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Kyoto University
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, \((\text{Z})-1\)-amino-2-thio-1-alkenes, in excellent yields with high selectivities. The products can be reduced by means of trifluoroacetic acid and triethyldisilane 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.⁴,⁵ Furthermore, additions to heteroatom-substituted internal alkynes have scarcely been reported.⁶

We have focused on \(N\)-alkynylamides (ynamides),⁷ as heteroatom-substituted internal alkynes in the radical addition reaction. Here we report radical hydrothiolation of ynamides,⁸ which yields synthetically useful \((\text{Z})-1\)-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-octynyl)-\(p\)-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

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 thyl 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 thyl 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 thyl 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.

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>product</th>
<th>isolated yield %</th>
<th>(Z/E)</th>
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<tr>
<td>1</td>
<td>(\text{Ph} (2a))</td>
<td>3aa</td>
<td>89 ([&gt; 99/1])</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(p)-(\text{Br-C}_6\text{H}_4 \ (2b))</td>
<td>3ab</td>
<td>88 ([&gt; 99/1])</td>
<td></td>
</tr>
</tbody>
</table>
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). 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-toluenesulphonamides 1a–1h but also camphorsulphonamides 1i and 1j and Boc-protected ynamide 1k underwent the radical addition smoothly (Scheme 4).

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

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>I</th>
<th>product</th>
<th>isolated yield /%</th>
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<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>Tol</td>
<td>1d</td>
<td>3da</td>
<td>73 [97/3]</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Tol</td>
<td>1e</td>
<td>3ea</td>
<td>15 [N.D.]</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>Tol</td>
<td>1f</td>
<td>3fa</td>
<td>97 [96/4]</td>
</tr>
<tr>
<td>4</td>
<td>1h</td>
<td>Tol</td>
<td>1g</td>
<td>3ga</td>
<td>84 [99/1]</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>Tol</td>
<td>1h</td>
<td>3ha</td>
<td>60 [99/1]</td>
</tr>
</tbody>
</table>

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 alkynylamides 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 moiety to afford desired N-2-phenylthioalkylamides 6aa in good yield (Scheme 6). Unfortunately, attempted diastereoselective reduction of chiral N-(1-alkynyl)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 have asymmetric carbons, they can be useful as chiral building blocks and chiral bidentate N,S-ligands of transition metal catalysts.


Acknowledgement
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References and Notes


(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-octynyl)-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 ºC. The solution was stirred for 30 min at the same temperature and concentrated in vacuo.

$^1$H 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-octynyl]-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$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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).
(14) It was reported that arylthiyl radicals behave as electron-deficient radicals: Ito, O.; Fleming, M. D. C. M. J. Chem. Soc., Perkin Trans. 2 1989, 689–693.

(15) The diastereoselectivity can be explained by steric effect. In reference 4b, Montevecchi and Spagnolo insisted that primary alkyl groups are bulkier than a phenylthio group. The Z form abstract hydrogen from benzzenethiol selectively. On the other hand, Montevecchi et al. also insisted that a methyl group is smaller than a phenylthio group. Indeed, the reaction of N-methyl-N-(1-propenyl)-p-toluenesulfonamide with benzzenethiol resulted in favorable formation of the corresponding Z adduct (E/Z = 2:3).

(16) The addition reaction of phenyl-substituted ynamide PhC≡NCTS(Bn) led to a mixture of stereo- and regioisomers.

(17) Alkenes and ketones can be reduced under these conditions. See: Kursaniov, D. N.; Parnes, Z. N.; Bassova, G. L.; Loim, N. M.; Zdanovich, V. I. Tetrahedron 1967, 23, 2235–2242.

(18) General experimental procedure for hydrogenations of the double bonds of enamides: Under argon atmosphere, triethylsilane (0.048 mL, 0.30 mmol) was added to a solution of 3aa (0.096 g, 0.20 mmol) in trifluoroacetic acid (1.0 mL, 13.5 mmol) at 0 °C. The solution was stirred for 11 h at the same temperature. Then the reaction was quenched with a saturated NaHCO₃ solution and extracted with ethyl acetate (10 mL × 2). The organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Silica gel column chromatography (hexane/ethyl acetate = 20/1) afforded N-benzyl-N-[2-(phenylthio)octyl]-p-toluenesulfonamide (6aa) as a colorless oil in 87% yield (0.084 g, 0.17 mmol).

6aa: IR (neat) 2926, 2855, 1599, 1456, 1439, 1342, 1162, 1092, 737, 654 cm⁻¹; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₃H₅₃NO₄S₂: C, 69.81; H, 7.32%.
