that this indeed is the favored conformer in the ground state.

Conclusions

Free-radical reactive intermediates have long had the reputation of reacting with little chemoselectivity and virtually no stereoselectivity. Most organic chemists first encounter free radicals in introductory courses by studying reactions that emphasize these characteristics. Chlorination of alkanes has minimal chemoselectivity, and polymerization of vinyl monomers occurs with virtually no control of stereochemistry. Research developments of the past 15 years indicate that this reputation is undeserved. Chain processes have been developed that are exquisitely chemoselective,[2-7] and high levels of stereoselection in cyclic systems have also been well-documented.[11] We now assert that there are straightforward solutions to the problem of free-radical acyclic stereoselectivity. The lessons of stereocontrol in carbanion and concerted reactions serve as a good guide for experiments in free-radical reactions, and the results of these first experiments indicate that free-radical acyclic stereoselectivity is comparable to that observed for other reactive intermediates in parallel reactions. Synthetic chemists can now approach complex problems with a "free-radical solution" and have every expectation that stereochemistry will not necessarily present an insurmountable barrier.

Alkynyl Carboxylate, Phosphate, and Sulfonate Esters

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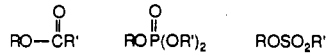
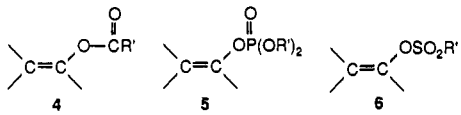
Among the most important compounds in organic chemistry are the three major classes of esters: carboxylate 1, phosphate 2, and sulfonate 3.[1] All three types are widely used in synthetic organic chemistry as well as in mechanistic investigations.[2] Carboxylate



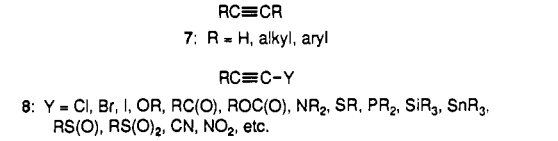
1 2 3

esters in particular are ubiquitous in nature and are the essence of the fragrances of many flowers and the major components in the characteristic flavors of most fruits, such as amyl butyrate (apricot), isopentyl acetate (banana), benzyl acetate (peach), octyl acetate (orange), etc. Phosphate esters in turn play a critical role in biochemistry.[3] Likewise, their unsaturated counterparts, vinyl (enol) esters 4-6 are well-known and have an important role in numerous organic processes.



4 5 6

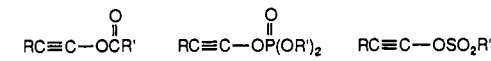
Another valuable functionality in organic chemistry is the carbon-carbon triple bond.[4] A wide variety of acetylenes, from ones bearing simple hydrocarbon substituents, 7, to diversely substituted, functionalized alkynes, 8, are well-known, are generally stable, and play a key role in diverse organic transformations. In fact, both the esters and acetylenes are so common and readily available that they are often taken for granted by most chemists.



7: R = H, alkyl, aryl

8: Y = Cl, Br, I, OR, RC(O), ROC(O), NR_2, SR, PR_2, SiR_3, SnR_3, RS(O), $RS(O)_2$, CN, NO_2, etc.

Despite the importance and widespread occurrence of both numerous esters 1-6 and alkynes 7 and 8, acetylenic esters of any kind, carboxylate 9, phosphate 10, or sulfonate 11, were unknown until the mid-1980s when we first prepared and reported them. This is all the more surprising as these acetylenic esters, 9-11, simply combine into a single, novel derivative two of the most common and readily available organic functionalities. In this Account, I wish to discuss our recent synthesis, properties, and reactions of these novel alkynyl esters 9-11.



9 10 11

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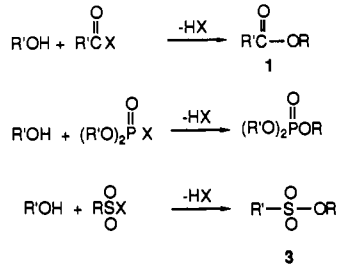
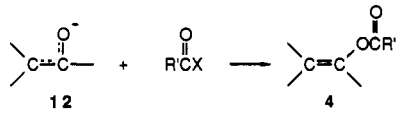
Synthesis

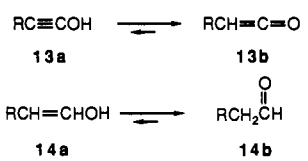
As described in all introductory organic texts, esters are most readily made[5] by the reaction of an alcohol with the respective acid halides:



Likewise, the enol esters, for example **4**, are made[2] by the interaction of an enolate **12** with acid halides.

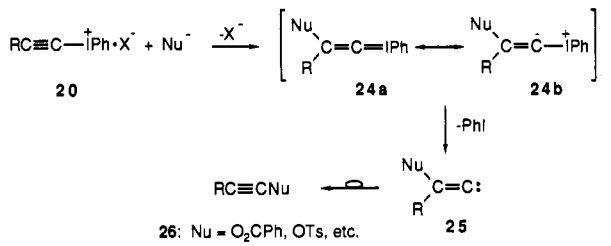


Therein lies a problem. The analogous preparation of alkynyl esters would require hydroxyacetylenes **13a**. Hydroxyacetylenes or ynoles, **13a**, are the triple-bond analogues of enols **14a**. Both ynols, **13a**, and enols, **14a**, are tautomers of carbonyl species, namely, ketenes, **13b**, and aldehydes (or ketones), **14b**, respectively. However, whereas enols[6] are readily accessible, and in many instances even isolable as stable compounds, the tautomeric equilibrium is completely on the side of ketenes **13b** and hence ynols are not available as reagents. In fact, high-level ab initio calculations[7,8] indicate that the hydroxyacetylene–ketene, $HC{\equiv}COH \rightleftarrows CH_2{=}C{=}O$, energy difference is 37 kcal/mol in favor of ketene compared to the energy difference of only 14 kcal/mol between $CH_2{=}CHOH$ and CH_3CHO.[8] Hence, ynols have only recently been observed[9] even as transient intermediates.

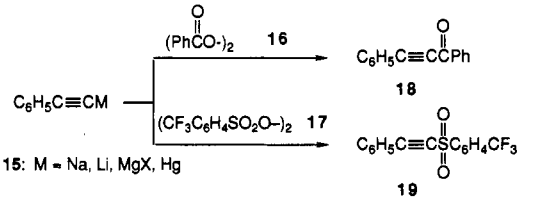


Similarly, there are numerous standard methods for the preparation of acetylenes including functionalized ones.[4] Undoubtedly the most common and widely used procedure involves elimination techniques, mostly dehydrohalogenations of appropriate olefin precursors. However, these and related procedures did not work for the preparation of the desired esters **9–11** as they gave either no reaction under mild conditions or only tar under forcing conditions.[10] Likewise, flash vacuum pyrolysis[11] of appropriate precursors or reaction of a variety of acetylide anions **15** with either benzoyl peroxide (**16**) or sulfonyl peroxide **17** failed to give any acetylenic esters **9–11**; the latter reactions yield ketone **18** and sulfone **19**, respectively, instead.[12]

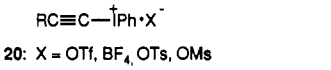
Scheme I
Mechanism of Formation of Alkynyl Esters via an S_N-A Process from Alkynyl(phenyl)iodonium Species 20 (Nu = $PhCO_2$, $(R'O)_2PO_2$, RSO_3)



Our successful preparation of acetylenic esters **9–11** involved the use of alkynyl(phenyl)iodonium species,[13] **20**, the newest member of the family of tricoordinate iodine, I(III), compounds.[14]



Alkynyl(phenyl)iodonium salts, **20**, are generally stable, usually microcrystalline solids and are now readily available by a variety of methods,[13,15–19] the most versatile of which is iodonium transfer via $PhI^+CN\cdot^-OTf$.[20,21]



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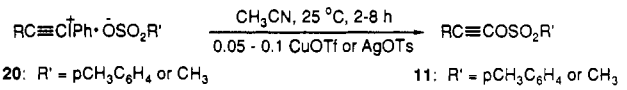
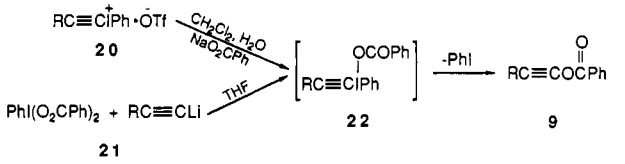
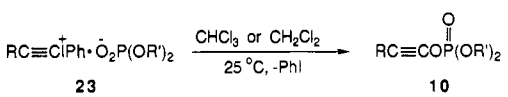
Reaction of alkynyl(phenyl)iodonium tosylates or mesylates, **20**, with 5–10% of CuOTf or AgOTs in dry CH_3CN at room temperature afforded[22] the desired alkynyl sulfonate esters, **11**, the first reported members of the family of novel acetylenic esters.[22] Likewise,



interaction of alkynyl(phenyl)iodonium triflates with $C_6H_5CO_2Na$ or reaction of $PhI(O_2CPh)_2$ (**21**) with acetylide ions in THF results[23,24] in the desired alkynyl carboxylates **9**, presumably via the intermediacy of **22**.

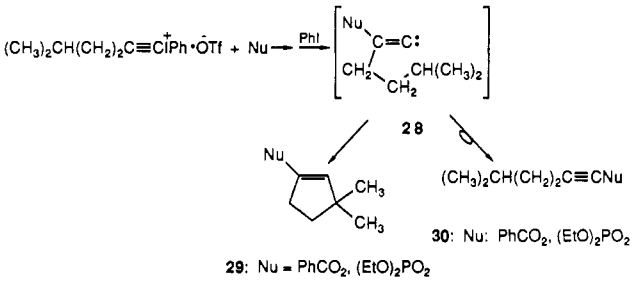


In an analogous manner, decomposition of alkynyl(phenyl)iodonium dialkyl phosphates **23** yields[23,25] a variety of alkynyl dialkyl phosphate esters **10**. The

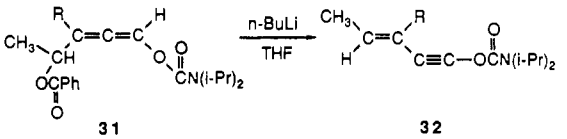


mechanism of these alkynyl ester formations from alkynyl(phenyl)iodonium species **20** is interesting. Formalistically, this is a nucleophilic acetylenic substitution process[26] (S_N-A) with carboxylates, dialkyl phosphates, and sulfonates acting as nucleophiles and the alkynyl(phenyl)iodonium species **20** as the electrophilic substrates. The actual details of the mechanism are considerably more complex, as seen in Scheme I.

The first step involves Michael addition of the nucleophile to give an ylide **24**. Loss of iodobenzene from **24b** results in the well-established[27] alkylidenecarbene, **25**, which is known[27] to rearrange to alkynes, **26**, in the absence of external traps and when R or Nu are groups of high or reasonable migratory aptitude. Evidence for this mechanism includes isolation of small amounts of cyclic vinyl esters **29**, along with the major, alkynyl ester products **30**.[28] These cyclic esters are the result of insertion by the intermediate carbene **28** into the tertiary C–H bond and hence provide indirect evidence for the intermediacy of **25**. Similar results involving the intermediacy of unsaturated carbenes **25** in the reaction



of alkynyl(phenyl)iodonium species **20** (X = BF_4) with a variety of other nucleophiles have been observed by Ochiai and co-workers,[29] as well as ourselves.[30] To date, with one exception,[31] all syntheses of alkynyl esters involve the use of alkynyl(phenyl)iodonium salts **20**. Treatment[31] of 4-(benzoyloxy)-1,2-alkadienyl carbamates **31** with BuLi resulted in the formation of enynyl carbamates **32**, a member of the family of alkynyl esters. However, this procedure is not general and works only for the specific allene depicted.



Properties and Characterization

All three classes of alkynyl esters, carboxylates **9**, dialkylphosphates **10**, and sulfonates **11**, are stable in pure form and may be stored (in a refrigerator) for extended periods. The overwhelming majority of alkynyl esters **9–11** known to date, like their saturated **1–3** and olefinic **4–6** counterparts, are colorless or pale yellow liquids. However, they are less stable than their more common saturated counterparts **1–3**. Of the three classes of alkynyl esters, the sulfonates **11** are the most stable and the carboxylates **9**, the least stable. In fact, so far we have only been able to isolate, in pure form, alkynyl benzoates (**9**: R' = Ar) and pivalates (**9**: R' = *t*-Bu). Simple alkyl esters such as formates, acetates, propanoates, etc. are too unstable to isolate.[24] Thermal stability does not seem to be the problem; rather, decomposition by hydrolysis (vide infra) is the major reason for their instability.

All three classes of alkynyl esters have highly characteristic spectral properties.[22,24,25] In the infrared region, all three classes **9–11** exhibit a medium to strong absorption in the 2260–2290 cm^{-1} (most often between 2270 and 2280 cm^{-1}) region due to the unsymmetrically substituted C≡C bond. The carboxylate esters **9** have an intense carbonyl stretch around 1760–1770 cm^{-1}, whereas the phosphates **10** show a very strong P=O signal around 1280–1300 cm^{-1}, and the sulfonates **11** have their characteristic SO_2 vibrations at ~1390 and 1185 cm^{-1}.

The mass spectra of these new compounds almost always have a peak for the molecular ion and easily identifiable, characteristic fragmentations.[22,24,25] Most interesting and highly characteristic are the ^{13}C NMR spectra and in particular the signals due to the two

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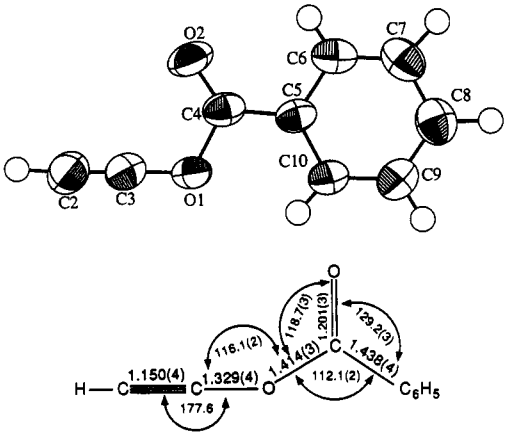
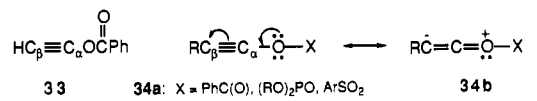


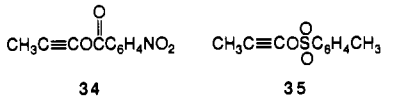
Figure 1. Top: ORTEP representation of **33**. Bottom: summary of key structural features (and their esd) of ethynyl benzoate (**33**). From ref 35.

triple-bonded carbons. In all cases, for all three classes of alkynyl esters **9**–**11**, the α-carbon is in the normal acetylenic region[32] of 70–90 ppm, whereas the β-carbon signals are shifted upfield and appear at 35–60 ppm. For example, for the parent ethynyl benzoate (**33**), C_α is at 80.1 ppm whereas C_β is at 40.2 ppm compared to 71.9 ppm for HC≡CH itself. This result, at first somewhat surprising, is readily rationalized by the contribution of resonance hybrid **34b**; it is well estab-



lished[33] that although all three ester moieties, carboxylate, phosphate, and sulfonate, are electron-withdrawing by induction, they are electron-donating by resonance. For example, $\sigma_P = +0.29$ and $\sigma_I = +0.54$ for the tosylate functionality, but $\sigma_R = -0.21$.[34] Hence, these alkynyl esters are in fact electron-rich acetylenes, in accord with theoretical calculations (vide infra).

To date, X-ray structural data are reported for three alkynyl esters: ethynyl benzoate[35] (**33**), propynyl *p*-nitrobenzoate[36] (**34**), and propynyl tosylate[35] (**35**).



ORTEP representations and key structural features for **33** and **35** are summarized in Figures 1 and 2, respectively. A number of interesting observations may be made from these structural data. Specifically, both alkynyl carboxylates **9** and alkynyl sulfonates **11**, as represented by **33** and **35**, are, as expected, essentially linear acetylenes with C≡C—O bond angles of 174.7° and 177.6°, respectively. Moreover, like all known acyclic saturated carboxylic esters,[37] ethynyl benzoate (**33**) adopts the antiperiplanar (syn) or *Z* conformation

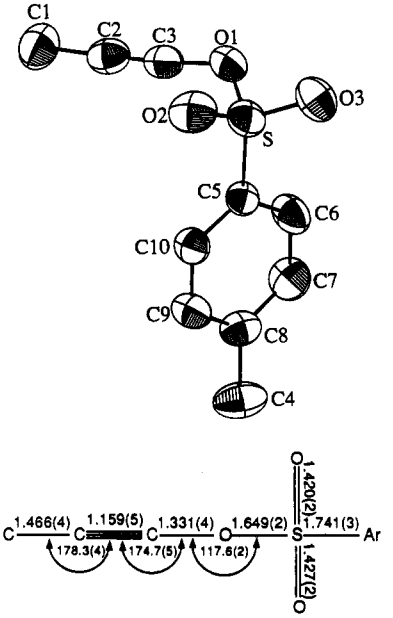
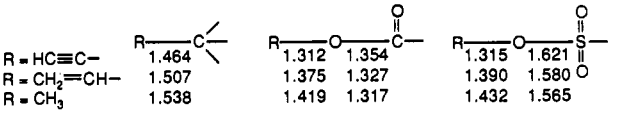


Figure 2. Top: ORTEP representation of **35**. Bottom: summary of key structural features (and their esd) of propynyl tosylate (**35**). From ref 35.

Chart I
Comparison of the Calculated[39] (6-31G*) R–C, R–O, and O–C (or O–S) Bond Distances (Å) as a Function of R[35,36]



around the OC=O carbonyl moiety. Furthermore, the general structural features of the ester moiety of both alkynyl carboxylates and sulfonates closely resemble those of their saturated and enol congeners **1**–**6**.

Perhaps the single most interesting structural feature for these molecules is the C_{sp}–O bond length of 1.329 Å and 1.331 Å for **33** and **35**, respectively, since, to our knowledge, this is the first time that any C_{sp}–O bond length has been experimentally determined.[35] It is instructive to compare and contrast these bond lengths to the corresponding ones in enol and saturated carboxylates and sulfonates as well as to the known[38] carbon–carbon bond length as a function of hybridization of carbon.

In order to get further insight and a better understanding of these unique structural features, theoretical calculations were carried out on carboxylate and sulfonate esters in a collaborative investigation with Apeloig and Karni of the Technion in Israel.[35,36] The relevant data are summarized in Chart I. It is evident that both the C–C bonds and the C–O bonds (in both carboxylate and sulfonate esters) become significantly *shorter* as the hybridization of the carbon changes from sp^3 to sp^2 to sp. In contrast, the corresponding O—C(O) and O—$S(O)_2$ bonds become *longer* along the series $CH_3 \rightarrow CH_2{=}CH \rightarrow HC{\equiv}C$. Similar changes have been observed[40] in the C—X bond distance in the

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(36) Stang, P. J.; Kitamura, T.; Arif, A. M.; Karni, M.; Apeloig, Y. *J. Am. Chem. Soc.* **1990**, *112*, 374.
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(38) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146.
(39) The experimental values are very similar and the trends identical,[35,36] but exact comparisons are more difficult because of many small structural variations within the experimentally determined compounds.
(40) Legon, A. C.; Millen, D. J.; Samson-Baktiari, A. *J. Mol. Struct.* **1979**, *52*, 71.

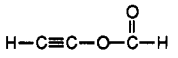
Table I
Hydrolysis Rates[a] of Typical Alkynyl Esters, H_2O, 25 °C

	k_{H^+}, M^{-1} s^{-1}	k_{H_2O}, s^{-1}	k_{OH^-}, M^{-1} s^{-1}	k_{H^+}/k_{D^+}	k_{H_2O}/k_{D_2O}
$CH_3C{\equiv}COBz$	3.02×10^{-5}	3.42×10^{-5}	73.7	2.7 ± 0.8	2.0 ± 0.0
n-$BuC{\equiv}COPO_3Et_2$	4.91×10^{-6}	1.80×10^{-4}	3.21	2.0 ± 0.1	2.8 ± 0.5
n-$BuC{\equiv}COTs$	1.30×10^{-5}	2.40×10^{-6}	13.0	4.1 ± 1.2	

[a] From ref 44.

analogous series $CH_3CH_2X \rightarrow H_2C{=}CHX \rightarrow HC{\equiv}CX$. The R–C and parallel R–O changes are largely due to changes in hybridization; i.e., as the carbon hybrid orbital acquires more s character, the bond shortens.[38,41] The changes (in the opposite direction) in the more remote O—C(O) and O—$S(O)_2$ bonds result from the greater electron-withdrawing ability[42] of $HC{\equiv}C > CH_2{=}CH > CH_3$, which in turn increases the electronegativity of the oxygen, and according to Bent's rule,[43] its bonds acquire a higher p character and thereby lengthen.

Finally, these calculations[36] also indicate a *net* charge distribution of –0.31 and +0.31 on the carbonyl moiety and the acetylenic unit, respectively, in propynyl formate (**36**) and a dipole moment of 1.53 D for **36** in accord with the aforementioned ^{13}C NMR data and the importance of resonance form **34b**.

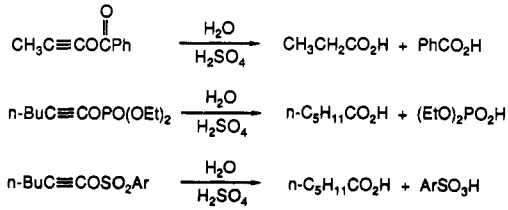


36

Reactions

Generally, esters readily undergo acid- as well as base-catalyzed hydrolysis. In a collaborative study with Tidwell and co-workers at Toronto, we investigated the hydrolysis mechanisms of these novel alkynyl carboxylate **9**, phosphate **10**, and sulfonate **11** esters.[44] The rates of hydrolysis of representative members of all three alkynyl esters **9**–**11** as a function of pH are shown in Figure 3 and summarized in Table I.[44] All three esters, as expected, hydrolyze rapidly under acidic as well as basic conditions. Surprisingly, unlike their saturated and enol counterparts **1**–**6**, they also hydrolyze under *neutral* conditions.

In aqueous H_2SO_4, the products in all three cases are the carboxylic acids derived from the alkynyl portion along with the respective acids derived from the "acyl" moiety of each ester:



These acid-catalyzed reactions proceed via an Ad_E2 process involving a rate-limiting proton transfer to the β-carbon and formation of a vinyl cation,[45] **37**, which reacts rapidly with H_2O to give **38** and upon tautomerism gives the mixed anhydride **39** and thence the final products. Similarly, the base-catalyzed reactions most likely involve ^-OH attack on the acyl moiety (i.e., C=O, P=O, SO_2) and the usual standard[2,5] mechanistic steps.

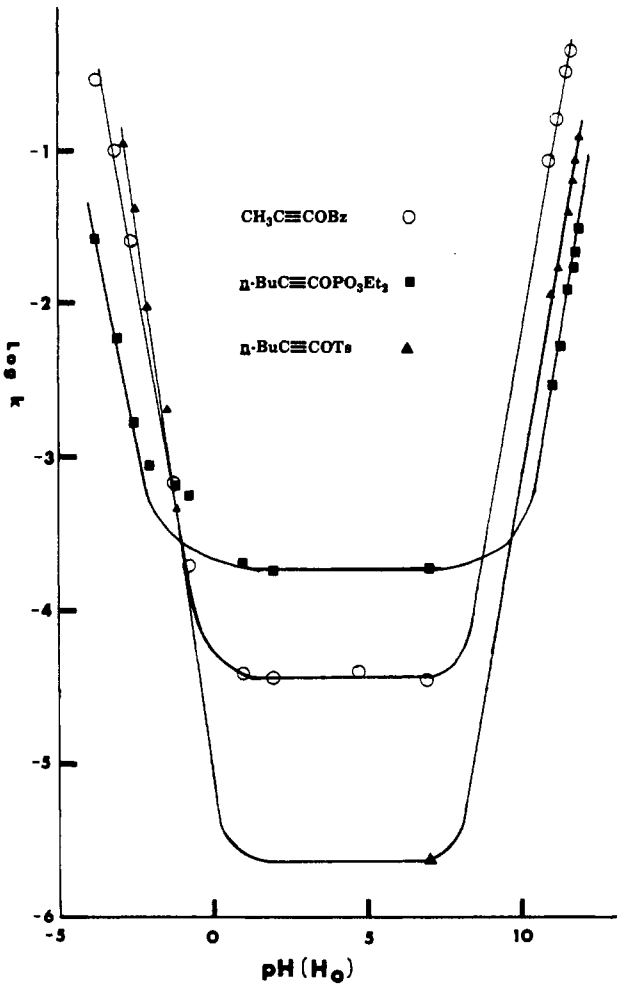
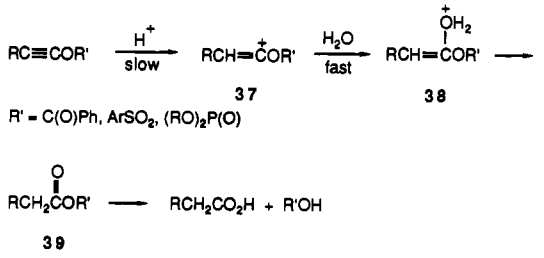


Figure 3. Rates of hydrolysis of $CH_3C{\equiv}COBz$, n-$BuC{\equiv}COPO_3Et_2$, and n-$BuC{\equiv}COTs$ as a function of pH (H_0 below pH 1). Reprinted with permission from ref 44. Copyright 1988 American Chemical Society.



The unique and interesting process is the neutral hydrolysis, which was investigated in greater detail for propynyl benzoates.[46] Besides the propanoic and

(41) Krygowski, T. M. *Prog. Phys. Org. Chem.* **1990**, *19*, 239.
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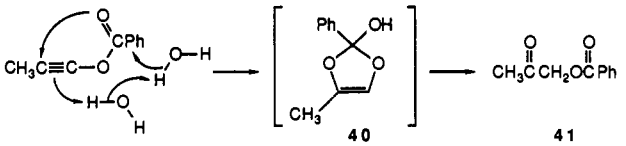
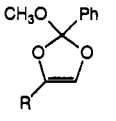
benzoic acids as products, 46% of the keto ester $CH_3C(O)CH_2OC(O)Ph$ (**41**) was also observed as the product of *neutral* hydrolysis in aqueous CH_3CN.[46] Labeling studies in $H_2{}^{18}O$ as well as careful NMR studies indicated that the mechanism of hydrolysis involved an unusual cyclization pathway including **40** as an intermediate.



40 **41**

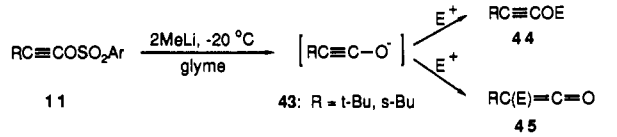
Further evidence for this novel hydrolysis mechanism comes from the isolation and NMR characterization of dioxolenes **42** when the reaction was carried out in anhydrous CH_3OH at 60 °C.[46] Although detailed inves-



42: R = H, Me, t-Bu

tigations were only carried out for the neutral hydrolysis of alkynyl benzoates, we have observed similar products, i.e., $RC(O)CH_2OP(O)(OR)_2$ and $RC(O)CH_2OTs$, in working with the alkynyl phosphate **10** and sulfonate **11** esters, and these results likely account for the aforementioned hydrolytic instability of these novel alkynyl esters.

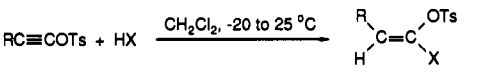
Enolates and enolate chemistry are among the most useful reagents and widely employed reactions in organic chemistry. Yet little was known[47] about their triple-bonded analogues, ynolates and ynolate chemistry. Reaction of alkynyl tosylates **11** with MeLi in glyme readily affords the desired ynolates, **43**, which can be easily trapped with a variety of electrophiles.[48]



11 **43**: R = t-Bu, s-Bu **44** **45**

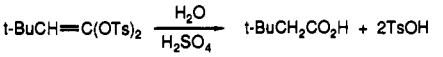
Trapping with R_3SiCl or $(RO)_2P(O)Cl$ resulted in O-trapped products **44** including previously little known[49] siloxyalkynes, $R'C{\equiv}COSiR_3$, whereas reaction with Et_3GeCl, *n*-Bu_3SnCl, or $PhC(O)Cl$ resulted[48] in C-trapping and novel, stable functionalized ketenes[50] **45**. Ynolates were independently generated, concurrent with our discovery, by Kowalski and co-workers[51] via an ester homologation process. Kowalski has made elegant use of ynolate-derived siloxyalkynes in synthesis.[52]

Acetylenes are well-known to undergo electrophilic additions.[4] Hence, we investigated the addition of a variety of acids HX to alkynyl sulfonates.[53] Reaction readily occurred in a regio- and stereospecific manner, resulting in diverse, previously unknown, vinyl 1,1-bis(esters), **46**. Reaction is believed to proceed via vinyl



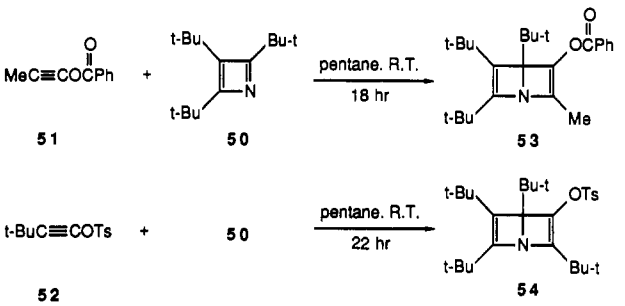
46: X = Cl, OTf, OTs, O_2CCF_3

cation ion pairs.[53] Acid-catalyzed hydration of the bis(tosylate) **47** resulted in acids **48** and **49** via a novel rate-determining protonation of one of the basic tosyl oxygens.[54]



47 **48** **49**

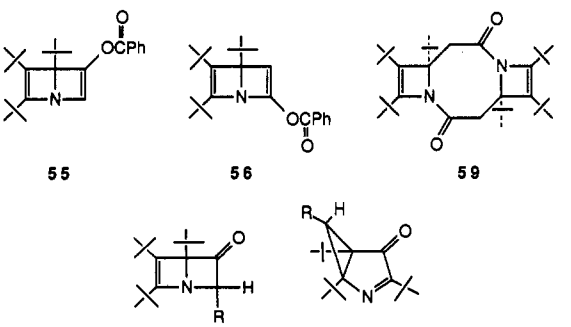
Acetylenes, in particular electron-deficient ones, readily undergo cycloadditions.[4] Since, as discussed above, alkynyl esters **9**–**11** are electron-rich acetylenes, they are not expected to undergo cycloadditions with normal dienes. Indeed, no reaction is observed between **9**–**11**, even under forcing conditions, and cyclopentadiene, furan, or even 1,3-diphenylisobenzofuran. However, in a collaborative study with Maas and Regitz in Kaiserslautern, Germany, we investigated[55] the cycloadditions of **9** and **11** with azete **50**. Reaction of **51** and **52** with **50** gave the novel Dewar pyridines **53** and **54** as products in 83% and 79% isolated yields, respectively. Two regioisomers **55** and **56** were observed[55]



51 **50** **53**

52 **54**

in the reaction of the parent ethynyl benzoate (**33**) with **50**. Similar products were found in the reaction of siloxyalkynes and $EtOC{\equiv}CH$ with **50**.[55] Further treatment of **53** or **54** with MeLi in THF at −78 °C results in either the hitherto unknown Dewar pyridones **57** or the azabicyclo[3.1.0]hexenone **58**, depending upon R, whereas treatment of **56** under similar conditions gives dimer **59**.[56]



55 **56** **59**

57 **58**

(47) For early attempts to generate ynolates, see: Woodbury, R. P.; Long, R. N.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376. Hopee, I.; Schöllkopf, U. *Justus Liebigs Ann. Chem.* **1979**, 219.

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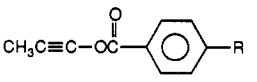
Biochemistry

As indicated at the beginning of this Account, esters play an important role in biochemistry. Moreover, from a fundamental as well as a practical perspective, enzyme inhibition is an important process. A relatively new and exciting class of specific inhibitors are enzyme-activated inhibitors, also referred to as "suicide substrates".[57,58] These molecules are structural analogues of a normal physiological substrate of the target enzyme, with a built-in, latently reactive functional group activated during normal catalytic action by the enzyme. This "action" turns the latent group into a chemically highly reactive one in the microenvironment of the active site of the enzyme.

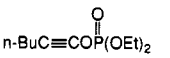
With the considerable current interest in protease and esterase inhibition[59] and the known biological activity of acetylene[60] in mind, we decided to examine, in a joint study[61] with Shalitin in Israel, the potential interaction of various proteases with alkynyl carboxylates **9**. Specifically, propynyl benzoates **60** were investigated as potential inhibitors of (bovine) α-chymotrypsin, trypsin, pronase, thrombin, and plasmin. All



60a: R = H, b: R = OCH_3

of these serine proteases were effectively inhibited by **60**. The inhibited enzymes underwent slow spontaneous reactivation, the rate of which was considerably increased by added hydroxylamine.[61] Propynyl benzoate (**60b**) inhibited α-chymotrypsin, the prototypical serine protease, 20–50-fold more effectively[61] than conventional powerful inhibitors of chymotrypsin such as diphenylcarbamoyl chloride,[62] phenylmethanesulfonyl fluoride (PMSF), and diisopropyl fluorophosphate (DFP).[63] In contrast, as expected, the saturated analogue of **60**, $CH_3CH_2CH_2OC(O)Ar$, failed to react with chymotrypsin.

Likewise, there is considerable interest in phosphotase and phosphokinase inhibitors.[64] In fact, much less is known about phosphotase inhibitors than about protease and esterase inhibitors, with few effective inhibitor substrates being known to date. Hence, in a preliminary study with Raushel at Texas A & M, we examined the inhibition of the phosphotriesterase[65] from *Pseudomonas diminuta*. Hexynyl diethyl phosphate (**61**) effectively inhibits this phosphotriesterase with <1% residual activity in less than 1 min.[66] The



61

partitioning ratio, the number of inhibitor molecules hydrolyzed per enzyme inactivated, is approximately 1200. The inactivated enzyme does not regain activity upon dialysis, nor does it reactivate upon incubation with hydroxylamine. Hence, these very preliminary results suggest that alkynyl phosphates might be potent inhibitors of other phosphotases and perhaps phosphokinases.

Conclusions

It is evident from the foregoing that alkynyl carboxylate **9**, phosphate **10**, and sulfonate **11** esters represent a simple new class of organic compounds that combine two of the most common and valuable organic functionalities into a single molecular framework. Although they have only been known for a scant half-dozen years, they have already emerged as an important and interesting new class of organic compounds. They were prepared by unconventional methods involving novel alkynyl(phenyl)iodonium species **20** as progenitors, as conventional ester or acetylene syntheses have not been successful for their preparation to date. They have unique spectral properties and allowed for the first time the experimental determination of the C_{sp}–O bond length, found to be 1.329 Å and 1.331 Å for esters **33** and **35**. They undergo hydrolysis in *neutral* media by a novel cyclic process. Alkynyl tosylates serve as precursors to hitherto unknown ynolates and thereby open up the examination of ynolate chemistry. They readily add electrophiles in a regio- and stereospecific manner to give unique vinyl 1,1-bis(esters) **46**. They undergo cycloadditions with azete **50** resulting in Dewar pyridines and Dewar pyridones. Finally, alkynyl benzoates and alkynyl dialkyl phosphates definitely show biological activity and considerable promise as potent, novel enzyme inhibitors. This is clearly but the beginning of the rich chemistry these new acetylenic esters are likely to exhibit. Detailed, systematic follow-up of the above, mostly preliminary, results coupled with new investigations and yet uncovered reactions is likely to provide much new and interesting chemistry involving these recently discovered molecules.

I am greatly indebted to many colleagues worldwide for the stimulating collaborations, as mentioned, and my able coworkers, as cited, for skillful and dedicated laboratory accomplishments in an experimentally often difficult area. Our own work in this field over the past decade (including early unsuccessful and frustrating attempts) was supported by the National Cancer Institute of the NIH (2RO1CA16903) and more recently also in part by the Dow Chemical Co., for which I am most grateful.

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