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Intermolecular Radical Addition of Alkylthio- and Arylthiodiphenylphosphines to Terminal Alkynes

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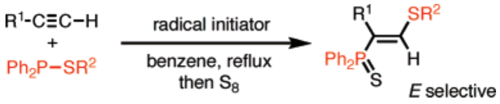
ABSTRACT



Intermolecular radical thiophosphination of terminal alkynes with alkylthio- and arylthiophosphines affords 1-thio-2-phosphino-1-alkenes in good yields. The addition reaction proceeds predominantly in an *anti* fashion to yield *E* isomers.

Radical additions of heteroatom−heteroatom bonds to carbon−carbon multiple bonds are powerful methods to install two heteroatoms efficiently in one operation. Among them, radical dichalcogenation reactions of carbon−carbon multiple bond have been extensively studied[1] and are useful for the synthesis of alkenyl sulfides,[2] selenides,[3] and tellurides.[4] On the other hand, little is known for radical additions of phosphorus-heteroatom bonds, despite the importance of organophosphorus compounds in organic chemistry.[5] Tetraorganodiphosphines add to terminal alkynes to yield (*E*)-1,2-diphosphino-1-alkenes.[6] Very recently, an example of intramolecular radical thiophosphinylation was reported.[7,8] Here we report intermolecular thiophosphination of terminal alkynes.

A mixture of 1-dodecyne (**1a**), diphenyl(phenylthio)phosphine (**2a**),[9] and 1,1′-bis(cyclohexanecarbonitrile) (V-40) was heated in benzene at reflux for 14 h (Scheme 1). The reaction proceeded predominantly in an anti fashion, yielding (*E*)-2-diphenylphosphino-1-phenylthio-1-dodecene (**3a**) as the main product. Since trivalent phosphine **3a** was sensitive to oxygen, the product was isolated as phosphine sulfide after treatment of the reaction mixture with elemental sulfur. The phosphine sulfide **4a** was obtained in 75% NMR yield as a 94:6 mixture of *E*/*Z* isomers. Neither regioisomer 1,2-bis(phenylthio)-1-dodecene nor 1,2-bis(diphenylthiophosphinyl)-1-dodecene was detected. The use of AIBN, instead of V-40, resulted in a lower yield (64% based on ^{31}P NMR).

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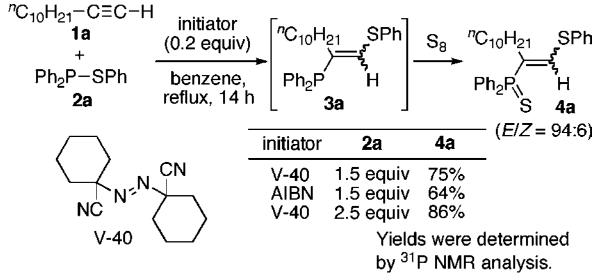
[9] Thiophosphines were readily synthesized from chlorodiphenylphosphine and thiols. They are stable under air.

10.1021/ol800059n CCC: $40.75

Scheme 1. Intermolecular Radical Thiophosphination of 1-Dodecyne with Diphenyl(phenylthio)phosphine

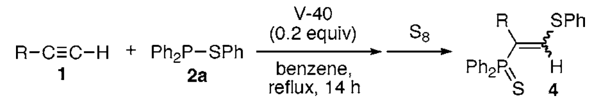


initiator	2a	4a
V-40	1.5 equiv	75%
AIBN	1.5 equiv	64%
V-40	2.5 equiv	86%

Yields were determined by ^{31}P NMR analysis.

Increasing the amount of thiophosphine **2a** improved the ^{31}P NMR yield of **4a** to 86%.[10]

Table 1. Intermolecular Radical Thiophosphination of Terminal Acetylenes with **2a**

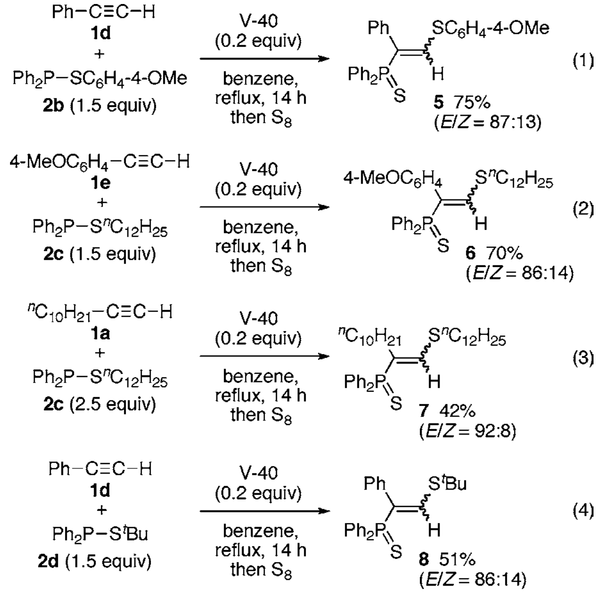


entry	1	R	**2a**/equiv	4	isolated yield/%	E/Z
1	**1a**	$^{n}C_{10}H_{21}$	2.5	**4a**	75	94:6
2	**1b**	$^{c}C_6H_{11}$	2.5	**4b**	61	88:12
3	**1c**	^{t}Bu	2.5	**4c**	trace	
4	**1d**	Ph	1.5	**4d**	83	89:11
5	**1e**	$4\text{-}MeOC_6H_4$	1.5	**4e**	75	89:11
6	**1f**	$2\text{-}MeOC_6H_4$	1.5	**4f**	85	89:11
7	**1g**	$4\text{-}AcC_6H_4$	1.5	**4g**	69	85:15
8	**1h**	$4\text{-}MeOCOC_6H_4$	1.5	**4h**	73	85:15
9	**1i**	$4\text{-}CF_3C_6H_4$	1.5	**4i**	69	84:16
10	**1j**	$4\text{-}H_2NC_6H_4$	1.5	**4j**	80	90:10
11	**1k**	$HO(CH_2)_3$	2.5	**4k**	66	94:6

A variety of 1-alkynes underwent the radical thiophosphination reaction (Table 1). Cyclohexylacetylene (**1b**) also reacted with **2a** to afford **4b** in good yield (entry 2), although *tert*-butylacetylene (**1c**) failed to react (entry 3). Not only alkyl-substituted acetylenes but also aryl-substituted ones participated in the reaction (entries 4−10). The arylacetylenes (**1d**−**j**) were more reactive than **1a**−**c**, which allowed us to use a smaller amount of **2a** (1.5 equiv). It is worth noting that functional groups such as keto (entry 7), ester (entry 8), amino (entry 10), and hydroxy (entry 11) were compatible under the reaction conditions. The *E* configuration of the major isomer of **4** was deduced from the X-ray crystallographic analysis of the major isomer of **4f**. Attempts on addition across internal alkynes resulted in failure.

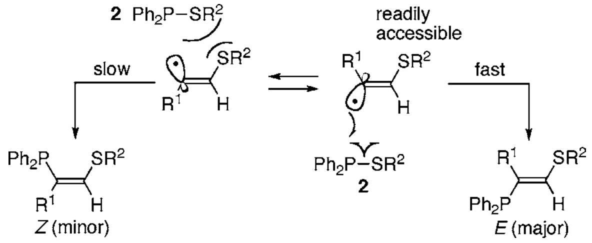
(4-Methoxyphenylthio)diphenylphosphine (**2b**) added to phenylacetylene (**1d**) as smoothly as **2a** (Scheme 2, eq 1).

Scheme 2. Addition of Various Thiophosphines



Alkylthiophosphine **2c** as well as arylthiophosphines **2a** and **2b** reacted with terminal alkynes (eqs 2 and 3). The addition of **2c** to alkyl-substituted alkyne **1a** was less efficient (eq 3). The reaction of phenylacetylene (**1d**) with bulky (*tert*-butylthio)diphenylphosphine (**2d**) proceeded to afford the adduct **8** in moderate yield (eq 4).

Scheme 3. Origin of the Stereoselectivity



The high *E* selectivity of the reaction can be explained as outlined in Scheme 3. Thiophosphine **2** would approach the intermediary alkenyl radical more readily from the opposite side of the R^2S group of the radical to avoid the steric repulsion.[11]

Radical desulfidation of the phosphine sulfides with tris(trimethylsilyl)silane (TTMSS) was facile to yield the parent

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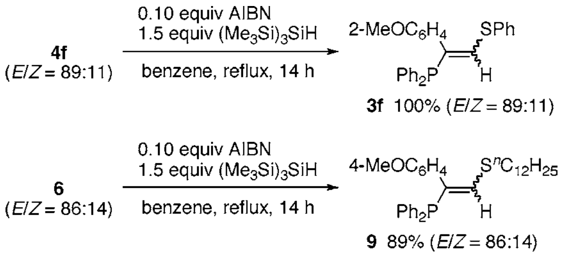
[10] **Experimental Procedure.** Under an atmosphere of argon, 1-dodecyne (**1a**, 83 mg, 0.50 mmol), diphenyl(phenylthio)phosphine (**2a**, 0.37 g, 1.25 mmol), and V-40 (24 mg, 0.10 mmol) were dissolved in benzene (1.5 mL) in a reaction flask. The mixture was heated at reflux for 14 h. After the mixture was cooled to room temperature, crystalline sulfur (0.058 g, 1.8 mmol) was added. The mixture was stirred for 1 h. The solvent was removed under reduced pressure to leave an oil. A P NMR analysis of the crude product by using trimethyl phosphate as an internal standard showed the formation of **4a** in 86% yield. Chromatographic purification on silica gel by using hexane/ethyl acetate = 20:1 as an eluent followed by further purification with gel permeation chromatography afforded **4a** (0.19 g, 0.38 mmol) in 75% yield (E/Z = 94:6).

[11] *Stereochemistry of Radical Reactions*; Curran, D. P., Porter, N. A., Giese, B., Eds.; VCH Publishers: New York, 1995; Chapter 6.3.

Scheme 4. Radical Desulfidation of Phosphine Sulfides with TTMSS



phosphines almost quantitatively (Scheme 4).[12] Treatment of **4f** and **6** with TTMSS in the presence of AIBN in refluxing benzene provided the corresponding phosphines **3f** and **9**, respectively. During the desulfidation, no isomerizations of the carbon−carbon double bonds took place. Notably, attempts to isolate **3f** immediately after the thiophosphination of **1f** with **2a** without adding sulfur always resulted in the formations of significant amounts of the corresponding phosphine oxide.[13] The sulfidation−desulfidation two-step protocol is quite effective to prevent the formation of the phosphine oxide.

In summary, we have devised intermolecular radical thiophosphination of terminal alkynes. In light of the importance of organophosphorus compounds, the products or their derivatives can be useful as ligands, reagents, and building blocks for organic synthesis.

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Supporting Information Available: Characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Romeo, R.; Wozniak, L. A.; Chatgilialoglu, C. *Tetrahedron Lett.* **2000**, *41*, 9899−9902.

[13] Probably, the use of a glovebox filled with inert gas would allow for direct isolation of **3f**.