Regio- and Stereoselective Hydrothiolation Reactions of Ynamides with Diphenyldithiophosphinic Acid: Straightforward Synthesis of Ketene *N*,*S*-Acetal Derivatives

Hiroto Yasui, Hideki Yorimitsu,* and Koichiro Oshima*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510

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E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp, oshima@orgrxn.mbox.media.kyoto-u.ac.jp)

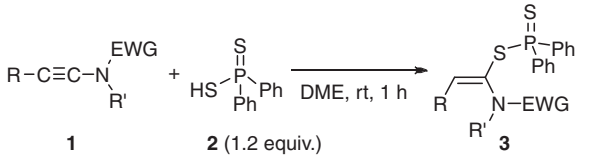
Treatment of *N*-1-alkynyl-*N*-methylarenesulfonamides with diphenyldithiophosphinic acid resulted in hydrothiolation reactions to provide ketene *N*,*S*-acetal derivatives regio- and stereoselectively.

Ynamides are ynamines having both good reactivity and sufficient stability to handle, thanks to the electron-withdrawing group on the nitrogen. In the past few years, the chemistry of ynamides has attracted considerable attention.[1] Reactions of ynamides have been developed on the basis of the reactivity of the electron-rich carbon–carbon triple bonds. Among them, Brønsted acid- or Lewis acid-promoted addition reactions to ynamides have been actively explored.[2] We report here hydrothiolation of ynamides with diphenyldithiophosphinic acid[3] leading to ketene *N*,*S*-acetal derivatives.

Treatment of *N*-ethynyl-*N*-methyl-*p*-toluenesulfonamide (**1a**) with diphenyldithiophosphinic acid (**2**) in 1,2-dimethoxyethane (DME) at room temperature for 1 h afforded 1-[methyl(*p*-tolylsufonyl)amino]ethenyl diphenyldithiophosphinate (**3a**) in 86% isolated yield regioselectively (Table 1, Entry 1).

A wide range of ynamides **1** were tested for the hydrothiolation reactions with **2**. Interestingly, internal ynamides also reacted with **2** smoothly. All the reactions proceeded in a syn fashion to furnish E isomers as the sole isomers.[4] Both *N*-1-propynylamide **1b** and *N*-phenylethynylamide **1c** afforded the corresponding products in high yields (Entries 2 and 3). In addition, *N*-arylethynylamides having an electron-donating group or an electron-withdrawing group on the aromatic rings provided the corresponding hydrothiolation products without difficulty (Entries 4–7). It is worth noting that the keto group in **1g** survived under the reaction conditions (Entry 7). Ynamide **1h**, which has a silyl group on the terminus of the triple bond, also furnished the desired product **3h** (Entry 8). Even *N*-methyl-*N*-phenylethynyl-*p*-nitrobenzenesulfonamide (**1j**), the carbon–carbon triple bond of which would be more electron-deficient, reacted with **2** smoothly to afford the corresponding product **3j** in 97% isolated yield (Entry 10).

Table 1. Hydrothiolation reactions of ynamides with diphenyldithiophosphinic acid



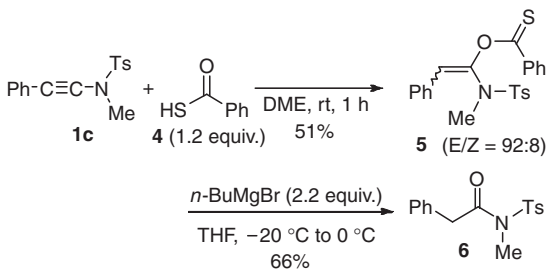
1 **2** (1.2 equiv.) **3**

Entry	**1**	R	R′	EWG	**3**	Yield/%[a]
1	**1a**	H	Me	Ts	**3a**	86
2	**1b**	Me	Me	Ts	**3b**	76
3	**1c**	Ph	Me	Ts	**3c**	87
4	**1d**	*p*-tolyl	Me	Ts	**3d**	91
5	**1e**	*o*-tolyl	Me	Ts	**3e**	97
6	**1f**	*p*-ClC_6H_4	Me	Ts	**3f**	88
7	**1g**	*p*-AcC_6H_4	Me	Ts	**3g**	97
8	**1h**	TMS	Me	Ts	**3h**	63[b]
9	**1i**	Ph	allyl	Ts	**3i**	95
10	**1j**	Ph	Me	*p*-Ns[c]	**3j**	97

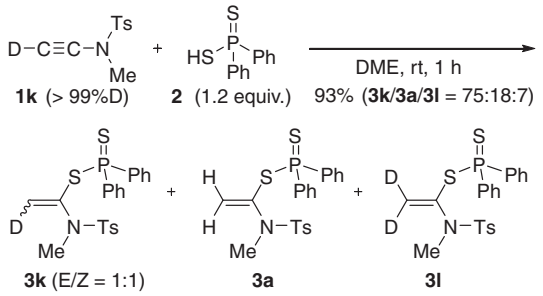
[a]Isolated yields by silica-gel column chromatography unless otherwise noted. [b]Isolated yield obtained by recrystallization. [c]*p*-Nitrophenylsulfonyl.

Treatment of ynamide **1c** with thiobenzoic acid (**4**) instead of **2** under otherwise the same conditions furnished ketene aminal **5** in 51% isolated yield (Scheme 1). When the adduct **5** reacted with butylmagnesium bromide in tetrahydrofuran (THF), amide **6** was obtained in 66% yield. Therefore, the result suggested that the adduct **5** was not *S*-alkenyl thioester but *O*-alkenyl thioester. On the other hand, when ynamide **1c** was treated with thiols such as benzenethiol and 1-dodecanethiol under otherwise the same conditions, no hydrothiolation reactions took place.[5] The result suggests that the acidity of the reagents is important.[6]

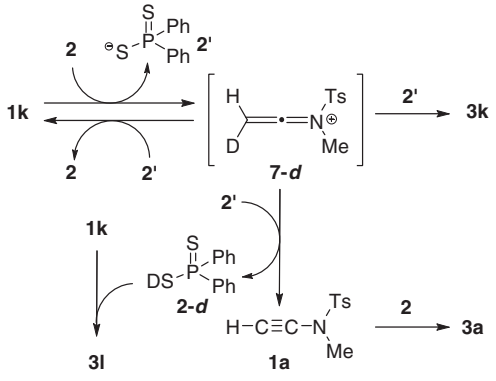
In order to reveal the mechanism of the hydrothiolation, the reaction of deuterium-labeled ynamide **1k** was performed. As a result, a mixture of adducts **3k**, **3a**, and **3l** was obtained in 93% combined yield in a ratio of 75:18:7 (Scheme 2). It is worth noting that **3k** was obtained as a 1:1 mixtuer of the E and Z isomers. The formation of the stereoisomeric mixture of **3k** suggests the stepwise mechanism for the hydrothiolation as shown in Scheme 3. Namely, protonation of **1k** with **2** would generate keteniminium intermediate **7-*d*** and diphenyldithiophosphinate anion **2′** as the first step.[7] Next **2′** would add to the intermediate **7-*d*** to furnish **3k**. Instead of the addition of **2′** to **7-*d***, when **2′** abstracted the deuterium in **7-*d***, **1a** and **2-*d*** were generated. Then, the reaction of **1a** with **2** would afford **3a**. In addition,



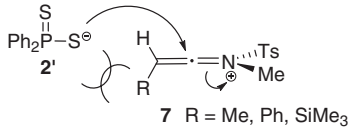
Scheme 1.



Scheme 2.



Scheme 3.



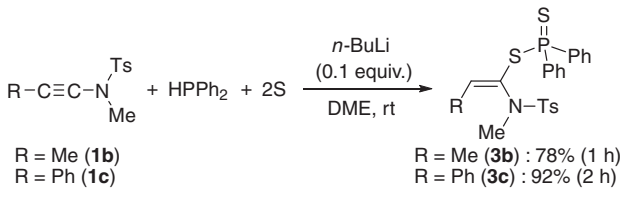
Scheme 4.

the reaction of **1k** with **2-*d*** would provide **3l**.

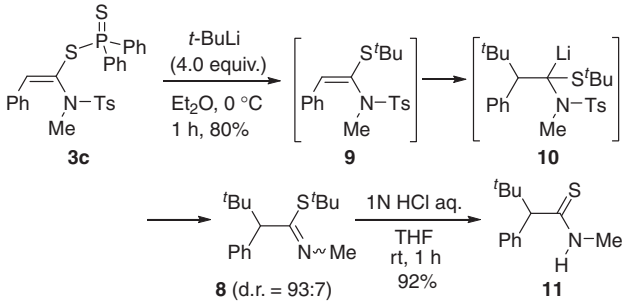
The mechanism that hydrothiolation of ynamides provided E isomers selectively is suggested as follows. Dithiophosphinate anion **2′** would attack to keteniminium intermediate **7** to avoid steric hindrance with a substituent R (Scheme 4).

We found that treatment of ynamides **1b** or **1c** with commercially available diphenylphosphine and sulfur in the presence of a catalytic amount of butyllithium in DME at room temperature afforded the same product **3b** or **3c** respectively in high yield (Scheme 5). It is reasonable that diphenyldithiophosphinic acid (**2**) would be generated in situ.[8]

Finally, we examined the reactivity of the ketene *N*,*S*-acetal **3**. Treatment of **3c** with 4.0 equimolar amounts of *tert*-butyllithium in diethyl ether at 0 °C provided thioimidate **8** in 80% yield (Scheme 6).[9] The formation of thioimidate **8** would proceed as follows. Substitution on the sp^3-hybridized sulfur atom in **3c** with *tert*-butyllithium occurred to afford **9**. Then, another *tert*-butyllithium added to **9** to give **10**, and the following elimination of lithium *p*-toluenesufinate furnished thioimidate **8**. Hydrolysis of thioimidate **8** led to *tert*-butyl-substituted thioamide **11** in 92% yield. Treatment of **3c** with 1.2 equimolar amounts of *tert*-butyllithium in THF at −40 °C for 90 min afforded the intermediate **9** in only 34% NMR yield. Unfortunately, the use of other organolithium compounds or organomagnesium compounds instead of *tert*-butyllithium provided complex mixtures.



Scheme 5.



Scheme 6.

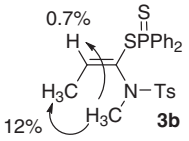
References and Notes

1 For reviews on the chemistry of ynamides, see: a) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar, L.-L. Wei, *Tetrahedron* **2001**, *57*, 7575. b) J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, *Synlett* **2003**, 1379.

2 For Brønsted acid-catalyzed addition reaction of allyl or propargyl alcohol followed by Claisen rearrangement, see: a) J. A. Mulder, R. P. Hsung, M. O. Frederick, M. R. Tracey, C. A. Zificsak, *Org. Lett.* **2002**, *4*, 1383. b) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder, M. P. Tracey, *Org. Lett.* **2003**, *5*, 2663. For hydrohalogenation, see: c) J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen, C. A. Zificsak, *Org. Lett.* **2003**, *5*, 1547. For Brønsted acid-catalyzed hydroarylaion, see: d) Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 6483. e) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer, A. Davis, *Org. Lett.* **2005**, *7*, 1047. For Lewis acid-catalyzed reaction with carbonyl compounds, see: f) K. C. M. Kurtz, R. P. Hsung, Y. Zhang, *Org. Lett.* **2006**, *8*, 231. g) L. You, Z. F. Al-Rashid, R. Figueroa, S. K. Ghosh, G. Li, T. Lu, R. P. Hsung, *Synlett* **2007**, 1656.

3 Diphenyldithiophosphinic acid was easily prepared from benzene and P_4S_{10} in the presence of $AlCl_3$. W. A. Higgins, P. W. Vogel, W. G. Craig, *J. Am. Chem. Soc.* **1955**, *77*, 1864.

4 Determined based on nuclear Overhauser effect. Syn addition reactions to ynamides under Brønsted acid catalysis was reported in Ref. 2d.



5 Hydrothiolation with aromatic dithiocarbonic acid could not be performed due to difficulty in preparing and purifying dithiocarbonic acid.

6 pK_a ($Ph_2P(=S)SH$, in 80% alcohol) = 2.6: a) M. I. Kabachnik, T. A. Mastrukova, A. E. Shipov, T. A. Melentyeva, *Tetrahedron* **1960**, *9*, 10. pK_a (PhC(=O)SH, in DMSO) = 5.2, pK_a (PhSH, in DMSO) = 9.8: b) J. Courtot-Coupez, M. Le Démézet, *Bull. Soc. Chim. Fr.* **1969**, 1033.

7 Keteniminium intermediates were also proposed in Ref. 2.

8 It was reported that reaction of Ph_2PH and 2 equimolar amounts of sulfur in refluxing benzene afforded $Ph_2P(=S)SH$: G. Peters, *J. Org. Chem.* **1962**, *27*, 2198. Catalytic amounts of *n*-BuLi would accelerate to form $Ph_2P(=S)SH$ due to generation of Ph_2PLi in situ.

9 Treatment of **3c** with 2.2 equimolar amounts of *t*-BuLi under similar conditions provided **8** in 44% ^{1}H NMR yield along with the recovery of **3c** in 33% ^{31}P NMR yield. It is not clear the reason why 4.0 equimolar amounts of *t*-BuLi were needed.

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