Nucleophilic Substitution at Acetylenic Carbon. The Last Holdout

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At one time nucleophilic substitution at an ethylenic carbon was considered to be impossible. Then, three groups—one of them at Illinois Institute of Technology—demonstrated that such substitutions were both possible and interesting.[1,2]

Nucleophilic substitution at acetylenic carbon (process 1) was another that had been written off. Thus, it

$$RC{\equiv}C{-}X + Nu^- \longrightarrow RC{\equiv}C{-}Nu + X^- \quad (1)$$

was said:[3] "The haloacetylenes in turn fail to give many of the characteristic substitution reactions common to the alkyl and aryl halides and in consequence are of little use in further synthesis". Also:[3] "Replacement of the halogen of haloacetylenes by reaction with alkali sulfides, cyanides or thiocyanides or with alkali salts of alcohols, phenols, oxyacids of mercaptans have not been reported".

Actually, several failures to achieve reaction according to process 1 were on record.[4,5] Perhaps most striking were experiments in which 1-bromoheptyne was heated with heavy metal hydroxides, e.g., of calcium, silver, or lead, with several solvents in an autoclave at 310 °C for several days in an effort to obtain 1-hydroxy-1-heptyne, a ketene tautomer; only starting material (ca. 50%) of improved purity was isolated.[6] An impression of the inertness of haloalkynes was also conveyed by a survey of reactivities of organic chlorides (k, relative) toward KI in acetone at 50–60 °C: n-BuCl (1.0), $CH_2{=}CHCH_2Cl$ (78), $PhCH{=}CHCH_2Cl$ (1370), $PhC{\equiv}CCH_2Cl$ (780), $PhCOCH_2Cl$ (1×10^5), PhCOCl (700), $PhC{\equiv}CCl$ (0).[7] Thus, it was natural—perhaps perverse—for us at IIT to investigate this problem.

Our work on process 1 began in 1957 when we were able to put literature data together with ours to form a rough reactivity order for nucleophilic attack on unsaturated carbon: allenic > acetylenic > ethylenic > aromatic.[2] Our efforts to use process 1 synthetically culminated in syntheses of ethynyl thioether and ethynylphosphonium salts.[4,8] At the same time kinetic data for eq 2 provided dramatic evidence that process

$$PhC{\equiv}CCl + p\text{-}CH_3C_6H_4S^- \xrightarrow[-25\,^\circ C]{DMF} PhC{\equiv}CSC_7H_7\text{-}p \quad (2)$$

1 could be carried out easily and that, in some cases, halogen at an sp carbon could be replaced more rapidly than at an sp^3 carbon: $k(PhC{\equiv}CCl)/k(n\text{-BuCl}) \simeq 60$ at −25 °C in dimethylformamide (DMF).[9] As it turned out, 1962 was a year of beginnings, since groups in several countries published successful syntheses according to eq 1.[8,10-13]

Table I is intended to provide the reader with an orientation and survey of the first syntheses by process 1, except that some earlier examples of organometallic couplings have been omitted.[14-16a] More details on some

Table I
Early Syntheses and Rate Studies of the Reaction[a]
$R'C{\equiv}CX + Nu^- \rightarrow R'C{\equiv}CNu + X^-$

Nu^-	Product	Synthesis	Kinetics
RLi	$R'C{\equiv}CR$	1962[b]	
RMgX	$R'C{\equiv}CR$	1959[c]	
R_3C^-	$R'C{\equiv}CCR_3$	1965[d]	
$(YCu)_n$	$R'C{\equiv}CY$	1964[e]	
R_2N^-	$R'C{\equiv}CNR_2$	1964[f]	
R_3N	$R'C{\equiv}CNR_3^+$	1964[g]	1972[h]
RO^-	$R'C{\equiv}COR$	1971[i,j]	1971[j]
Cl^-, Br^-, I^-	$R'C{\equiv}CHal$	1973[k]	
R_2P^-	$R'C{\equiv}CPR_2$	1962[l]	
R_3P	$R'C{\equiv}CPR_3^+$	1962[m]	1972[n]
$(RO_2)_2PO^-$	$R'C{\equiv}CPO(OR_2)$	1965[o]	
$(RO_3)P$	$R'C{\equiv}CPO(OR_2)$	1962[p]	1971[q]
RS^-	$R'C{\equiv}CSR$	1962[r]	1962[s]
R_3SnNa, R_3PbNa	$R'_3C{\equiv}CMR_3$	1962[t]	

[a] See also ref 5. Note that Nu^- stands for both anionic and neutral nucleophiles. [b] Reference 10. [c] References 13 and 15 and H. G. Viehe, *Chem. Ber.*, **92**, 3064 (1959). [d] F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **30**, 1930 (1965). [e] Reference 39. [f] H. G. Viehe and M. Reinstein, *Angew. Chem., Int. Ed. Engl.*, **3**, 506 (1964). [g] H. G. Viehe, S. I. Miller, and J. I. Dickstein, *Angew. Chem., Int. Ed. Engl.*, **3**, 582 (1964); see also ref 10. [h] Reference 21. [i] Reference 22. [j] Reference 18. [k] R. Tanaka (Kyushu University), private communication; see also footnote *d*. [l] Reference 11. [m] References 8 and 10. [n] Reference 20. [o] Reference 26. [p] Reference 12. [q] Reference 19. [r] Reference 8. [s] Reference 9. [t] Reference 13.

(1) For reviews, see Z. Rappoport, *Adv. Phys. Org. Chem.*, **7**, 1 (1969); G. Modena, *Acc. Chem. Res.* **4**, 73 (1971).
(2) S. I. Miller and P. K. Yonan, *J. Am. Chem. Soc.*, **79**, 5931 (1957).
(3) J. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene", Reinhold, New York, N.Y., 1945, p 71.
(4) G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa, and S. I. Miller, *J. Am. Chem. Soc.*, **85**, 1648 (1963).
(5) S. Y. Delavarenne and H. G. Viehe, in "The Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 10.
(6) V. Grignard and H. Perrichon, *Ann. Chim. (Paris)*, [10] **5**, 5 (1926).
(7) M. J. Murray, *J. Am. Chem. Soc.*, **60**, 2662 (1938). J. B. Conant, W. R. Kirner, and R. E. Hussey, *ibid.*, **47**, 488 (1925).
(8) C. E. Orzech, C. A. Welch, G. R. Ziegler, J. I. Dickstein, and S. I. Miller, *J. Am. Chem. Soc.*, **84**, 2020 (1962).
(9) A. K. Kuriakose and S. I. Miller, *Tetrahedron Lett.*, 905 (1962).
(10) H. G. Viehe and E. Franchimont, *Chem. Ber.*, **95**, 319 (1962).
(11) K. Isslieb and G. Harzfeld, *Chem. Ber.*, **95**, 268 (1962).
(12) B. I. Ionin and A. A. Petrov, *Zh. Obshch. Khim.*, **32**, 2387 (1962); **33**, 2863 (1963).
(13) (a) S. V. Zavgorodnii and A. A. Petrov, *Dokl. Akad. Nauk SSSR*, **143**, 855 (1962); *Chem. Abstr.*, **57**, 3466 (1962); (b) V. S. Zavgorodnii and A. A. Petrov, *Zh. Obshch. Khim.*, **32**, 3527 (1962); *Chem. Abstr.*, **58**, 12593 (1963).
(14) E. Ott and G. Dittus, *Chem. Ber.*, **76**, 80 (1943).

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Table II
Selected Substitutions: Haloalkynes and Other Halides with Neutral and Ionic Nucleophiles

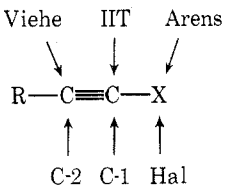
Reactants	Solvent	Temp, °C	k, $M^{-1}\,s^{-1}$	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu	Ref
$HC{\equiv}CBr + (C_2H_5)_3N$	DMF	81	6.1×10^{-5}	11.8	43	43
n-PrBr + $(CH_3)_3N$	C_6H_6	81	1.8×10^{-4}	11		*a*
$H_2C{=}CHBr + C_5H_{10}NH$	$C_6H_5NO_2$	100	~0 (100 h)			*b*
$PhBr + C_5H_{10}NH$	C_6H_6	130	0 (200 h)			*c*
$PhC{\equiv}CCl + CH_3O^-$	CH_3OH	78	1.6×10^{-4}			18
n-BuCl + $C_2H_5O^-$	C_2H_5OH	77	1.0×10^{-4}	21		*d*
$CH_2{=}CHCl + CH_3O^-$	CH_3OH	93	$<7 \times 10^{-6}$			*e*
$(p\text{-}O_2NC_6H_4)_2C{=}CHCl + C_2H_5O^-$	C_2H_5OH	50	3.8×10^{-3}	19	12.5	*f*
$PhCl + CH_3O^-$	CH_3OH	232	$\sim 6.6 \times 10^{-7}$			*g*
$PhC{\equiv}CCl + Ph_3P$	DMF	36	1.8×10^{-4}	14.5	29	20
$PhC{\equiv}CCl + (C_2H_5O)_3P$	THF[h]	60	3.8×10^{-5}	17.6	26	19
$p\text{-}ClC_6H_4C{\equiv}CCl + p\text{-}CH_3C_6H_4S^-$	DMF	−25	0.39	12	20	32
$PhC{\equiv}CBr + I^-$	D-W	127	~0.5			*i*

[a] C. A. Winkler and C. N. Hinshelwood, *J. Chem. Soc.*, 1147 (1935). [b] G. Salomon and A. J. Ultée Sr., *Recl. Trav. Chim. Pays-Bas*, **69**, 95 (1950). [c] F. Kalberer, *Bull. Soc. Frib. Sci. Nat.*, **44**, 225 (1954); *Chem. Abstr.*, **50**, 16718 (1956). [d] C. A. Vernon, *J. Chem. Soc.*, 4462 (1954). [e] S. I. Miller, *J. Org. Chem.*, **26**, 2619 (1961). [f] P. Beltrame, P. L. Beltrame, O. Sighinolfi, and M. Simonetta, *J. Chem. Soc. B*, 1103 (1967). [g] J. Miller and W. Kai-Yan, *J. Chem. Soc.*, 3492 (1963). [h] Tetrahydrofuran. [i] P. K. Yonan, M.S. Thesis, Illinois Institute of Technology, 1956; the solvent was dioxane–water (9:1).

of the relevant families and reactions appear in Viehe's excellent book on acetylene chemistry.[5,16] With the representative kinetic data of Table II one may make reactivity comparisons and obtain an impression of a few of the more well-behaved reactions. In what follows we shall emphasize general mechanistic or theoretical considerations as they apply to eq 1 and conclude with some new synthetic findings.

Mechanisms

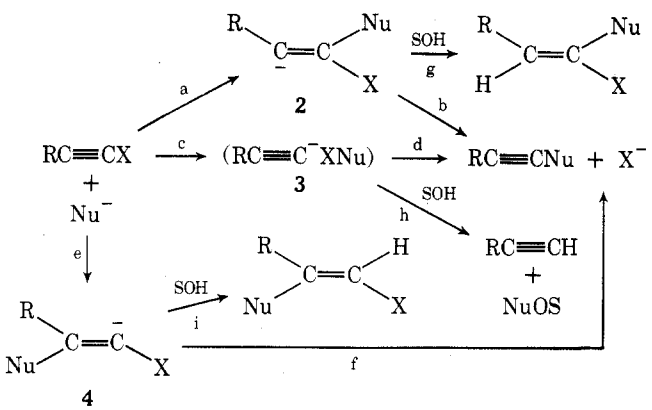
A key to the discussion of process 1 is the fact that a haloalkyne is *triphilic*, that is, susceptible to nucleophilic attack at three sites (1):



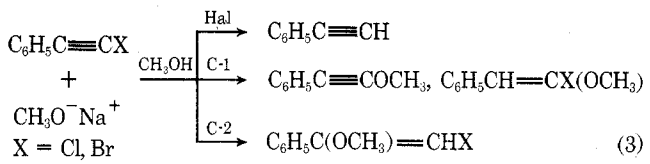
1

Three known paths to product are outlined in Scheme I; other mechanisms will be touched on later. Attack at C-1 yields anion **2**; attack at C-2 gives anion **4**; abstraction of halogen gives the ion–molecule pair, **3**. In eq 1 and Scheme I, Nu^- represents both anionic and neutral nucleophiles (e.g., R'_3N, R'_3P); likewise, it should be understood that intermediates formed from R'_3N, say, will be an ion pair (**3**, $RC{\equiv}C^{-+}XNR'_3$) or a zwitterion (**2**, $R\bar{C}{=}CX(NR'_3)^+$; **4**, $R(R'_3N^+)C{=}CX^-$). On all three paths the proposed carbanion intermediates can be, and often have been, trapped in a proton solvent (SOH). Although one or other of these mechanisms was favored or even strongly advocated by three different groups, i.e., Arens', Viehe's, and ours, we believe that all three should at least be considered for any given system.[17–21]

Scheme I



Three modes of attack by methoxide ion in methanol on a haloalkyne are illustrated in eq 3. In accordance



(3)

with Scheme I, products from abstraction of halogen ($PhC{\equiv}CH$) and from addition to C-1 ($PhC{\equiv}COCH_3$, $PhCH{=}CXOCH_3$) and C-2 ($PhCOCH_3{=}CHX$) are generated.[18] Graphic evidence for the competition is provided by the time–product profile (Figure 1).[18] Additional check experiments established that the first products probably lie on separate reaction paths, that is, they are competitively rather than consecutively formed. Although the synthesis of $PhC{\equiv}COCH_3$ by process 1 is far simpler in an aprotic solvent,[22] the complex reaction in methanol (eq 3) is certainly more revealing.

The Arens Mechanism. In 1963, Arens found it necessary to remind chemists that "there are numerous

(15) E. Ott and W. Bossaler, *Chem. Ber.*, **76**, 88 (1943).
(16) H. G. Viehe, Ed., "Chemistry of Acetylenes", Marcel Dekker, New York, N.Y., 1969: (a) P. Cadiot and W. Chodkiewicz, Chapter 9, on coupling reactions; (b) G. Köbrich and P. Buck, Chapter 2, on syntheses by eliminations; (c) L. Brandsma, H. J. T. Bos, and J. F. Arens, Chapter 11, on ethynyl ethers and thioethers; (d) H. G. Viehe, Chapter 12, on ynamines; (e) P. Cadiot and W. Chodkiewicz, Chapter 13, on ethynyl compounds of tin, phosphorus, etc.
(17) A. Fujii, J. I. Dickstein, and S. I. Miller, *Tetrahedron Lett.*, 3435 (1970).
(18) R. Tanaka, M. Rodgers, R. Simonaitis, and S. I. Miller, *Tetrahedron*, **27**, 2651 (1971).
(19) A. Fujii and S. I. Miller, *J. Am. Chem. Soc.*, **93**, 3694 (1971).
(20) J. Dickstein and S. I. Miller, *J. Org. Chem.*, **37**, 2168 (1972).
(21) J. Dickstein and S. I. Miller, *J. Org. Chem.*, **37**, 2175 (1972).
(22) R. Tanaka and S. I. Miller, *Tetrahedron Lett.*, 1753 (1971).

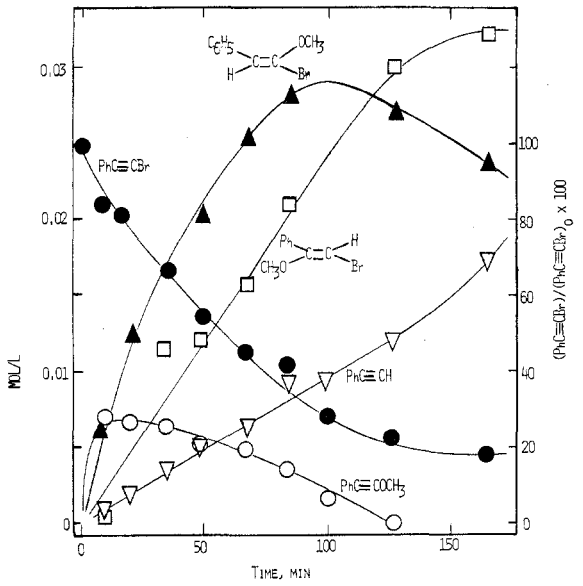


Figure 1. A reaction profile of phenylbromoacetylene (0.30 M) and sodium methoxide (1.95 M) in methanol at 78 °C.

other reactions of organic compounds which can be interpreted as being nucleophilic substitutions at atoms other than carbon ... Nucleophilic substitutions at atoms other than carbon may occur especially when rather stable carbanions can be expelled".[23] Two of many examples in haloalkyne chemistry are the Strauss synthesis of haloacetylenes and its reversion, which involve attacks on hydrogen and halogen (eq 4, X = Cl, Br).[5,24,25] Accordingly, Arens concluded that process 1 would be effected in steps c and d of Scheme I via intermediate **3.**

$$RC{\equiv}CH + OH^- + X_2 \rightleftharpoons RC{\equiv}CX + X^- + H_2O \quad (4)$$

In the Arens' mechanism the normal leaving group effect would be $k(Cl) < k(Br) < k(I)$. For that part of process 3 in which attack is on X, $k(Cl)/k(Br) = 0.4$.[18] Likewise for eq 5, $k(Cl):k(Br):k(I) = 9 \times 10^{-3}:24:3 \times 10^4$.[25] Direct evidence of the abstraction of halogen is found in the interception of one or other of the partners of the ion–molecule pair (**3**) in Scheme I, e.g., by proton delivery to $RC{\equiv}C^-$ in eq 3 and 5 or by capture of XNu where this may be R′SX, R'_3PX^+, $(R'O)_3PX^+$, ROX, X_2, etc.[18-20,24-26]

$$\text{thienyl}{-}C{\equiv}CX + EtS^- \xrightarrow[26\ ^\circ C]{CH_3OH\text{-}H_2O} (RC{\equiv}C^-XSEt) \longrightarrow \text{thienyl}{-}C{\equiv}CH + Et_2S_2 \quad (5)$$

The IIT Mechanism. The IIT channel of eq 3 involves attack at C-1 (step a, Scheme I) to form intermediate **2** and then expulsion of halide ion (step b).[8] Unexpectedly, our initial advocacy of this mechanism for reaction 2 drew a fair amount of criticism.[5,16c,23,27] This was despite the facts that nucleophilic substitutions at other unsaturated carbon atoms, i.e., aryl and vinyl, went by analogous association–dissociation mechanisms[1] and that analogs of intermediate **2** arose during stepwise addition to alkynes or elimination from alkenes.[28-30] It is not surprising, therefore, that various kinds of experimental support for the IIT mechanism materialized. Since abstraction of "positive" fluorine is unlikely, the IIT mechanism had to be used for reactions of HC≡CF.[5,10] Moreover, highly activating substituents on C-2, as in NCC≡CCl, would direct a nucleophile to C-1 in accordance with this mechanism.[31] Probing the system that sparked the controversy, Beltrame et al. introduced ethanol as a trap into reaction 2. Since they found negligible quantities of PhC≡CH and a "correct" leaving group effect (see below), Beltrame concluded that the IIT mechanism held for this case.[32] From comparing reactions 2 and 5, one would have to conclude that the change in the nucleophile from aryl to alkyl thiolate and/or in the solvent from DMF to CH_3OH alters the site of attack from C-1 to X.

The usual leaving group order for substitutions at unsaturated carbon, e.g., at C-1 in haloalkenes or haloaromatics, is $k(F) > k(Cl) \sim k(Br) > k(I)$.[1] This trend is in accord with rate-determining association and is rationalized on the basis that electron-withdrawing substituents facilitate this step. Consistent with analogous C-1 attack in haloalkynes, one finds that ethynyl chlorides are somewhat more reactive than ethynyl bromides, and that, in one case, a fluoride is much more reactive than the chloride. Thus, $k(Cl)/k(Br) \simeq 1.9$ for $PhC{\equiv}CX + CH_3O^-$ at 78 °C,[18] 1.3 for $PhC{\equiv}CX + N(CH_2CH_2)_3N$ at 80 °C,[21] 2 for $PhC{\equiv}CX + Ph_3P$ at 36 °C,[20] 2–4 for $ArC{\equiv}CX + p\text{-}C_7H_7S^-$ at −25 °C,[32] and 1.1–1.3 for $ArC{\equiv}CX + (EtO)_3P$ at 102 °C;[19] $k(F)/k(Cl) > 400$ for $HC{\equiv}CX + Ph_3P$.[10,20]

The Viehe Mechanism. Unusual and ingenious, the Viehe "onium" mechanism consists of steps e and f of Scheme I. It is initiated by attack at C-2 to give anion **4** which presumably rearranges to the product via eq 6.

$$4 \longrightarrow \underset{Nu}{\overset{R}{\diagdown}}C{=}C: \longrightarrow \underset{Nu^+}{\overset{R}{\diagdown}}C{=}C^- \longrightarrow RC{\equiv}CNu \quad (6)$$

As precedents, there are the rearrangement evident in eq 7[16b] and some model reactions (eq 8, 9).[33,34] Ac-

$$Ar_2C{=}CHX \xrightarrow{base} ArC{\equiv}CAr \quad (7)$$

$$(R_2N)_2C{=}CHCl \xrightarrow{LiNR_2} R_2NC{\equiv}CNR_2 \quad (8)$$

$$t\text{-BuClC}{=}CHSPh \text{ or } t\text{-BuSPhC}{=}CHCl \xrightarrow[ether]{LiNEt_2} t\text{-BuC}{\equiv}CSPh$$

$$t\text{-BuC}{\equiv}CCl + PhS^- \xrightarrow{DMF} \quad (9)$$

(23) J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **82**, 183 (1963).
(24) R. R. Lii and S. I. Miller, *J. Am. Chem. Soc.*, **95**, 1602 (1973).
(25) (a) M. C. Verploegh, L. Donk, H. J. T. Bos, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **90**, 765 (1971); (b) M. C. Verploegh, Ph.D. Thesis, "Nucleofiele Substitutie op Halogeen in 1-Halogeen-1-alkynen", University of Utrecht, 1971.
(26) (a) G. Sturtz and C. Charrier, *C. R. Hebd. Seances Acad. Sci.*, **261**, 1019 (1965); (b) G. Sturtz, C. Charrier and H. Normant, *Bull. Soc. Chim. Fr.*, 1707 (1966).
(27) (a) B. Miller, *Top. Phosphorus Chem.*, **2**, 133 (1965); (b) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, pp 111, 112.
(28) S. I. Miller and R. Tanaka in "Selective Organic Transformations," B. S. Thyagaragan, Ed., Wiley, New York, N.Y., 1970, p 143.
(29) Unpublished observations at IIT by: (a) T. Izumi; (b) G. R. Ziegler; (c) J. I. Dickstein.
(30) S. I. Miller and W. G. Lee, *J. Am. Chem. Soc.*, **81**, 6313 (1959); W. K. Kwok, W. G. Lee and S. I. Miller, *ibid.*, **91**, 468 (1969).
(31) T. Sasaki, A. Kojima, and M. Ohta, *J. Chem. Soc. C*, 196 (1971).
(32) P. Beltrame, P. L. Beltrame, M. G. Cattania, and M. Simonetta, *J. Chem. Soc., Perkin Trans. 2*, 63 (1973).
(33) S. Y. Delavarenne and H. G. Viehe, *Chem. Ber.*, **103**, 1209 (1970).
(34) H. G. Viehe and S. Y. Delavarenne, *Chem. Ber.*, **103**, 1216 (1970).

cording to Viehe, this mechanism applies generally, except when the IIT (X = F) or the Arens process is facile.[5,33-35]

Although there is no difficulty in finding attacks at C-2, the applicability of the onium mechanism is uncertain. In process 3, for example, neither PhC(OCH$_3$)=CHBr nor PhCOCH$_2$Br, which are conceivable intermediates, rearranges to the observed C-1 products under the reaction conditions. Moreover, the few apparent onium examples (eq 8 and 9) involve conditions which are as yet indistinguishable from those which could lead to elimination (eq 10), followed either

$$(CH_3)_2N(n\text{-BuS})C{=}CH_2 \xrightarrow[\text{HMPT}]{KNH_2} HC{\equiv}CN(CH_3)_2 + n\text{-BuS}^- \quad (10)$$

by addition–elimination or the IIT mechanism.[16c,36] This is not a hypothetical objection, because the conditions under which heteroalkenes and heteroalkynes interconvert, e.g., elimination (−HY), addition (+HY), association (+Y$^-$), and dissociation (−Y$^-$), may be competitive both under forcing (RO$^-$, ROH, >150 °C) and mild (RLi, ether, <0 °C) conditions.[16b-d,33-36] Thus, the question of the Viehe mechanism is still open.

Evaluation of Mechanisms. Most mechanisms must be qualified, and the three we have mentioned for eq 1 are no exception. They all conform, or could conform, to second-order kinetics (first order in nucleophile, first order in haloalkynes) and would be indistinguishable.[23] The detection of certain stable or unstable intermediates in the reaction medium by spectroscopic means, chemical traps, etc. does not necessarily require that the product arise on a path which included this species. With respect to stable species, e.g., eq 3, 8, 9, it is possible to show that some of the compounds that turn up do interconvert and others do not. The postulation of the unstable intermediates in Scheme I or eq 6, which have seldom been observed, gives rise to uncertainty in the overall mechanism. Indeed, the conditions of a trapping environment may be sufficiently different from the original so that a significant change in relative rates along different paths may be observed.[17,20,25,32,37] One would probably be safe, however, to begin with the triphilic model 1 and to proceed to evaluate the mechanistic evidence for competitive paths.

Other Mechanisms. We shall now pass quickly over the "other" mechanisms for eq 1. The fourth mechanism—actually a class of mechanisms—we term "aggregate". Certain couplings, e.g.,

$$RC{\equiv}CH + BrC{\equiv}CR' \xrightarrow[\text{amine}]{Cu(I)} RC{\equiv}C{-}C{\equiv}CR' \quad (11)$$

$$RC{\equiv}CX + CuCN \longrightarrow PhC{\equiv}CCN \quad (12)$$

are typical in that polymeric, usually organometallic, species are the nucleophiles.[16a,27c,38,39] The defining characteristic is that the rate-determining step must involve an ion pair, dimer, or higher polyspecies as well as RC≡CX. At one limit of the aggregate mechanisms they will, of course, go over to or become competitive with those of Scheme I. Such may in fact be the coupling of eq 13.[14]

$$ClC{\equiv}CCl + NaCC_2H_5(COOC_2H_5)_2 \xrightarrow{\text{ether}} ClC{\equiv}CCC_2H_5(COOC_2H_5)_2 \quad (13)$$

Apart from the useful Cadiot–Chodkiewicz coupling (eq 11), which has been reviewed,[16a] there are few results in this area (Table I).[5] Nevertheless, one can reasonably expect to find the variety and complexity of mechanism known for analogs of process 1 in the chemistry of organolithiums, -magnesiums, etc.

In the fifth mechanism, labeled "radical", we again lump together a variety of processes summarized by eq 1. Here the reacting species may be simple or aggregate: what is necessary is that radical species lie on the reaction path. Two probable examples in this group are:[5,16a,38]

$$RMgBr + R'C{\equiv}CCl \xrightarrow{CoCl_2} RC{\equiv}CR' \quad (14)$$

$$2\,RC{\equiv}CH \xrightarrow{Cu^+,\ RNH_2,\ O_2} (RC{\equiv}C)_2 \quad (15)$$

The radical mechanisms comprise a diverse group which may share features with the preceding types or take the form of radical anion substitutions ($S_{RN}1$). Such an "electron-transfer" process for eq 1 has been considered,[25] and a probable example is provided in the useful ynamine synthesis:[40]

$$PhC{\equiv}CH + R_2NH + Cu(OAc)_2{\cdot}H_2O \xrightarrow[0\ ^\circ C]{O_2,\ PhH} PhC{\equiv}CNR_2 + (PhC{\equiv}C)_2 \quad (16)$$

In our laboratory the incursion of radical processes has often been inferred when "wrong" products arose:[29a,b]

$$PhC{\equiv}CBr + Na^{+-}CH(COOEt)_2 \xrightarrow{DMF} ((EtOOC)_2CH)_2 \quad (17)$$

$$PhC{\equiv}CCl + Ph_2CH_2 \xrightarrow[Me_2SO]{KOH,} (PhC{\equiv}C)_2 \quad (18)$$

Clearly, the identification of radical-prone examples of eq 1 is essential before it can be studied and its course controlled.

The S_N1 mechanism is the sixth type for eq 1. We hasten to point out that (1) no examples are known, (2) it may be "inaccessible", and (3) some attempts to generate ethynyl cations in solution have been made.[41] Judging by the gas-phase heats of reaction, the ethynyl cation is by far the most difficult to form from the parent hydrocarbon ($\Delta H_r°$ (298 K), kcal/mol): t-C$_4$H$_9^+$ (251), C$_2$H$_5^+$ (291), C$_2$H$_3^+$ (306), C$_6$H$_5^+$ (302), C$_2$H$^+$ (397).[42]

Our initial effort in this area was more from a sense of duty than of hope:[29c]

(35) S. Y. Delavarenne and H. G. Viehe, *Chem. Ber.*, **103**, 1198 (1970).

(36) (a) L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **90**, 265 (1971); (b) H. J. Boonstra and J. F. Arens, *ibid.*, **79**, 866 (1960); (c) A. Halleux, H. Reimlinger, and H. G. Viehe, *Tetrahedron Lett.*, 3141 (1970).

(37) D. W. Burt and P. Simpson, *J. Chem. Soc. C*, 2872 (1971).

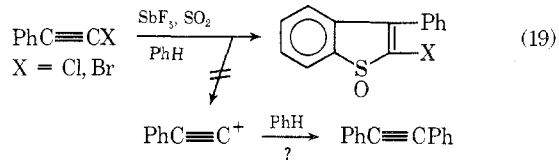
(38) (a) J. Normant, *Bull. Soc. Chim. Fr.*, 1876 (1963); (b) L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **7**, 846 (1958); *Chem. Abstr.*, **53**, 1107 (1959).

(39) A. M. Sladkov and L. Yuhkhin, *Izv. Akad. Nauk SSSR, Ser. Khim*, 392 (1964); *Usp. Khim.*, **37**, 1750 (1968).

(40) L. I. Peterson, *Tetrahedron Lett.*, 5357 (1968); U.S. Patent No. 3 499 928; *Chem. Abstr.*, **73**, 014 430 (1970); U.S. Patent No. 3 499 904; *Chem. Abstr.* **73**, 045 145 (1970); U.S. Patent No. 3 657 342; *Chem. Abstr.*, **77**, 048 068 (1972).

(41) M. Hanack (Saarbrucken) and Z. Rappoport (Jerusalem), private communications.

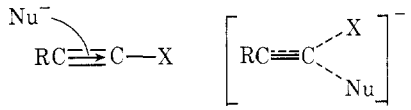
(42) (a) J. D. Dill, P. v. R. Schleyer, and J. A. Pople, *Tetrahedron Lett.*, 2857 (1975); (b) F. P. Lossing and G. P. Semeluk, *Can. J. Chem.*, **48**, 955 (1970); F. P. Lossing, *ibid.*, **49**, 357 (1971); (c) NSRDS-NBS 26, "Ionization Potentials, Appearance Potentials, and Heats of Formation of Gaseous Positive Ions", National Bureau of Standards, U.S. Government Printing Office, Washington, D.C., 1969.



(19)

The cation was not formed and therefore was not trapped by benzene. As a consolation prize we stumbled onto a thiophene oxide synthesis which also succeeds when X is not halogen. Obviously, the ethynyl cation must be sought elsewhere, if, in fact, it can be prepared in solution.

At this stage the direct or SN2 mechanism for process 1 appears to be simply an hypothesis to be rejected. Its activated complexes can be pictured in two ways:



5 6

The one-step backside attack, given by **5**, may be an amusing analog to the Walden inversion but is obviously impossible.[18] An attack from the side as in **6** appears to be more reasonable. There are, however, a number of objections to such a one-step process, none of which is absolute; prominently, the great majority of displacements at other unsaturated carbon sites proceed in at least two steps; and species **6** appears to be geometrically close to the related vinyl anion which is normally at a potential minimum on the energy surface.[18]

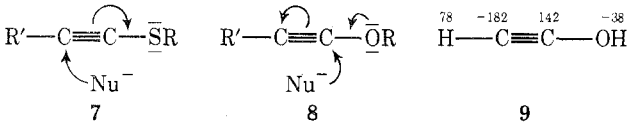
To conclude this section, we note that of the seven mechanisms considered for process 1, two have been firmly established, three are probable but require more critical evidence, and two are still paper exercises.

Reactivity

If haloalkynes were as unreactive as the introductory paragraphs of this Account intimated, where did all their reactivity come from? For the reactions of Table II, the C-1 reactivity order in aprotic solvents is alkynyl ≫ alkenyl > aryl.[20,21,43] Moreover, considerable activation in the form of favorable substituents must be present in vinyl and aryl systems to achieve reasonable reactivities—the inclusion of two sp^3 examples merely provides points of reference for the scale of k's. The important conclusion for both molecule–molecule and ion–molecule reactions is that the unsaturated carbon site with the highest s character, i.e., the most electronegative, is the most reactive.

Not unexpectedly, the rates of ion–molecule examples of eq 1 are lower in protic than in aprotic solvents. For example, the rates of formation of $PhC{\equiv}COCH_3$ from $NaOCH_3$ and PhC≡CCl in methanol at 80 °C and in dimethyl sulfoxide, a heterogeneous system, at ~25 °C are roughly similar.[18,22] Likewise, there is a rough rate comparison for the reaction of PhC≡CBr with p-$C_7H_7S^-$ at −25 °C: $k_{Br}(CH_3OH) \simeq 10^{-4}$ vs. $k_{C\text{-}1}(DMF) \simeq 2 \times 10^{-2}\ M^{-1}\ sec^{-1}$, in which the point of attack in PhC≡CBr is indicated.[32] Since PhC≡CSAr is not observed in methanol,[25] $k_{C\text{-}1}(CH_3OH) \leq 10^{-6}\ M^{-1}\ s^{-1}$, so that there is a rate factor of *at least* 10^4 favoring C-1 attack in DMF over CH_3OH. For comparison, the system n-BuBr + PhS^- has $k(CH_3OH)/k(DMF) = 10^{-4}$ at −25 °C.[44] It would appear that as large as enhancements are in $k(sp^3)$ for the change from protic to aprotic solvent, they can be even larger in $k(sp)$.

Another reactivity issue is the matter of nucleophilic attack on C-1 vs. C-2 or Markownikoff vs. anti-Markownikoff addition: electron-donating substituents, e.g., R′ = alkyl in **1**, direct attack to C-2 while electron-withdrawing substituents, e.g., R′ = phenyl, facilitate attack at C-1.[5]



7 8 9

In contrast to the dominant C-1 products in process 3, the attack of PhONa on t-BuC≡CCl yields one C-2 product, t-Bu(PhO)C=CHCl.[34] Nevertheless, the deactivating effect of alkyl on the sp carbons may be large enough so that nucleophilic attack may be directed elsewhere, e.g., to halogen, as in $(CH_3)_2CORC{\equiv}CBr + (EtO)_2PO^-Na^+$,[19] or a C-3 hydrogen, as in R′-$CH_2C{\equiv}CBr + RO^-$.[45]

Orientation of attack in species **1** will be modified by the terminal substituent X. Both theory and experiment indicate that first row elements (X = F, OR, NR_2) direct nucleophilic attack to C-1, as in **8** and **9**, while elements of higher atomic number generally promote attack on C-2, as in **7**.[16c] In **9** we have attached relative CNDO/2 charge densities to the important sites which indicate both the polarization in the heteroalkyne and a rationale for regioselectivity.[22] Thus, a bromoalkyne should have more C-2 attack than a chloro compound (eq 3).[18] Perhaps the most interesting effects here are given by the "normally" reluctant leaving groups F and OR, since the C-1 substitution rates are enhanced enormously even when an alkyl group is at C-2.[5,16c,35]

Additional support for the above picture derives from extended HMO calculations for the attack of HS^- on RC≡CX (R = aryl, alkyl, and X = F, Cl, Br, I) in which potential energy surfaces were explored in the region of the possible intermediates (**2**–**4**).[46] A particularly interesting finding is the strong charge separation that results from attack at halogen as compared with that at C-1. The inference that attack at halogen would be more probable in protic solvents[46] is borne out by the observations on thiolates (eq 5)[25] and Bu_3P as nucleophiles.[20]

Synthesis

In this section we restrict our attention to two facets of process 1, namely, an "underdeveloped" class of nucleophiles and an interesting family of products.

Only infrequently have carbanions been used in process 1.[5] Recently, a new route to ethynylferrocenes was found when syntheses of the labile[47] ethynylcyclopentadienes were attempted (eq 20).[29a] The triphenylmethide reaction is relatively simple (eq 21); other anions that we have used derive from weaker acids—this and the fact that Me_2SO–KOH is not really

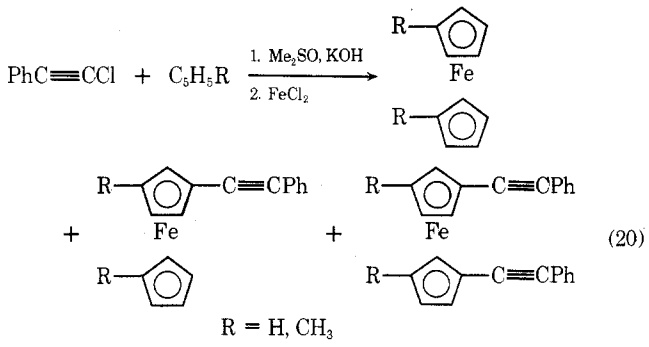
(43) R. Tanaka and S. I. Miller, *J. Org. Chem.*, **36**, 3856 (1971).

(44) E. C. F. Ko and A. J. Parker, *J. Am. Chem. Soc.*, **90**, 6447 (1968).

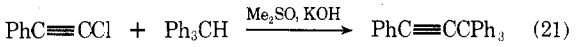
(45) C. D. Beard, J. C. Craig, and M. D. Solomon, *J. Am. Chem. Soc.*, **96**, 7944 (1974).

(46) P. Beltramé, A. Gavezzoti, and M. Simonetta, *J. Chem. Soc., Perkin Trans. 2*, 502 (1974).

(47) W. D. Crow and M. N. Paddon-Row, *J. Am. Chem. Soc.*, **94**, 4746 (1972).

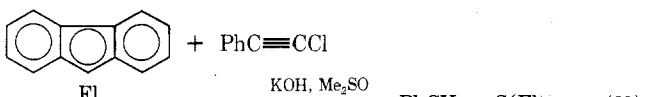


(20)

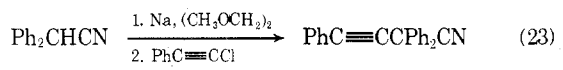


(21)

"aprotic" appear to facilitate additions (eq 22) or other diversions (eq 17, 18). Therefore we have also utilized aprotic conditions (eq 23). As a final example, we have used the conditions of eq 23 with a masked form of HC≡CCl, namely $Hg(C{\equiv}CCl)_2$, to obtain $Hg(C{\equiv}CCPh_2CN)_2$.[29a]

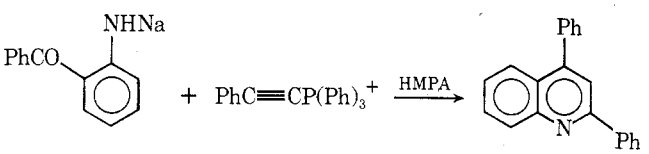


(22)



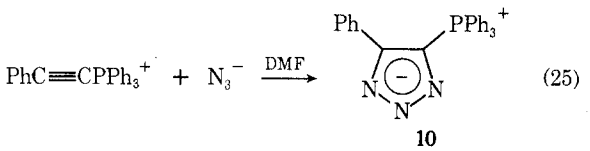
(23)

"Second generation" chemistry deriving from products of eq 1 can be useful. Just as ynamines have become key synthetic intermediates,[16d,48] we regard the ethynylphosphonium salts as having high potential.[49] The difunctional character of these compounds is well illustrated in eq 24.[29c] A rather simple addition of azide



(24)

ion leads to the novel triazole ylides (eq 25) whose

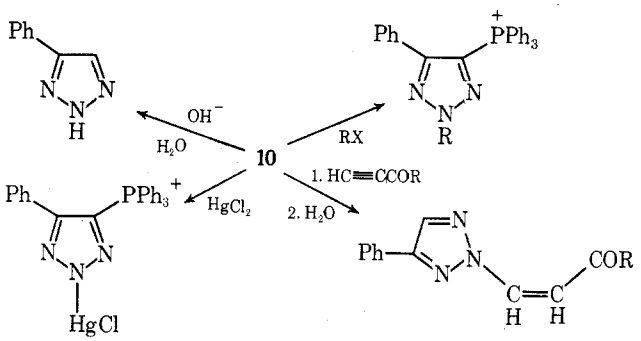


(25)

(48) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. II, Academic Press, New York, N.Y., 1971, Chapter V.

(49) H. Hoffmann and H. Förster, *Tetrahedron Lett.*, 983 (1964).

Scheme II



chemistry is illustrated in Scheme II.[50] Because of the activating power of the phosphonium group and the ease of its removal as triphenylphosphine oxide, we believe that many more applications of the ethynylphosphonium series await us.

Perspective

In a general way, the mechanistic complexity of process 1 may also be taken as "normal" for nucleophilic attacks at multiple sites in other nucleophiles, e.g., aryl–X, vinyl–X, –CO–X, $-COCH_2-X$, $-SCH_2X$, etc. By pointing out the troublesome issues in our system, we believe that analogous problems have been flagged in related systems.

For eq 1 the typical history and background of many important processes have been telescoped into less than 15 years. The strategems used to promote reactivity or selectivity in evolving routes to the various products are typical of the last decade: the nucleophile, the leaving groups, activating substituents, and "faster" solvents have all played a role. Nevertheless, our understanding of the five probable mechanisms of process 1 is far from complete and we are still trying to learn how to apply and control them. It is in this sense that the familiar acetylenic function is "holding out". It is fitting, therefore, to inject into this ongoing area of research the possibility of an SN1 mechanism. This has the virtue of providing a difficult, perhaps inaccessible, goal in the ethynyl cation for which the search could be interesting and productive.

It is a pleasure to acknowledge our associates whose work has been cited. Others whose names do not appear are Drs. Richard Wielesek, Hiroshi Taniguchi, Noboru Morita, Alessandro Dondoni, and Kimiaki Imafuku. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for current support of this research.

(50) Y. Tanaka and S. I. Miller, *J. Org. Chem.*, 38, 2708 (1973).