp, °C	IR, cm^{-1}	^{1}H-NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ) C-1, C-2, C=O (other signals)	MS (EI, 70 eV)
6a	50[a] (22[b], 40[c]); oil	2285, 2255 (sh) (C≡C), 1770 (C=O)[d]	1.32 (s, 9 H), 7.35–7.75 (m, 3 H), 7.95–8.15 (m, 2 H)[g]	79.09, 59.95, 163.20, (27.15, 31.55, 126.93, 129.13, 130.51, 134.81)[g]	202 (3.5, M^+), 146 (3.7, $M^+ - C_6H_8$), 105 (100, PhCO), 77 (3, Ph)
6b	16;[c] oil	2270 (C≡C), 1770 (C=O)[d]	1.02 (t, 3 H), 1.19 (d, 3 H), 1.48 (m, 2 H), 2.47 (m, 1 H), 7.20–7.55 (m, 3 H), 7.85–8.05 (m, 2 H)	79.82, 55.92, 163.05, (11.82, 21.07, 26.62, 30.21, 126.57, 128.70, 130.24, 134.38)	201 (0.3, $M^+ - 1$), 105 (100, PhCO), 77 (34, Ph)
6c	10;[c] oil	2283, 2250 (sh) (C≡C), 1765 (C=O)[e]	1.26 (s, 9 H), 3.80 (s, 3 H), 6.88, 7.92 (AA′XX′, J_{AX} = 9.5 Hz, 4 H)	78.80, 59.30, 162.42, (26.77, 31.41, 55.13, 114.02, 118.61, 132.41, 164.41)	232 (2, M^+), 135 (100, *p*-$CH_3OC_6H_4CO$), 107 (1.4, *p*-$CH_3OC_6H_4$), 77 (11, Ph)
6d	16;[c] oil	2275 (C≡C), 1760 (C=O)[e]	1.03 (t, 3 H), 1.20 (d, 3 H), 1.50 (m, 2 H), 2.48 (m, 1 H), 6.88, 7.92 (AA′XX′, J_{AX} = 9.5 Hz, 4 H)	79.96, 55.30, 162.47 (11.76, 21.04, 26.53, 30.17, 55.46, 113.96, 118.50, 132.37, 164.38)	232 (0.6, M^+), 135 (100, *p*-$CH_3OC_6H_4CO$), 107 (5.5, *p*-$CH_3OC_6H_4$), 77 (15, Ph)
6e	57[a] (31[b]); 40–41[h]	2280 (C≡C), 1770 (sh), 1755 (C=O)[d]	1.87 (s, 3 H), 7.30–7.70 (m, 3 H), 7.93–8.07 (m, 2 H)	77.95, 47.27, 163.06 (2.01, 126.28, 128.60, 130.15, 134.36)	160 (1.2, M^+), 122 (12, $PhCO_2H$), 105 (100, PhCO), 77 (67, Ph)
6f	32;[b] oil	2280 (C≡C), 1770 (C=O)[d]	1.20 (d, 6 H), 2.68 (hept, 1 H), 7.30–7.70 (m, 3 H), 7.90–8.10 (m, 2 H)	78.90, 57.09, 162.95 (19.58, 23.38, 126.47, 128.67, 130.22, 134.40)	188 (10, M^+), 106 (38, PhCO + 1), 105 (100, PhCO), 77 (48, Ph)
6g	44[a] (7[b]); oil	2280 (C≡C), 1768 (C=O)[d]	0.80–1.05 (m, 3 H), 1.30–1.70 (m, 4 H), 2.15–2.40 (m, 2 H), 7.30–7.70 (m, 3 H), 7.90–8.10 (m, 2 H)	79.11, 51.67, 162.97 (13.63, 17.05, 21.90, 31.00, 126.36, 128.60, 130.15, 134.32)	202 (0.7, M^+), 201 (3, $M^+ - 1$), 146 (1.8, $M^+ - C_6H_8$), 105 (100, PhCO), 77 (50, Ph)
6h	48[a] (25[b]); oil	2280 (C≡C), 1770 (C=O)[e]	1.50 (s, 6 H), 3.37 (s, 3 H), 7.30–7.67 (m, 3 H), 7.93–8.03 (m, 2 H)	82.80, 53.11, 162.09 (28.42, 51.25, 70.16, 125.92, 128.65, 130.15, 134.54)	219 (0.3, $M^+ + 1$), 187 (83, $M - OCH_3$), 105 (100, PhCO), 77 (31, Ph)[i]
6i	44;[a] 58–59[h]	2280 (C≡C), 1765 (C=O)[d]	1.86 (s, 3 H), 3.80 (s, 3 H), 6.87, 7.93 (AA′XX′, J_{AX} = 9 Hz, 4 H)	78.13, 46.62, 164.57 (1.85, 55.40, 114.00, 118.37, 132.49, 162.70)	190 (1, M^+), 135 (100, *p*-$CH_3OC_6H_4CO$), 107 (6, *p*-$CH_3OC_6H_4$), 92 (9, C_6H_4O), 77 (27, Ph)
6j	45;[a] 103–105[h]	2290 (C≡C), 1765 (C=O), 1520, 1355, 1320 (NO_2)[f]	1.90 (s, 3 H), 8.17–8.33 (m, 4 H)	77.36, 48.54, 161.68 (1.81, 123.87, 131.44, 131.72, 151.28)	205 (0.3, M^+), 150 (100, $NO_2C_6H_4CO$), 120 (5, 150 – NO), 104 (54, 150 – NO_2)
6k	56;[a] 57–57.5[h]	2270 (C≡C), 1770 (C=O), 1530, 1345, 1315 (NO_2)[f]	0.80–1.00 (m, 3 H), 1.30–1.75 (m, 4 H), 2.15–2.40 (m, 2 H), 8.17–8.33 (m, 4 H)	78.36, 52.57, 161.36 (13.22, 16.60, 21.59, 30.56, 123.66, 131.18, 131.50, 151.03)	247 (1.0, M^+), 246 (2.4, $M^+ - 1$), 230 (7.3, 246 – O), 150 (100, $NO_2C_6H_4CO$), 120 (28.1, 150 – NO), 104 (68.3, 120 – O), 76 (47, C_6H_4)
6l	35;[a] 71–72[h]	2290 (C≡C), 1770 (C=O), 1535, 1345, 1315 (NO_2)[f]	1.31 (s, 9 H), 8.24–8.37 (m, 4 H)	78.04, 60.85, 161.43 (26.68, 31.12, 123.93, 130.94, 131.40, 151.25)	247 (0.2, M^+), 246 (0.2, $M^+ - 1$), 230 (2.9, 246 – O), 150 (100, $NO_2C_6H_4CO$), 120 (2.5, 150 – NO), 104 (12.5, 120 – O), 76 (10, C_6H_4)
6m	33;[a] 37–40[h]	2275 (C≡C), 1770 (C=O)[f]	0.91–0.96 (m, 3 H), 1.45–1.55 (m, 4 H), 2.27–2.32 (m, 2 H), 3.81 (s, 6 H), 6.68 (t, $J_{H,H}$ = 2 Hz, 1 H), 7.15 (d, $J_{H,H}$ = 2 Hz, 2 H)	79.08, 51.64, 162.94 (13.46, 16.90, 21.77, 30.88, 52.42, 107.08, 107.63, 128.01, 160.69)	262 (2, M^+), 247 (3.6, $M^+ - CH_3$), 206 (4.6, $M^+ - C_4H_8$), 165 (100, $C_9H_9O_3$), 137 (26, 165 – CO), 122 (10, 137 – CH_3), 107 (4, 122 – CH_3), 57 (12, C_4H_9)
6n	35;[a] 52–53[h]	2280, 2240 (sh) (C≡C), 1770 (C=O)[f]	1.30 (s, 9 H), 3.80 (s, 6 H), 6.67 (t, $J_{H,H}$ = 2 Hz, 1 H), 7.13 (d, $J_{H,H}$ = 2 Hz, 2 H)	78.59, 59.68, 162.71 (26,62, 31.20, 55.41, 107.04, 107.61, 128.11, 160.70)	262 (3.7, M^+), 247 (7.1, $M^+ - CH_3$), 206 (94, $M^+ - C_4H_8$), 165 (100, $C_9H_9O_3$), 137 (43.7, 165 – CO), 122 (34.4, 137 – CH_3), 107 (8, 122 – CH_3), 57 (9.4, C_4H_9)

Table I (Continued)

alkynyl carboxylates	yield, %; mp, °C	IR, cm^{-1}	^1H-NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ) C-1, C-2, C=O (other signals)	MS (EI, 70 eV)
6o	15; oil	2880 (C≡C), 1805 (C=O)[e]	0.91 (t, 3 H), 1.38–1.55 (m, 4 H), 2.18 (s, 3 H), 2.23 (t, 2 H)	78.94, 50.76, 166.90 (13.51, 16.81, 19.28, 21.81, 30.92)	207 (7) 195 (9, 2 × 97 + H), 167 (9, 195 − CO), 151 (6, 167 − O), 67 (100, C_6H_9O)[i]
6p	9; oil	2270 (C≡C), 1800 (C=O)[e]	0.99 (t, 3 H), 1.16 (d, 2 H), 1.40–1.52 (m, 1 H), 2.20 (s, 3 H)	79.58, 54.87, 166.76 (11.59, 19.31, 20.82, 26.30, 30.02)	274 (43), 247 (3), 231 (8), 227 (7), 195 (2, 2 × 97 + 1), 178 (8), 161 (50, 2 × 81 − 1), 97 (100, C_6H_9O), 81 (7, C_6H_9), 57 (13, C_4H_9)[i]
6g	5.5; oil	2280 (C≡C), 1780 (C=O)[e]	1.24 (s, 9 H), 1.25 (s, 9 H)	78.65, 59.23, 174.49 (26.60, 26.83, 31.30, 38.82)	260 (10), 245 (5, 260 − O), 216 (4, 245 − CO), 196 (5, 2 × 97 + 2 H), 167 (2, 196 − CO), 151 (1, 176 − O), 97 (22, C_6H_9O), 57 (100, C_4H_9)
6r	2; oil	2280 (C≡C), 1790 (C=O)[e]	1.84 (s, 3 H), 2.76 (t, 2 H), 2.98 (t, 2 H), 7.18–7.30 (m, 5 H)	77.72, 46.59, 169.25 (1.82, 30.43, 34.48, 126.63, 128.34, 128.66, 139.26)	188 (10, M^+), 133 (19, $PhCH_2CH_2CO$), 105 (66, $PhCH_2CH_2$), 105 (66, $PhCH_2CH_2$), 91 (100, $PhCH_2$), 77 (8, Ph)
6s	6; oil	2280 (C≡C), 1795 (C=O)[e]	1.24 (s, 9 H), 2.74 (t, 2 H), 2.94 (t, 2 H), 7.18–7.34 (m, 5 H)	78.36, 58.97, 168.84 (26.56, 30.38, 31.25, 34.44, 126.60, 128.24, 128.64, 139.34)	230 (0.3, M^+), 215 (13, $M^+ - CH_3$), 133 (10, $PhCH_2CH_2CO$), 105 (42, $PhCH_2CH_2$), 91 (39, $PhCH_2$)
6t	25; 63[h]	2280 (C≡C), 1780 (C=O)[e]	1.83 (s, 3 H), 5.09 (s, 1 H), 7.28–7.34 (m, 10 H)	77.81, 47.27, 169.02 (1.67, 55.50, 127.71, 128.35, 128.73, 136.71)	250 (2, M^+), 195 (5, Ph_2CHCO), 194 (4, $Ph_2C{=}C{=}O$), 181 (3), 168 (60), 167 (100, Ph_2CH), 166 (30), 165 (54), 152 (11), 115 (3)[i]
6u	25; 46–48[h]	2280 (C≡C), 1775 (C=O)[e]	1.21 (s, 9 H), 5.06 (s, 1 H), 7.26–7.32 (m, 10 H)	78.44, 59.58, 168.73 (26.50, 31.14, 55.59, 127.72, 128.41, 128.75, 136.81)	292 (0.2, M^+), 195 (0.6, Ph_2CHCO), 194 (1.7, $Ph_2C{=}C{=}O$), 168 (1), 167 (100, $CHPh_2$), 165 (30), 152 (6), 125 (9, $BuC{\equiv}COCO$), 57 (37, C_4H_9)

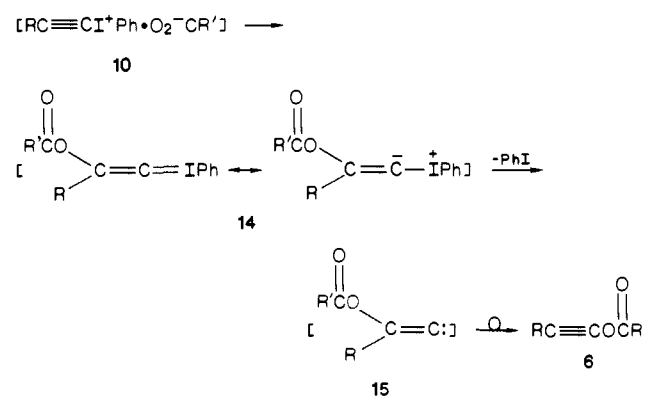
[a] Method A. [b] Method B. [c] Method C. [d] Nujol film. [e] Neat. [f] KBr pellet. [g] In CD_2Cl_2. [h] Recrystallized from pentane (−20 °C). [i] CI, CH_4 as ionizing gas.

structural identity of these new alkynyl carboxylate esters is firmly established.

$$RC{\equiv}COC(O)R' + H_2O \xrightarrow{H^+} RCH_2CO_2H + R'CO_2H$$

Mechanistic Considerations. There is little doubt that the first formed intermediate in the reaction of **8** with **9** is an alkynylphenyliodine(III) carboxylate **10**. However, the exact mode of decomposition of **10** to alkynyl carboxylates **6** is not clear. Since decomposition of **10** to **6** does not require metal catalysis, our previously proposed metal-assisted nucleophilic acetylenic substitution[14] process for the formation of the analogous alkynyl sulfonates is not likely. A reasonable pathway involves unsaturated carbenes and/or their iodonium ylides as outlined in Scheme I, analogous to the mechanism recently proposed by Ochiai and co-workers.[22]

Scheme I



Attack of the carboxylate nucleophile on the β-carbon of **10** results in an (alkylidenecarbene)iodonium ylide **14**. Although

(22) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281.

stable carbeneiodonium ylides are well known,[23,24] to date only indirect evidence has been reported for the intermediacy of species analogous to **14**.[25] Loss of iodobenzene from **14** results in unsaturated carbene **15** that rapidly rearranges to the product ester **6**. Alkylidenecarbenes are of course well known,[26] albeit few, if any, with β-heteroatom substituents. Their rearrangement to alkynes is well precedented.[26] However, our attempts to trap **15** via insertion into Et_3SiH have to date failed. This is likely due to the considerable migratory aptitude of a carboxylate, and hence the concomitant unimolecular, intramolecular rearrangement is faster than the bimolecular, intermolecular insertion reaction. Another possibility is that rearrangement and loss of iodobenzene from **14** are essentially concerted, and hence **14** goes directly to **6** without the intermediacy of the free carbene **15**. Efforts are under way to provide evidence for **14** and **15** and thereby firmly establish this mechanism.

Conclusions

Hitherto unknown alkynyl carboxylates **6** have been prepared in two simple steps in moderate yields via tricoordinate iodonium species. A variety of alkynyl benzoates are reasonably stable crystalline solids or pale yellow oils.

The simpler alkynyl acetates seem to be more sensitive and decompose during the workup procedures, as indicated by the lower isolated yields. However, in pure form, as oils or crystalline solids, their stability is comparable to those of the alkynyl benzoates.

All alkynyl carboxylates show very characteristic spectral properties in the infrared and ^{13}C NMR analyses. Preliminary results indicate that some of these simple alkynyl carboxylates are potent inhibitors of serine-based proteases such as bovine pancreatic chymotrypsin and trypsin.[27] Further work on the chemistry and biochemistry of these novel esters is under way and will be reported in future papers.

Experimental Section

General Methods. Melting points (uncorrected) were obtained with a Mel-Temp capillary melting point apparatus. NMR spectra were recorded on either a Varian EM 390 or a Varian XL 300 spectrometer. Chemical shifts (^1H, ^{13}C) are reported relative to internal tetramethylsilane. EI, CI, and high-resolution mass spectra were obtained on a VG Micromass 7070-E double-focusing high-resolution mass spectrometer, operating at 5 kV with a VG Analytical DS 2050 data system.

Materials. (Diacetoxyiodo)benzene, which is also commercially available, was prepared by the method of Pausacker.[17] Acetylenes were purchased from Farchan. *tert*-Butylacetylene was prepared according to the method of Collier and Macomber.[28] 2-Methoxy-2-methyl-3-butyne was prepared according to Corey's method.[29] The synthesis of the phenylalkynyliodonium tosylates was described in detail in a previous paper.[14] Phenyliodine(III) dicarboxylates were prepared by the method of Merkushev.[18] THF was dried over Na/K alloy and distilled under argon prior to use. The reaction flasks were flame-dried and flushed with argon. Silica gel (Davisil) was not activated.

General Procedure for the Preparation of Phenyliodine(III) Dicarboxylates.[18] **[Bis[(3,5-dimethoxybenzoyl)oxy]iodo]benzene (8d).** A mixture of phenyliodine(III) diacetate **7** (6 g, 18.6 mmol) and 3,5-dimethoxybenzoic acid (6.8 g, 37.2 mmol) was dissolved in chlorobenzene (75 mL). The flask was placed on a Rotovap, and at aspirator vacuum the reaction mixture was heated to 50–55 °C. After complete evaporation of the solvent and the resulting acetic acid, a white solid remained, which was washed with ligroin (100 mL). The yield of **8d** was 9.7 g (92%). Mp: 140–143 °C. IR (KBr): 1580–1600 cm^{-1} (C=O). (This general procedure was also used for the preparation of **8a–c**. The isolated yields were nearly quantitative (>90%). Melting points and spectroscopic data agreed well with the literature[18] values.)

General Procedure for the Preparation of Alkynyl Benzoates. 1-Propynyl Benzoate (6e). Method A. At −78 °C, propyne (85%, stabilized with allene) (1 mL) was condensed into THF (40 mL), and 2.5 M *n*-BuLi (4 mL, 10 mmol) was added dropwise. The resulting solution was stirred for 30 min at this temperature and was then added to a mechanically stirred suspension of phenyliodine(III) dibenzoate **8a** (4.8 g, 15 mmol) and *t*-BuNO (7 mg, 0.08 mmol) in THF (100 mL). The reaction mixture was allowed to come to room temperature, and the solvent was removed in vacuo. The resulting solid was treated with ligroin (100 mL), insoluble lithium benzoate was filtered off, and the filtrate was concentrated. Column chromatography on silica gel (50 g) with CH_2Cl_2–hexane as eluent (1:5) gave 910 mg (57%) of **6e** as colorless crystals from pentane (−20 °C).

1-Propynyl Benzoate (6e). Method B. At −78 °C, propyne (85%, stabilized with allene) (1 mL) was condensed into THF (30 mL). A solution of 2.5 M *n*-BuLi (4 mL, 10 mmol) was added dropwise, and the resulting solution was stirred for 30 min at this temperature. Then phenyliodine(III) dibenzoate **8a** (4.5 g, 10 mmol) was added. The reaction mixture was allowed to warm up to room temperature (over a period of 2 h), and the solvent was removed in vacuo. The solid residue was treated with ligroin (150 mL), insoluble lithium benzoate was filtered off, and the filtrate was concentrated. Column chromatography on silica gel (50 g) first with hexane (eluation of iodobenzene) and then with CH_2Cl_2–hexane (1:5) gave 500 mg (31%) of **6e** as colorless crystals after recrystallization from pentane. HRMS (CI, CH_4 as ionizing gas) for $C_{10}H_9O_2(M + 1)$: calcd 161.0599, found 161.06012.

3,3-Dimethylbutynyl Benzoate (6a). Method C. (Ion-Exchange Reaction). (a) Preparation of Ion-Exchange Resin. A chromatograhy column was packed with Amberlyst A-26 ion-exchange resin (150 mL) and was successively rinsed with H_2O (300 mL), 1 N NaOH (300 mL), H_2O (300 mL), 2 M aquous sodium benzoate solution (500 mL), H_2O (300 mL), CH_3CN (500 mL), and finally with CH_2Cl_2 (500 mL). The resulting benzoate-loaded Amberlyst resin was air-dried by standing at room temperature for 3 days.

(b) Ion-Exchange Reaction. The air-dried, benzoate-loaded Amberlyst column was rinsed with CH_2Cl_2 (300 mL). (*tert*-Butylalkynyl)phenyliodinium tosylate **4a** (2.28 g, 5 mmol), dissolved in CH_2Cl_2 (20 mL), was placed on the resin, and the products were eluted with CH_2Cl_2 (150 mL) at a drop rate of 1 drop/s. After evaporation of the solvent, column chromatography of the crude product on silica gel (50 g) with CH_2Cl_2–hexane (1:9) [1.0 g (98%) PhI] and then with CH_2Cl_2–hexane (1:1) gave 400 mg (40%) of **6a** as a colorless oil.

Method A. Addition of **9e** [from 3,3-dimethyl-1-butyne (1 mL, 8 mmol) and 2.5 M *n*-BuLi (2.9 mL, 7.25 mmol) in THF (30 mL) at −78 °C] to a suspension of **8a** (3.53 g, 7.9 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C. The yield was 730 mg (50%) of **6a** as a colorless oil after chromatography with CH_2Cl_2–hexane as eluent.

Method B. Addition of **8a** (3.2 g, 7.2 mmol) to a solution of **9e** [from 3,3-dimethyl-1-butyne (600 mg, 7.3 mmol) and 2.5 M *n*-BuLi (3 mL, 7.5 mmol) in THF (40 mL) at −50 °C]. The yield of **6a** was 350 mg (24%) as a colorless oil after chromatography, first with CH_2Cl_2–hexane (1:4) and then with CH_2Cl_2–hexane (1:1).

4-Methylpentynyl Benzoate (6b). Prepared by Method C. The ion-exchange resin was charged with 2 M $PhCO_2Na$ solution (500 mL). (4-Methylpentynyl)phenyliodonium tosylate **4b** (1.59 g, 3.45 mmol) was dissolved in CH_2Cl_2 (20 mL) and added to the resin. The column was rinsed with CH_2Cl_2 (200 mL). Chromatography with CH_2Cl_2–hexane (1:5) [550 mg (78%) PhI] and then with CH_2Cl_2–hexane (1:1) gave 110 mg (16%) of **6b** as a colorless oil.

3,3-Dimethylbutynyl *p*-Methoxybenzoate (6c). Prepared by Method C. The ion-exchange resin (100 mL) was charged with 0.7 M *p*-$CH_3OC_6H_4CO_2Na$ solution (800 mL). (3,3-Dimethylbutynyl)phenyliodonium tosylate **4a** (2.28 g, 5 mmol) was dissolved in CH_2Cl_2 (20 mL) and placed on the resin. The column was rinsed with CH_2Cl_2 (150 mL). Column chromatography first with CH_2Cl_2–hexane (4:1) and then with CH_2Cl_2–hexane (1:1) afforded 120 mg (10%) of **6c** as a colorless oil.

4-Methylpentynyl *p*-Methoxybenzoate (6d). Prepared by Method C. The ion-exchange resin was charged with 0.7 M *p*-$CH_3OC_6H_4CO_2Na$ solution (800 mL). (4-Methylpentynyl)phenyliodonium tosylate **4b** (2.28 g, 5 mmol) was dissolved in CH_2Cl_2 (20 mL) and added to the column, and the column was rinsed with CH_2Cl_2 (150 mL). After chromatographic workup with CH_2Cl_2–hexane (4:1) and then with CH_2Cl_2–hexane (1:1) as eluent, 190 mg (16%) of **6d** was obtained as a pale yellow oil.

3-Methylbutynyl Benzoate (6f). Prepared by Method B. Addition of **8a** (4.46 g, 10 mmol) to a solution of **9b** [from 3-methyl-1-pentyne (1 mL) condensed into THF (40 mL) and 2.5 M *n*-BuLi (4 mL, 10 mmol)

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at −50 °C] in THF (40 mL) at −50 °C gave 600 mg (32%) of **6f** as a colorless oil after column chromatography first with CH_2Cl_2–hexane eluent (4:1) and then with CH_2Cl_2–hexane (1:1).

1-Hexynyl Benzoate (6g). Compound **6g** was prepared by method B, by addition of **8a** (4.46 g, 10 mmol) to a solution of **9d** [from 1-hexyne (820 mg, 10 mmol) and 2.5 M *n*-BuLi (4 mL, 10 mmol) in THF (40 mL) at −50 °C]. The yield of **6g** was 150 mg (7%) as a colorless oil after chromatography with CH_2Cl_2–hexane as eluent.

Method A. Upon addition of **9d** [from 1-hexyne (0.9 mL, 8 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (30 mL) at −78 °C] to a suspension of **8a** (3.53 g, 7.9 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C, the yield of **6g** was 620 mg (44%) as a colorless oil after chromatography with CH_2Cl_2–hexane (1:4) as eluent.

3-Methoxy-3-methylbutynyl Benzoate (6h). Method A. Addition of **9c** [from 2-methoxy-2-methyl-3-methylbutyne (1.18 g, 12 mmol) and 2.5 M *n*-BuLi (4 mL, 10 mmol) in THF (20 mL) at −78°C] to a suspension of **8a** (6.4g; 20 mmol) and *t*-BuNO (20 mg, 0.23 mmol) in THF (80 mL) at −78 °C yielded after chromatography with CH_2Cl_2–hexane eluent 1.05 g (48%) of **6h** as a colorless oil. HRMS (CI, CH_4 as ionizing gas) for $C_{12}H_{11}O_2$ (M − OCH_3): calcd 187.0757, found 187.075 996.

1-Propynyl *p*-Methoxybenzoate (6i). Method A. Addition of **9a** [prepared by condensation of propyne (85%, stabilized with allene) (1 mL) into THF (40 mL) at −78 °C and 2.5 M *n*-BuLi (4 mL, 10 mmol)] to a suspension of **8b** (7.59, 15 mmol) in THF (60 mL) at −78 °C yielded 0.85 g (44%) of **6i** as colorless crystals after chromatography with CH_2Cl_2–hexane eluent and recrystallization from pentane. HRMS (CI, CH_4 as ionizing gas) for $C_{11}H_{11}O_3$ (M + 1) calcd 191.0705, found 191.0706.

1-Propynyl *p*-Nitrobenzoate (6j). Method A. Addition of **9a** [from propyne (85%, stabilized with allene) (2.5 mL), condensed into THF (20 mL) at −78 °C and 2.5 M *n*-BuLi (4.5 mL, 11.25 mmol)] to a suspension of **8c** (8.5 g, 16 mmol) and *t*-BuNO (20 mg, 0.23 mmol) in THF (80 mL) at −78 °C gave, after chromatography with CH_2Cl_2–hexane as eluent and recrystallization from pentane, 1.45 g (45%) of **6j** as colorless crystals. HRMS (CI, CH_4 as ionizing gas) for $C_{10}H_8O_4N$ (M + 1): calcd 206.0444, found 206.0447.

1-Hexynyl *p*-Nitrobenzoate (6k). Method A. At −78 °C, **9d** [from 1-hexyne (0.9 mL, 7.8 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL) at −78 °C] was added to a suspension of **8c** (4.3 g, 8 mmol) and *t*-BuNO (7 mg, 0.08 mmol) in THF (100 mL). After column chromatography with CH_2Cl_2–hexane as eluent [hexane first, then CH_2Cl_2–hexane (1:1)] and recrystallization from pentane, 970 mg (56%) of **6k** was obtained as colorless crystals.

3,3-Dimethylbutynyl *p*-Nitrobenzoate (6l). Method A. Compound **9e** [from 3,3-dimethyl-1-butyne (0.9 mL, 7.3 mmol) and 2.5 M *n*-BuLi (2.9 mL, 7.25 mmol) in THF (30 mL) at −78 °C] was added to a suspension of **8c** (4.3 g, 8 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C. After chromatography with CH_2Cl_2–hexane as eluent and recrystallization from pentane, 600 mg (35%) of **6l** was obtained as colorless crystals.

1-Hexynyl 3,5-Dimethoxybenzoate (6m). Method A. Addition of **9d** [from 1-hexyne (1 mL, 8.7 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL) at −78 °C] to a suspension of **8d** (4.36 g, 7.7 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after chromatography with CH_2Cl_2–hexane as eluent and recrystallization from pentane, 610 mg (33%) of **6m** as a white solid.

3,3-Dimethylbutynyl 3,5-Dimethoxybenzoate (6n). Method A. Addition of **9e** [from 3,3-dimethyl-1-butyne (1 mL, 8.1 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL) at −78 °C] to a suspension of **8d** (4.36 g, 7.7 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after chromatography with CH_2Cl_2–hexane as eluent and recrystallization from pentane, 650 mg (35%) of **6n** as colorless crystals. HRMS (EI) for $C_{15}H_{18}O_4$ (M^+): calcd 262.1197, found 262.120 097 1.

Preparation of 3-Methoxy-3-methylbutynyl Benzoate (6h). According to Method A in the Absence of Radical Trap. Addition of **9c** [from 2-methoxy-2-methyl-3-butyne (1.18 g, 12 mmol) and 2.5 M *n*-BuLi (4 mL, 10 mmol) in THF (20 mL) at −78 °C] to a solution of **8a** (6.4 g, 20 mmol) in THF (80 mL) at −78 °C yielded, after chromatography with CH_2Cl_2–hexane as eluent, 540 mg (25%) of **6h** as a colorless oil.

Isolation of Coupling Product. Bis(*tert*-butylacetylene). At −60 °C, **8c** (804 mg, 1.5 mmol) was added to a THF solution of **9e** [prepared by dropwise addition of 2.5 M *n*-BuLi (0.6 mL, 1.5 mmol) to 3,3-dimethyl-1-butyne (123 mg, 1.5 mmol) in THF (10 mL) at −60 °C]. The reaction mixture was allowed to come to room temprature. The solvent was removed in vacuo (25 °C (12 Torr)), and the residue was transfered to a sublimation apparatus. Over a period of 15 h, the volatile iodobenzene was evaporated (25 °C (0.05 Torr)), and 60 mg (25%) of sublimed *t*-BuC≡CC≡C-*t*-Bu was isolated as colorless crystals. MP: 130–132 °C (lit.[30] mp: 129.5–131.5 °C). ^1H NMR ($CDCl_3$–TMS): δ 1.22 (s, *t*-Bu) [lit.[30] ^1H NMR (CCl_4): δ 1.22]. ^{13}C NMR ($CDCl_3$) δ 27.90, 30.63 (*t*-Bu), 63.75, 86.00 (C≡C). MS (EI, 70 eV): 162 (100), 147 (47.5), 119 (57.6), 105 (56.8), 91 (49.6), 77 (12.4), 55 (13.2), 41 (54).

The remaining solid residue was treated with CH_2Cl_2 (50 mL), *p*-$NO_2C_6H_4CO_2Li$ was filtered off, and the filtrate was concentrated. Column chromatography on silica gel (50 g) with CH_2Cl_2–hexane (2:1) as eluent yielded 60 mg (16%) of **6l**.

Attempt To Trap Carbene 14 with $SiEt_3H$. At −78 °C, **9e** [prepared by addition of 2.5 M *n*-BuLi (2.8 mL, 7 mmol) to 3,3-dimethyl-1-butyne (1 mL) in THF (30 mL) at −78 °C] was added to a suspension of **8a** (6.4 g, 20 mmol), *t*-BuNO (32 mg, 0.4 mmol), and $SiEt_3H$ (8.1 g, 70 mmol) in THF (100 mL). The reaction mixture was allowed to come to room temperature, and the solvent was removed in vacuo. The residue was treated with ligroin (150 mL) and insoluble lithium benzoate, excess **8a** was filtered off, and the filtrate was concentrated. Column chromatography on silica gel (50 g) first with hexane (PhI + $SiEt_3H$) and then with CH_2Cl_2–hexane (1:1) yielded 710 mg (50%) of **6a** as a colorless oil. No carbene insertion product was detected at all.

General Procedure for the Preparation of Alkynyl Acetates. 3,3-Dimethylbutynyl Trimethylacetate (6q). At −78 °C, 3,3-dimethyl-1-butyne (1 mL, 8 mmol) was added dropwise to a solution of 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL). The lithium acetylide solution (**9e**) was stirred for 30 min at that temperature and then added to a mechanically stirred solution of **8e** (3.13 g, 7.7 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C. The reaction mixture was allowed to warm up to room temperature, and the solvent was removed in vacuo. The solid residue was treated with ligroin (100 mL), the insoluble lithium acetate was filtered off, and the filtrate was concentrated in vacuo. Column chromatography on silica gel (50 g) with hexane first (PhI) and then with CH_2Cl_2–hexane eluent yielded 70 mg (5.5%) of **6q** as a colorless oil.

1-Hexynyl Acetate (6o). At −50 °C, **9d** [from 1-hexyne (2.5 mL, 22 mmol) and 2.5 M *n*-BuLi (5.6 mL, 14 mmol) in THF (20 mL) at −78 °C] was added to a suspension of **7** (5 g, 15.5 mmol) and *t*-BuNO (64 mg, 0.7 mmol) in THF (100 mL). The reaction mixture was allowed to warm up to −30 °C and was then poured into 200 mL of chilled, aqueous NaO_2CCH_3 (60 g). The organic layer was separated, and the aqueous phase was extracted with ligroin (2 × 100 mL). The combined organic layers were dried briefly over $MgSO_4$, and the solvent was removed in vacuo. Chromatographic workup on silica gel (50 g) first with hexane (PhI) and then with CH_2Cl_2–hexane eluent gave 300 mg (15%) of **6o** as a pale yellow oil. HRMS (CI, CH_4 as ionizing gas) for $C_{12}H_{19}O_2$ [(*n*-BuCH=C=O)$_2$ − 1]: calcd 195.138 495, found 195.138 882.

4-Methylpentynyl Acetate (6p). Addition of **9f** [from 4-methyl-2-pentyne (1.2 mL, 10 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL) at −78 °C] to a suspension of **7** (11.5 g, 36 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C yielded 90 mg (9%) of **6p** as a colorless oil after chromatographic workup on silica gel (50 g) with hexane first (PhI) and then with CH_2Cl_2–hexane eluent.

1-Propynyl 3-Phenylproplonate (6r). Addition of **9a** [prepared by condensation of propyne (85%, stabilized with allene) (2 mL) into THF (40 mL) at −78 °C and 2.5 M *n*-BuLi (2.8 mL, 7 mmol)] to a suspension of **8f** (5.27 g, 10 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after column chromatography on silica gel (50 g) with CH_2Cl_2–hexane eluent, 30 mg (2.3%) of **6r** as a pale yellow oil. HRMS (EI, 70 eV) for $C_{12}H_{12}O_2$ (M^+): calcd 188.083 720, found 188.083 20.

3,3-Dimethylbutynyl 3-Phenylpropionate (6s). Addition of **9e** [from 3,3-dimethyl-1-butyne (1 mL, 8 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (30 mL) at −78 °C] to a suspension of **8f** (5.27 g, 10 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after column chromatography on silica gel (50 g) with CH_2Cl_2–hexane eluent, 100 mg (6%) of **6s** as a colorless oil. HRMS (CI, CH_4 as ionizing gas) for $C_{15}H_{19}O_2$ (M^+ + 1): calcd 231.138 495, found 231.136 454.

1-Propynyl Diphenylacetate (6t). Addition of **9a** [prepared by condensation of propyne (2 mL) into THF (20 mL) at −78 °C and 2.5 M *n*-BuLi (2.8 mL, 7 mmol)] to a suspension of **8g** (11 g, 18 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after column chromatography on silica gel (50 g) with CH_2Cl_2–hexane eluent and recrystallization from pentane, 420 mg (24%) of **6t** as colorless crystals. HRMS (CI, CH_4 as ionizing gas) for $C_{17}H_{14}O_2$ (M^+): calcd 250.099 37, found 250.098 71.

3,3-Dimethylbutynyl Diphenylacetate (6u). Addition of **9e** [from 3,3-dimethyl-1-butyne (1 mL, 8 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (30 mL) at −78 °C] to a suspension of **8g** (6.6 g, 10 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL) at −78 °C gave, after column chromatography on silica gel (50 g) with CH_2Cl_2–

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hexane eluent and recrystallization from pentane, 520 mg (25%) of **6u** as colorless crystals. HRMS (EI, 70 eV) for $C_{20}H_{20}O_2$ (M^+): calcd 292.146 320, found 292.145 777 5.

1,1,1-Trichlorooct-3-yn-2-one (13). At -78 °C, **9d** [from 1-hexyne (1 mL, 8.7 mmol) and 2.5 M *n*-BuLi (2.8 mL, 7 mmol) in THF (20 mL) at -78 °C] was added to a mechanically stirred suspension of **8h** (4.07 g, 7.7 mmol) and *t*-BuNO (32 mg, 0.4 mmol) in THF (100 mL). The reaction mixture was allowed to warm up to room temperature, and the solvent was removed in vacuo. The white solid residue was treated with ligroin, lithium trichloroacetate was filtered off, and the filtrate was concentrated in vacuo. Column chromatography on silica gel (50 g) with hexane gave iodobenzene (1.17 g, 82%) as the first fraction and 280 mg of a not completely pure second fraction. Chromatography on silica gel (50 g) of the second fraction, with hexane, yielded 200 mg (12%) of **13** as a colorless oil. ^{1}H NMR ($CDCl_3$, TMS): δ 0.93-0.98 (m, 3 H), 1.42-1.55 (m, 2 H), 1.60-1.70 (m, 2 H), 1.45-1.50 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 13.38, 19.12, 21.88, 29.20 (*n*-Bu), 74.33 (C≡C), 95.40 (CCl_3), 104.24 (C≡C), 168.28 (C=O). IR (neat): 2210 (vs. C≡C), 1705 (vs, C=O), 1195 (vs, C—O), 900, 805, 765, 730, 660 cm^{-1}. MS (CI, CH_4 as ionizing gas): 229 (15, $M^+ + H + 2$), 227 (15, $M^+ + H$), 193 (4, 229 - Cl), 191 (6, 227 - Cl), 165 (2, 193 - CO), 163 (3, 191 - CO), 129 (2, 165 - Cl), 127 (5, 163 - Cl), 109 (100, C_7H_9O). HRMS (CI, CH_4 as ionizing gas) for $C_8H_{10}OCl_3$ ($M^+ + H$): calcd 226.979 860, found 226.978 386.

Reversibly and Irreversibly Formed Products from the Reactions of Mercaptalbumin (AlbSH) with Et_3PAuCN and of $AlbSAuPEt_3$ with HCN

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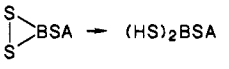
Abstract: The reactions of $AlbSAuPEt_3$ (cysteinyl-34-(triethylphosphine)gold(I) albumin) with HCN and of mercaptalbumin (AlbSH) with Et_3PAuCN were examined by ^{13}C and ^{31}P NMR spectroscopy, gel exclusion chromatography, and $^{14}CN^-$ radiotracer methods. The reaction of HCN with $AlbSAuPEt_3$ yields irreversibly formed products, Et_3PO, $[Au(CN)_2]^-$, and a protein-gold complex, AlbSAuX, where X ≠ CN^- or PEt_3. During the reaction, a transient, reversibly formed product, Et_3PAuCN, is generated but reacts further to yield the final products. The reaction of independently prepared Et_3PAuCN with AlbSH gives the same set of irreversibly formed products. Here, also, transient, reversibly formed products, $AlbSAuPEt_3$ and HCN, are observed. Thus, each set of reactants yields the same irreversibly formed products and the other set as transient, equilibrium products. These results are explained by proposing a common three-coordinate transition state, $[AlbSAu(PEt_3)CN^-]^*$, for the equilibration of the two sets of reactants/products and the formation of the irreversibly formed products. Et_3P and $AlbSAuCN^-$ are proposed to be intermediates leading from the transition state to the irreversibly formed products. We report the first direct evidence that the oxidation of Et_3P to Et_3PO is accompanied by the reduction of the albumin disulfide bonds



$[(Et_3P)_2Au]^+$, which is generated in solutions of Et_3PAuCN via ligand disproportionation, reacts with AlbSH to produce $AlbSAuPEt_3$ and Et_3PO. The new thiol groups, $(HS)_2BSA$, generated by the phosphine oxidation, react with the $[(Et_3P)_2Au]^+$ to produce $(Et_3PAuS)BSA$, which is characterized by a ^{31}P NMR resonance at 35.8 ppm. The relevance of these biochemical reactions to the gold metabolism of cigarette smoking chrysotherapy patients is discussed.

The metabolism of anti-arthritic gold drugs can be altered by the absorption of HCN from tobacco smoke.[2,3] Gold metabolites of the oligomeric drugs such as aurothiomalate (AuSTm[4]) enter the red blood cells of smoking patients but not of nonsmoking patients[2,3] or laboratory animals.[5,6] Smokers have earlier and more frequent toxic reactions to gold drugs.[2] Metabolites of auranofin ((triethylphosphine)(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)gold(I), $Et_3PAuSATg$) enter rbc's irrespective of smoking habits.[3,7] To our knowledge, ligand exchange reactions of auranofin metabolites and HCN, which might induce other, more subtle metabolic changes, have not been investigated.

Cyanide binds to gold very tightly (log β_2 = 36.6),[8] although exchange of free HCN (the form present at neutral pH due to hydrolysis of CN^-) with bound cyanide is very rapid. Independent studies by this laboratory and Sadler's demonstrate that the equilibrium competition of HCN and thiols for gold(I) favors cyanide and that the mixed ligand complexes, $[RSAuCN^-]$, form

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(4) Abbreviations: AAS = atomic absorption spectroscopy; $AlbSAuPEt_3$ = cysteinyl-34-(triethylphosphine)gold(I) albumin; AlbSAuSTm = cysteinyl-34-(thiomalato)gold(I) albumin; AlbSH = mercaptalbumin; ATgSH = 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-thioglucose; AuSTm = sodium ((*S*)-thiomalato)aurate(I); BSA = microheterogenous bovine serum albumin; DTNB = 5,5′-dithiobis(2-nitrobenzoic acid); $Et_3PAuSATg$ or AF = Auranofin (triethylphosphine)(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*)gold(I); GtHS = reduced glutathione; HSA = human serum albumin; RSH = reduced thiol; TMP = trimethyl phosphate; TSP = 3-(trimethylsilyl)-propionic-2,2,3,3-d_4 acid, sodium salt.

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