Vinylphosphonate Formation via a Novel Cyclization−Vinyl Radical Trapping Sequence

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Carbon radicals (C•) potentially react with trialkyl phosphites via the free-radical Arbuzov process depicted in eq 1.[1] However,

$$C\bullet + (MeO)_3P \xrightarrow{a} [C\text{-}\overset{\bullet}{P}(OMe)_3] \xrightarrow{b} C\text{-}P(O)(OMe)_2 + Me\bullet \qquad (1)$$
$$\qquad\qquad\qquad\qquad\quad \mathbf{1} \qquad\qquad\qquad \mathbf{2}$$

unless the SOMO of the radical has significant *s* character (*σ* radicals) and can bond, therefore, relatively strongly to phosphorus on formation of the phosphoranyl radical intermediate (**1**), generation of **1** (eq 1a) is highly reversible and gives phosphonate **2** only if a very rapid *β* scission process (eq 1b) is available (formation of PhCH$_2$• rather than Me•). Thus, (MeO)$_3$P fails to react with *π* radicals, e.g., methyl and primary alkyls, to give phosphonate **2**.[1]

By contrast, phenyl radical[2] (sp^2-hybridized SOMO) and the pyramidal, bicyclo[1.1.1]pent-1-yl radical,[1] both *σ* species, do react according to eq 1, presumably because of the strong C−P bond formed in **1**. Furthermore, the phosphoranyl radical formed on phenyl radical reaction with (MeO)$_3$P (**1**, C = Ph) is a delocalized ligand−*π* species with the odd electron in a *π** orbital on phenyl[3] and, therefore, possibly of intrinsically increased stability.

We report herein the high-yield trapping of vinyl radicals (**4**, **8**, and **9**) by (MeO)$_3$P (eq 1a) to form vinylphosphonate dimethyl esters (**5** and **10**). Radical **4**, for example, is formed readily by the well-known[4] 5-exo-dig-cyclization of the 5-hexynyl radical **3** ($k_C = 2.5 \times 10^4$ s^{-1}),[5] generated under standard thermal AIBN/Bu$_3$SnH conditions[6] from its precursor bromide. Intermediate **3**, as a primary alkyl radical, will be unreactive[1] toward (MeO)$_3$P. Since vinyl radicals are normally nonlinear (bent) species[7] with SOMO hybridizations approximating sp^2, radical **4**, as might be predicted,[8] evidently reacts rapidly and *irreversibly* with (MeO)$_3$P[1] in a reaction similar to that of its close analogue, the phenyl radical.[1,2] Vinyl phosphoranyl radicals, e.g. [CH$_2$=CHP(OR)$_3$]•, like their phenyl counterparts, are ligand−*π* radicals.[9]

The significance of these results stems from: (1) the concept of increasing the reactivity of a carbon-centered radical toward a trialkyl phosphite by allowing it to undergo a well-studied, prior rearrangement; (2) the broad synthetic usefulness of vinylphosphonates, formed here in high yields, as set forth in a recent review article;[10] and, (3) the current interest in phosphonates as biologically active molecules.[11]

Table 1 gives *isolated yields* of **5** for the cases R = H, Me, isoPr, *tert*-Bu, and Ph from reactions run under identical conditions (0.08 M alkyne, 1.0 M Bu$_3$SnH, 12 M (MeO)$_3$P) to total consumption of precursor bromide.[6] Except for the inclusion of an excess of (MeO)$_3$P, these conditions are typical of those used for cyclization of 6-bromohexynes to generate alkenes (**6**).[6] A rate constant (k_H) for abstraction of hydrogen from Bu$_3$SnH by a vinyl radical is not available.[12a] However, a reliable estimate of k_H for abstraction by phenyl radical at 80 °C has been given ($k_H = 1 \times 10^9$ M^{-1} s^{-1}).[12b] Therefore, the ability of 12 M (MeO)$_3$P to trap efficiently intermediate vinyl radical **4** in the presence of 1 M Bu$_3$SnH means that k_P for **4** → **5a** is of the order 10^8–10^9 M^{-1} s^{-1}. The same reaction of phenyl radical with (MeO)$_3$P has $k_P = 3.5 \times 10^8$ at 25 °C.[2,13] A close similarity in rate constants for reactions of phenyl and vinyl radicals with (MeO)$_3$P is not unexpected, considering their structural analogy as *σ* radicals and the effects of structure on reactivity set forth earlier.[1]

The reduction in yields of **5**, noted for R = isoPr and Ph, is accompanied by 10−15% yields of **6** (GC/MS). This suggests that k_P is reduced relative to k_H in these cases. When R = *tert*-Bu, no phosphonate is generated. Instead large amounts of **6** (R = *tert*-Bu) are formed (GC/MS). Evidence for the linear, *π* radical nature of vinyl radicals α-substituted with a *tert*-butyl group has been presented.[7b] Such a radical with a *p*-hybridized SOMO (**4**,

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(4) For a recent review of cyclization of substituted 5-hexynyl radicals, see: Chatgilialoglu, C.; Ferreri, C. *Chem. Triple-Bonded Funct. Groups* **1994**, *Suppl. C2*, 917. For a review, including 5-exo-dig cyclizations with alkynes in synthesis, see: Curran, D. P. *Synthesis* **1988**, 417.

(5) At 25 °C $k_{cyc} = 2.5 \times 10^4$ s^{-1}. Beckwith, A. L. J. *Radical Reaction Rates in Liquids*, Landolt-Boernstein; Fischer, H., Ed; Springer-Verlag: Berlin: 1984; Vol. 13a.

(6) Reactants were mixed at reflux by syringe pump co-addition over a 4 h period followed by a 2 h reflux. See procedures in Motherwell, W. B.; Crich, D.;*Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1993.

(7) For reviews of vinyl radicals, see: Singer, L. A. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley: New York, 1972; Vol. 3, p 239. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980. See also ref 4. For selected experimental and theoretical papers on the geometries, barriers to inversion, and chemistry of substituted vinyl radicals, see: (a) Galli, C.; Guarnieri, A.; Koch, H.; Mencarelli, P.; Rappoport, Z *J. Org. Chem.* **1997**, *62*, 4072. (b) Rubin, H.; Fischer, H. *Helv. Chim. Acta* **1996**, *79*, 1670 and references therein. (c) Guerra, M. *Res. Chem. Intermed.* **1996**, *22*, 369. (d) Galli, C.; Gentili, P.; Guarnieri, A. Rappoport, Z. *J. Org. Chem.* **1996**, *61*, 8878. (e) Metzger, J. O.; Blumnenstein, M. *Chem. Ber.* **1993**, *126*, 2493. (f) Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169. (g) Rhodes, C. J.; Roduner, E. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1729. (h) Korth, H.-G.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2*, **1990**, 1997. (i) Rhodes, C. J.; Symons, M. C. R. *J. Chem. Soc. Faraday Trans.* 1, **1988**, *84*, 4495. (i) Griller, D.; Cooper, J. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1975**, *97*, 4269. (k) Liu, M. S.; Soloway, S.; Wedegaertner, D. K.; Kampmeier, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3809. Singer, L. A.; Kong, N. P. *Tetrahedron Lett.* **1967**, 643. (l) Early exptl work for linear Ph-substituted vinyls. Kopchik, R. M.; Kampmeier, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 6733. Singer, L. A.; Chen, J. *Tetrahedron Lett.* **1969**, 4849. (m) Fessenden, R. W. *J. Chem. Phys.* **1967**, *71*, 74 and references therein: Cochran, E. L.; Adrian, F. J.; Bowers, V. A. *J. Chem. Phys.* **1964**, *40*, 213.

(8) We are aware of one other report of the probable reaction of a vinyl radical with a phosphite; the photolysis of *trans*-1-chloro-2-iodoethylene and triethyl phosphite gave *trans*-ClHC=CHP(O)(OEt)$_2$, along with a minor amount of the *cis*-isomer. Daniewski, W. M.; Gordon, M.; Griffin, C. E. *J. Org. Chem.* **1966**, *31*, 2083.

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(10) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

(11) See: Engel, R. The Use of Carbon-Phosphorus Analogue Compounds in the Regulation of Biological Process. *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 10.

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Table 1. Effects of R on Formation of **5**

R	H	Me	isoPr	Ph	*tert*-Bu
yield (%)[a]	77	88	70	65	0

[a] Isolated yield.

Scheme 1
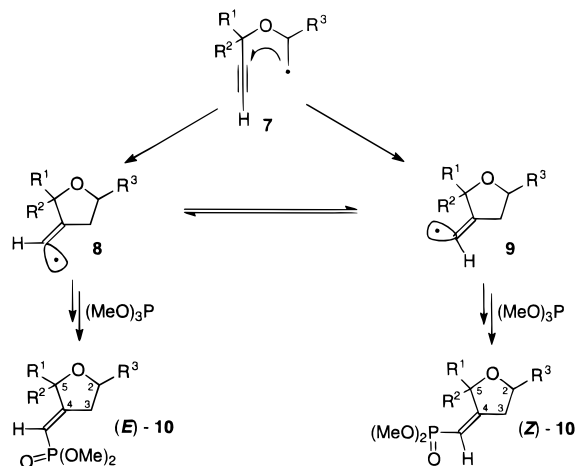
Table 2. Effects of Substituents on Stereochemistry of **10**

case	R^1	R^2	R^3	product	yield (%)[a]	E/Z[b]
1	H	H	H	**10a**	84	51/49
2	H	H	EtO	**10b**	85	56/44
3	H	H	Ph	**10c**	93	48/52
4	Me	Me	EtO	**10d**	89	>99/1
5	Me	Me	Ph	**10e**	88	>99/1
6	PhCH$_2$OCH$_2$	H	EtO	**10f**	76	82/18
7	Ph	H	EtO	**10g**	74	93/7

[a] Isolated yield. [b] Determined by ^{31}P NMR and GC from crude product mixture.

R = *tert*-butyl) is intrinsically unreactive toward (MeO)$_3$P.[1] Regardless of whether vinyl radical **4** is linear or bent, attack by (MeO)$_3$P in this case will be greatly hindered sterically by the *t*-Bu group.
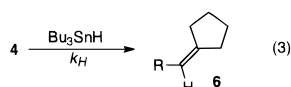
As noted earlier, carbon radicals normally react with (MeO)$_3$P only if the SOMO contains some degree of s-character.[1,2] It is perhaps surprising, therefore, that radical **4** with R = Ph *gives reasonably high yields of 5 (R = Ph)*; because this result could mean that α-phenylvinyl radical **4** is *a bent, σ radical*. The implications of this finding deserve further consideration, as *linear* geometries have been ascribed to α-phenylvinyl radicals by theory, stereochemical studies, and both ESR and muon spin rotation spectroscopy.[7a,b,d,e,g,l] An exception is recent stereochemical evidence for bent geometries at 250 °C.[7e]

Oxacyclopentane ring systems, with an attached exocyclic phosphonomethylene functionality (**10**), also are formed in excellent yields under the same thermal AIBN/Bu$_3$SnH initiation conditions.[6] As depicted in mechanistic Scheme 1, both (*E*)- and (*Z*)-isomers of phosphonates **10** are potentially formed. In Table 2 it is seen that substituent R^3 has little effect on the *E/Z* ratio (case 1 vs cases 2 and 7). However, a single PhCH$_2$OCH$_2$ (case 6) or Ph (case 3) substituent at C-5 strongly perturbs the ratio. Strikingly, dimethyl substitution (cases 4 and 5) leads exclusively to *E*-**10d** within GC detection limits.

Potential kinetic control of the *E/Z* isomer ratio is depicted in Scheme 1. Since for bent, α-alkyl vinyl radicals the rate of

inversion (**8** ⇌ **9**) is very rapid,[14] the system could be under Curtin–Hammett kinetic control. Steric considerations predict the predominant formation of phosphonate *E*-**10** when R^1 and/or R^2 are not hydrogen. However, strong evidence was obtained that shows *the AIBN/Bu$_3$SnH processes to be under thermodynamic control*. Thus, when tris(trimethylsilyl)silane, (TMS)$_3$SiH, is used in place of Bu$_3$SnH as the hydrogen atom donor, cyclization of radical **11** (eq 4) *gives exclusive formation of (Z)-10d* (67%
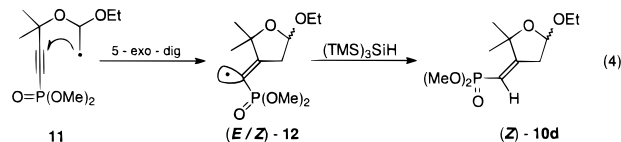
isolated yield). Furthermore, subjection of a solution of (*Z*)-**10d** to the standard, thermal AIBN/Bu$_3$SnH conditions, using a catalytic amount of Bu$_3$SnH (see Supporting Information), converts (*Z*)-**10d** totally to (*E*)-**10d** (eq 5), the same isomer which
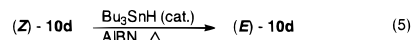
is formed *exclusively* from the bromide precursor of **8** under Bu$_3$SnH/AIBN conditions (Table 2, case 4). The potential for thermodynamic equilibration of alkene *cis/trans*-isomers by tin radicals at higher temperatures has been well-established.[15]

Clearly, the very bulky (TMS)$_3$SiH selectively transfers hydrogen to the (*Z*)-isomer of vinyl radical intermediate **12** to avoid the easily envisioned steric repulsions encountered with (*E*)-**12**. Tributylstannyl radicals catalyze the stereochemical equilibration (*E*)-**10** ⇌ (*Z*)-**10** by *adding reversibly to the carbon–carbon double bond of* **10**. By contrast, thermal (TMS)$_3$SiH/AIBN conditions *failed to bring about even partial equilibration of (Z)-10d with its (E)-isomer or individual stereoisomers of other vinylphosphonate isomers of Table 2 with their E/Z counterparts, except at very extended reaction times.*[16]

The above study provides a novel route to new vinylphosphonates. Such molecules are of broad interest as synthetic intermediates,[10] and biologically active phosphonates are targets of current research.[11] The trapping by (MeO)$_3$P of a vinyl radical, formed on 5-exo-dig cyclization of a 5-hexynyl radical, nicely embellishes the latter, very useful reaction.[4] The potential application of the above cyclization–trapping approach to the synthesis of unusual nucleoside-based phosphonate analogues is in progress.

Supporting Information Available: Experimental procedures for preparation of bromo precursors to **5**, **10a–g**, and preparation of **5**, **10a–g**; spectroscopic data and elemental analyses for products **5** and **10a–g** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The ability of tris(trimethylsilyl)silyl radical to catalyze the cis/trans isomerization of alkenes evidently depends on the nature of the double bond. Lowinger, T. B.; Weiler, L. *J. Org. Chem. Soc.* **1992**, *57*, 6099. Ferreri, C.; Bailestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* **1993**, *34*, 5147.