

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

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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 acid³ 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*-tolylsulfonyl)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).

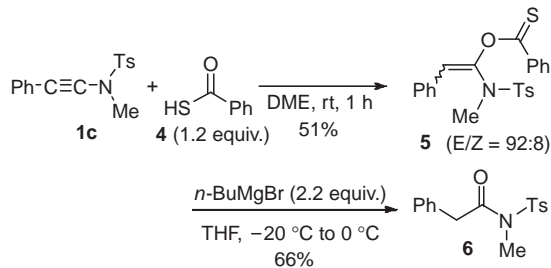
Treatment of ynamide **1c** with thiobenzoic acid (**4**) instead of **2** under otherwise the same conditions furnished ketene acetal **5** in 51% isolated yield (Scheme 1). When the adduct **5** reacted with butylmagnesium bromide in tetrahydrofuran (THF), amide **6** was obtained in 66% yield. Therefore, 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 mixture 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,

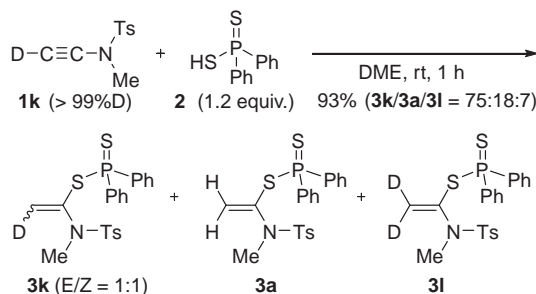
Table 1. Hydrothiolation reactions of ynamides with diphenyldithiophosphinic acid

	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	<i>p</i> -tolyl	Me	Ts	3d	91
5	1e	<i>o</i> -tolyl	Me	Ts	3e	97
6	1f	<i>p</i> -ClC ₆ H ₄	Me	Ts	3f	88
7	1g	<i>p</i> -AcC ₆ H ₄	Me	Ts	3g	97
8	1h	TMS	Me	Ts	3h	63 ^b
9	1i	Ph	allyl	Ts	3i	95
10	1j	Ph	Me	<i>p</i> -Ns ^c	3j	97

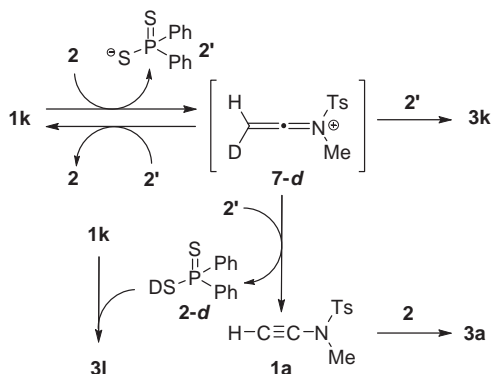
^aIsolated yields by silica-gel column chromatography unless otherwise noted. ^bIsolated yield obtained by recrystallization. ^c*p*-Nitrophenylsulfonyl.



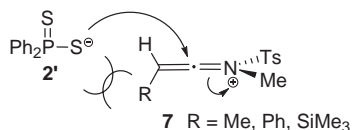
Scheme 1.



Scheme 2.



Scheme 3.



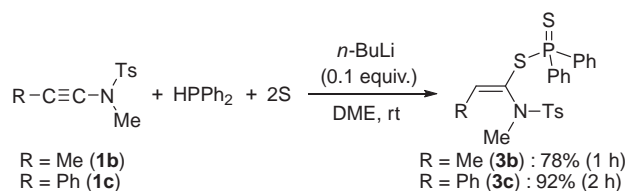
Scheme 4.

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

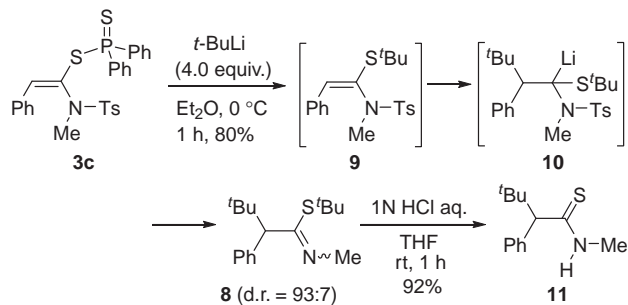
The mechanism that hydrothiolation of ynamides provided E isomers selectively is suggested as follows. Dithiophosphinate anion **2'** would attack to keteniminium intermediate **7** to avoid steric hindrance with a substituent R (Scheme 4).

We found that treatment of ynamides **1b** or **1c** with commercially available diphenylphosphine 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 equivolar amounts of *tert*-butyllithium in diethyl ether at 0 °C provided thioimide **8** in 80% yield (Scheme 6).⁹ The formation of thioimide **8** would proceed as follows. Substitution on the sp³-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*-toluenesulfinate furnished thioimide **8**. Hydrolysis of thioimide **8** led to *tert*-butyl-substituted thioamide **11** in 92% yield. Treatment of **3c** with 1.2 equivolar 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

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- Keteniminium intermediates were also proposed in Ref. 2.
- It was reported that reaction of Ph₂PH and 2 equivolar amounts of sulfur in refluxing benzene afforded Ph₂P(=S)SH: G. Peters, *J. Org. Chem.* **1962**, 27, 2198. Catalytic amounts of *n*-BuLi would accelerate to form Ph₂P(=S)SH due to generation of Ph₂PLi in situ.
- Treatment of **3c** with 2.2 equivolar amounts of *t*-BuLi under similar conditions provided **8** in 44% ¹H NMR yield along with the recovery of **3c** in 33% ³¹P NMR yield. It is not clear the reason why 4.0 equivolar amounts of *t*-BuLi were needed.