

Regio- and Stereoselective Radical Additions of Thiols to Ynamides

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Abstract: Regioselective and stereoselective radical additions of arenethiols to various ynamides have been developed. Mixing ynamides and arenethiols in the presence of a catalytic amount of triethylborane affords the corresponding adducts, (*Z*)-1-amino-2-thio-1-alkenes, in excellent yields with high selectivities. The products can be reduced by means of trifluoroacetic acid and triethylsilane to yield 1-amino-2-thioalkanes.

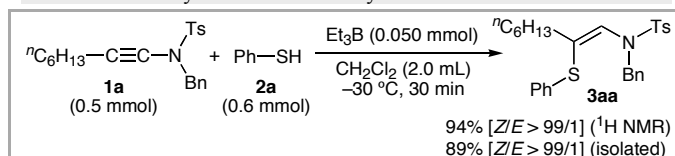
Key words: Radical, Hydrothiolation, Ynamide, Hydrogenation

Because of the high importance of organosulfur compounds, development of new reactions to introduce sulfur atoms to organic molecules is indispensable.¹ Radical addition of thiols to unsaturated bonds is one of the most basic and concise methods to achieve the purpose.^{2,3} Although radical additions of thiols to terminal alkynes are well-known, examples of additions to internal alkynes are limited.^{2c,4} Furthermore, additions to heteroatom-substituted internal alkynes have scarcely been reported.⁵

We have focused on *N*-alkynylamides (ynamides),⁶ as heteroatom-substituted internal alkynes in the radical addition reaction. Here we report radical hydrothiolation of ynamides,^{7,8} which yields synthetically useful (*Z*)-1-amino-2-thio-1-alkene derivatives⁹ regio- and stereoselectively.¹⁰

Under air, a catalytic amount of triethylborane¹¹ was added to a solution of *N*-benzyl-*N*-(1-octynyl)-*p*-toluenesulfonamide¹² (**1a**) and benzenethiol (**2a**, 1.2 equiv) in dichloromethane at –30 °C. After the mixture was stirred for 30 min at the same temperature, the mixture was concentrated. NMR analysis of the crude mixture indicated the formation of *N*-benzyl-*N*-(2-phenylthio-1-octenyl)-*p*-toluenesulfonamide (**3aa**, 94%, *Z/E* > 99/1). We confirmed by NOE experiments that the *Z* isomer was exclusively formed. Silica gel column chromatography afforded **3aa** in 89% yield (Scheme 1).¹³

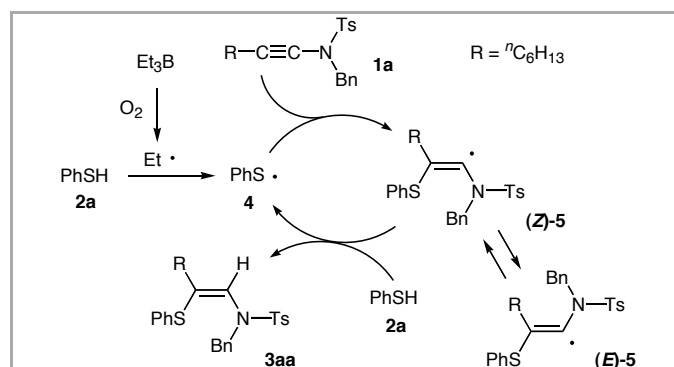
Scheme 1. Triethylborane-initiated Hydrothiolation of Ynamide **1a**.



This reaction would proceed as follows (Scheme 2). Initially, an ethyl radical, generated from triethylborane

with a trace amount of molecular oxygen, abstracts hydrogen atom from benzenethiol to form thiyl radical **4**. The electron-deficient radical¹⁴ immediately reacts with ynamide **1a**, an electron-rich alkyne, to furnish vinyl radical **5**. The carbon–sulfur bond formation occurs regioselectively at the 2-position of ynamide **1a**, where the higher electron density resides. The *Z* isomer of vinyl radical **5** selectively abstracts hydrogen atom from benzenethiol.¹⁵ Product **3aa** is thus formed, and thiyl radical **4** is regenerated to complete the radical chain.

Scheme 2. Plausible Reaction Mechanism.



Electron-deficient arenethiol participated smoothly in this radical reaction (Table 1, entries 2 and 3). On the other hand, additions of electron-rich arenethiols were not efficient (entries 4–6). These poor yields would be due to the low reactivity of the electrophilic thiyl radicals that are stabilized by electron-donating aryl groups. Addition of a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to the reaction system or the absence of triethylborane almost prevented the reaction (entries 7 and 8). These results strongly support that the reaction would proceed via the radical chain mechanism.

Table 1. Hydrothiolation of **1a** with Various Arenethiols.

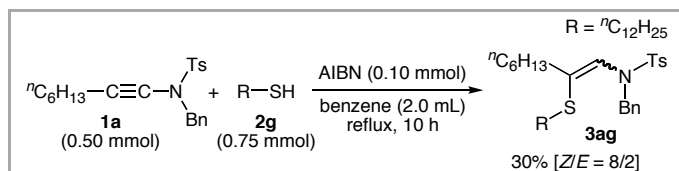
entry	Ar	product	isolated yield /% [<i>Z/E</i>]
1	Ph (2a)	3aa	89 [<i>Z/E</i> > 99/1]
2	<i>p</i> -Br-C ₆ H ₄ (2b)	3ab	88 [<i>Z/E</i> > 99/1]

3	C ₆ F ₅ (2c)	3ac	93 [$> 99/1$]
4	<i>o</i> -Me-C ₆ H ₄ (2d)	3ad	31 ^d [N.D. ^e]
5	<i>p</i> -Me-C ₆ H ₄ (2e)	3ae	23 ^d [N.D. ^e]
6 ^a	<i>p</i> -MeO-C ₆ H ₄ (2f)	3af	35 [$> 99/1$]
7 ^b	Ph (2a)	3aa	6 ^d [59/41]
8 ^c	Ph (2a)	3aa	$< 2^d$ [N.D. ^e]

^a The reaction was performed at room temperature. ^b With TEMPO (0.10 mmol). ^c Without triethylborane. ^d NMR yield. ^e Not determined.

The addition of dodecanethiol (**2g**) to ynamide **1a** did not proceed at -30 °C. The reaction in boiling benzene with AIBN [2,2'-azobis(isobutyronitrile)] instead of Et₃B proceeded, although the yield and stereoselectivity were unsatisfactory (Scheme 3).

Scheme 3. Hydrothiolation of **1a** with Dodecanethiol.



A wide range of ynamides were subjected to the radical addition of benzenethiol (**2a**) (Table 2). Not only **1a** but also ynamides bearing an acid-sensitive THP ether moiety and a base-sensitive ester moiety underwent the addition reactions without loss of the functional groups (entries 2 and 3). Benzenethiol added to ynamide **1d** substituted by a secondary alkyl group in lower yield with slightly lower selectivity (entry 4). Ynamide **1e** having a tertiary alkyl group resisted the addition reaction (entry 5).¹⁶ Replacement of the benzyl group of **1a** by a methyl group slightly decreased the regioselectivity of the reaction (entry 1 vs. entry 6). The allyl group of **1g** remained unchanged under the reaction conditions (entry 7). *N*-Phenyl ynamide **1h** was less reactive than the *N*-benzyl analogue **1a** (entry 8). Not only *p*-toluenesulfonamides **1a–1h** but also camphorsulfonamides **1i** and **1j** and Boc-protected ynamide **1k** underwent the radical addition smoothly (Scheme 4).

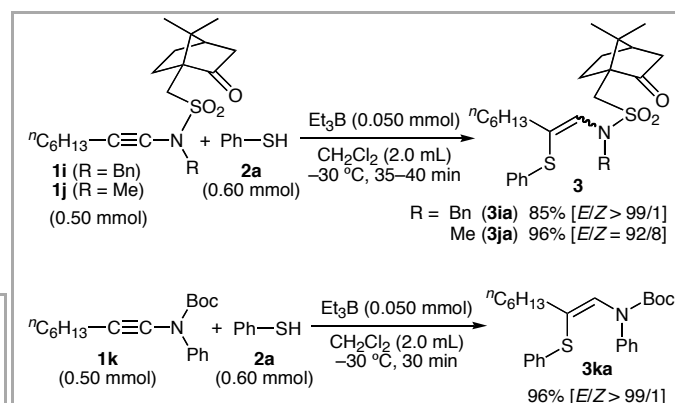
Table 2. Radical Hydrothiolation of *p*-Toluenesulfonyl-substituted Ynamides with Benzenethiol..

entry	R ¹	R ²	1	product	isolated yield [%] [Z/E]
1	ⁿ C ₆ H ₁₃	Bn	1a	3aa	89 [$> 99/1$]
2	THPOCH ₂	Bn	1b	3ba	90 [$> 99/1$]
3	EtO ₂ C(CH ₂) ₄	Bn	1c	3ca	97 [$> 99/1$]

4	^c C ₆ H ₁₁	Bn	1d	3da	73 [97/3]
5	^t Bu	Bn	1e	3ea	15 [N.D. ^a] ^b
6	ⁿ C ₆ H ₁₃	Me	1f	3fa	97 [96/4]
7	ⁿ C ₆ H ₁₃	allyl	1g	3ga	84 [$> 99/1$]
8	ⁿ C ₆ H ₁₃	Ph	1h	3ha	60 [$> 99/1$]

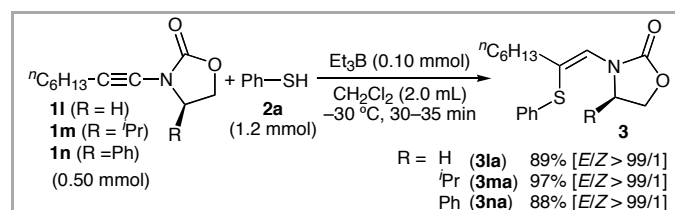
^a Not determined. ^b NMR yield.

Scheme 4. Radical Hydrothiolation of Various Ynamides with Benzenethiol.



The addition reactions to *N*-(1-alkynyl)oxazolidinones led to the exclusive formation of the corresponding *Z* adducts in excellent yields (Scheme 5). In these cases, 2.4 equiv of benzenethiol and a larger amount of triethylborane were needed.

Scheme 5. Radical Hydrothiolation of *N*-(1-Alkynyl)oxazolidinone with Benzenethiol.

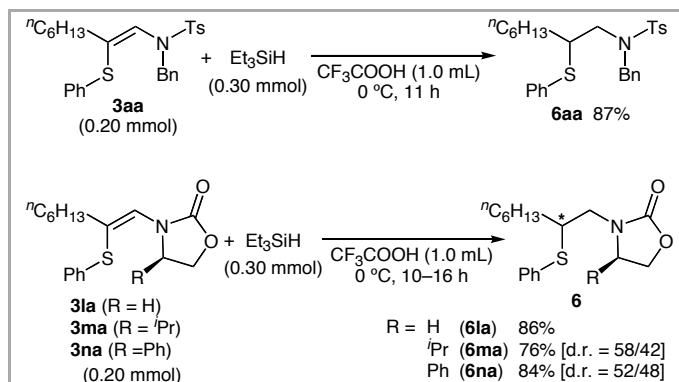


Hydrogenation of the double bonds of adducts **3** could provide interesting structures having a phenylthiolated chiral center. We hence examined to reduce alkenylamides **3**. Many attempts to reduce the double of **3aa** in the presence of various transition metal complexes under hydrogen atmosphere resulted in failure, suffering from no conversions.

On the other hand, treatment of **3aa** with triethylsilane in trifluoroacetic acid reduced the alkene moiety¹⁷ to afford desired *N*-(2-phenylthioalkyl)amides **6aa** in good yield (Scheme 6).¹⁸ Unfortunately, attempted diastereoselective reduction of chiral *N*-(1-alkenyl)oxazolidinones **3ma** and **3na** resulted in the formation of 1:1 mixtures of diastereomers. However, the diastereomers were separable from each other by flash column chromatography on silica gel.

In summary, we have developed a concise method to synthesize (Z)-1-amino-2-thio-1-alkene derivatives in high yields with excellent regio- and stereoselectivity. The products can be hydrogenated by the action of triethylsilane in trifluoroacetic acid. Since reduced products **6** have asymmetric carbons, they can be useful as chiral building blocks¹⁹ and chiral bidentate *N,S*-ligands of transition metal catalysts.²⁰

Scheme 6. Reduction of Double Bonds of Adducts **3**.



Acknowledgement

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- (13) **General experimental procedure for radical hydrothiolation of ynamides:** Under air, triethylborane (1.0 M hexane solution, 0.050 mL, 0.050 mmol) was added to a solution of *N*-benzyl-*N*-(1-octenyl)-*p*-toluenesulfonamide (**1a**, 0.18 g, 0.50 mmol) and benzenethiol (**2a**, 0.062 mL, 0.60 mmol) in dichloromethane (2.0 mL) at –30 °C. The solution was stirred for 30 min at the same temperature and concentrated in vacuo. ¹H NMR analysis of the crude mixture showed a 94% yield of the adduct (*Z/E* > 99/1). Silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) afforded *N*-benzyl-*N*-[(Z)-2-phenylthio-1-octenyl]-*p*-toluenesulfonamide (**3aa**) as a white solid in 89% yield (0.21 g, 0.45 mmol). **3aa**: IR (Nujol) 2925, 1456, 1351, 1339, 1161, 1089, 1024, 741, 661 cm^{–1}; ¹H NMR (CDCl₃) δ 0.83 (t, *J* = 7.5 Hz, 3H), 1.02–1.15 (m, 4H), 1.16–1.35 (m, 4H), 1.89 (t, *J* = 7.0 Hz,

2H), 2.45 (s, 3H), 4.46 (s, 2H), 5.64 (s, 1H), 6.90–6.94 (m, 2H), 7.13–7.21 (m, 3H), 7.26–7.35 (m, 5H), 7.36–7.41 (m, 2H), 7.76–7.80 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.04, 21.57, 22.50, 28.09, 28.25, 31.40, 33.36, 54.15, 124.26, 127.14, 127.62, 127.67, 128.32, 128.58, 128.77, 129.60, 132.31, 133.10, 135.63, 135.83, 142.86, 143.59. Found: C, 70.00; H, 6.94%. Calcd for $\text{C}_{28}\text{H}_{33}\text{NO}_2\text{S}_2$: C, 70.11; H, 6.93%.

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- 6aa:** IR (neat) 2926, 2855, 1599, 1456, 1439, 1342, 1162, 1092, 737, 654 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.88 (t, J = 7.5 Hz, 3H), 1.02–1.31 (m, 8H), 1.34–1.46 (m, 1H), 1.65–1.75 (m, 1H), 2.42 (s, 3H), 2.95–3.05 (m, 2H), 3.26–3.34 (m, 1H), 4.05 (d, J = 14.5 Hz, 1H), 4.31 (d, J = 14.5 Hz, 1H), 7.17–7.32 (m, 12H), 7.57–7.61 (m, 2H); ^{13}C NMR (CDCl_3) δ 14.07, 21.49, 22.58, 26.62, 28.94, 30.82, 31.64, 47.40, 53.96, 54.26, 126.75, 127.30, 127.96, 128.58, 128.62, 128.83, 129.69, 131.62, 134.66, 135.82, 136.21, 143.37. Found: C, 70.03 H, 7.38%. Calcd for $\text{C}_{28}\text{H}_{35}\text{NO}_2\text{S}_2$: C, 69.81; H, 7.32%.
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