**Regular Article**

**Cyclic Sulfamidite as Simultaneous Protecting Group for Amino Alcohols: Development of a Mild Deprotection Protocol Using Thiophenol**

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Received June 26, 2020; accepted July 20, 2020

This study describes the novel utility of cyclic sulfamidite as a simultaneous protecting group for 1,2- or 1,3-amino alcohols. An exceptionally mild and neutral condition for the removal of the cyclic sulfamidite was developed. The deprotection condition demonstrated a broad range of functional-group compatibility, including a substrate bearing a Z-enzyme structure without any loss of double-bond stereochemistry.

**Key words** protecting group; amino alcohol; protection; deprotection; cyclic sulfamidite

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**Introduction**

Amino alcohols, often found in a wide range of biologically active natural products, agricultural chemicals, and pharmaceutical agents, are one of the most important functional groups in organic synthesis.\(^1\)\(^-\)\(^9\) Therefore, great efforts have been made by several synthetic chemists to develop a variety of synthetic methods for amino alcohols.\(^5\)\(^-\)\(^9\) In sharp contrast, the choice of protecting group for the amino alcohols, particularly in terms of simultaneous protecting groups for 1,2- and 1,3-amino alcohols, is limited to two types only.\(^10\)\(^-\)\(^24\) (Chart 1).

The most frequently used type is isopropylidene N-O acetal (acetonide), the introductions and removals of which are generally performed under acidic conditions.\(^12\)\(^-\)\(^15\) (Chart 1a). The other major protecting group is cyclic carbamate (Chart 1b), the formation of which is conducted under mild conditions using a carbonyl equivalent such as triphosgene or carbonyldiimidazole in the presence of weak bases. However, its removal requires strongly basic conditions, even for the activated cyclic carbamate of 1,2- and 1,3-amino alcohols, limited to two types only.\(^10\)\(^-\)\(^24\) (Chart 1).

Although these two types of protecting groups are highly useful for the synthesis of small building blocks or less-functionalized early-stage intermediates in multi-step synthesis, the protection, and particularly, the deprotection of the highly functionalized advanced intermediates, are often problematic owing to the chemoselectivity issue.

We unexpectedly found that cyclic sulfamidite was useful for the simultaneous protection of 1,3-amino alcohol during our synthetic studies on \((-\)histrionotoxin (HTX).\(^5\)\(^-\)\(^7\)\(^,\)\(^25\)\(^-\)\(^27\)\) Previous synthetic studies conducted by Stork and Zhao\(^28\) as well as our own investigation into the endgame sequence,\(^29\) demonstrated that the highly congested 1,3-amino alcohol of \((-\)HTX 235A (I) completely resists protection as its acetonide or carbamate form. However, the protection of the 1,3-amino alcohol was unavoidable in elongating two terminal alkenes to enynes to complete the total synthesis (Chart 2). We attempted to protect the 1,3-amino alcohol of \((-\)HTX 235A (I) as its cyclic sulfamidate form through a stepwise manner incorporating initial treatment with SOCl\(_2\)/imidazole and subsequent oxidation with sodium periodate (NaIO\(_4\)) based on the known protocol.\(^10\)\(^-\)\(^24\) Although the initial reaction proceeded smoothly and provided cyclic sulfamidite 2 in high yield, no oxidation occurred at all. Furthermore, no reports exist that used cyclic sulfamidate as the simultaneous protecting group for 1,3-amino alcohol. Nevertheless, we successfully conducted the elongation of the terminal alkenes through ozonolysis, Wittig olefination, and Sonogashira coupling to provide enyne 4. The cyclic sulfamidite thus introduced was found to be sufficiently robust to tolerate these elongation steps. Finally, the cyclic sulfamidite was removed under reduction conditions with lithium aluminum hydride (LiAlH\(_4\)) to complete the total synthesis of \((-\)HTX (5).

Preparation of five- or six-membered cyclic sulfamidites from 1,2- or 1,3-amino alcohols through treatment with thionyl chloride (SOCl\(_2\)) in the presence of weak bases (Chart 3) and the investigation of the synthetic utility of these compounds as a reactive alkylating reagent has been conducted to provide a wide range of substituted amines and amino acids.\(^9\)\(^,\)\(^30\)\(^-\)\(^32\) However, few examples of the utility of these compounds as a protected form of the corresponding amino alcohol have surfaced, possibly owing to the lack of mild and chemoselective deprotection conditions, with the exception of our use of LiAlH\(_4\). Under this context, we conducted detailed studies on the deprotection condition for cyclic sulfamidites and herein report a general- and functional-group-compatible deprotection protocol using benzenethiol.

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Results and Discussion

At the outset, we investigated the deprotection conditions using \(N\)-benzyl-cyclic sulfamidite \(7a\) prepared from 3-(benzylamino) propan-1-ol (6a) as the test substrate (Table 1). Considering deprotection through an \(S_N\) 2 process at the sulfur atom, we initially screened various nucleophiles. The treatment of \(7a\) with LiAlH\(_4\) produced \(N\)-benzyl-3-aminopropanol 6a in high yield (Table 1, entry 1), whereas NaBH\(_4\) did not promote the deprotection at all (Table 1, entry 2). No \(S_N\) 2 reaction at the sulfur atom occurred when a Grignard reagent or tetrabutylammonium fluoride (TBAF) were employed as the nucleophile (Table 1, entries 3 and 4). Moreover, the treatment of \(7a\) with thiophenol (PhSH) in tetrahydrofuran (THF) produced amino alcohol 6a in low yield (Table 1, entry 5), whereas the addition of Et\(_3\)N increased the yield to 51% (Table 1, entry 6). We then found that switching the solvent from THF to MeOH shortened the reaction time and drastically improved the yield to 88% (Table 1, entry 7). The reaction time was again shortened with the addition of acetic acid (AcOH) (Table 1, entry 9), while the yield of 6a slightly decreased. It should be noted that the best yield of 6a (90%) was obtained when \(7a\) was treated with benzeneselenol in MeOH (Table 1, entry 10).

Table 1. Optimization of Deprotection Conditions

| Entries | Reagents (eq) | Solvent | Time (h) | Yield (%) \(^{a}\) |
|---------|--------------|---------|----------|-------------------|
| 1       | LiAlH\(_4\) (5 eq) | THF     | 1        | 82                |
| 2\(^{b}\) | NaBH\(_4\) (5 eq) | MeOH    | 24       | 0                 |
| 3       | MeMgCl (5 eq) | THF     | 0.5      | Trace             |
| 4\(^{b}\) | TBAF (3 eq) | THF     | 4        | 0                 |
| 5       | PhSH (5 eq) | THF     | 5        | 6                 |
| 6       | PhSH (5 eq), Et\(_3\)N (5 eq) | THF     | 7        | 51                |
| 7       | PhSH (5 eq) | MeOH    | 0.5      | 88                |
| 8\(^{c}\) | PhSH (3 eq) | MeOH    | 3        | 47                |
| 9       | PhSH (5 eq), AcOH (10 eq) | MeOH    | 5 min    | 77                |
| 10      | PhSeH (5 eq) | MeOH    | 1        | 90                |

\(^{a}\) Yields are of isolated products. \(^{b}\) \(7a\) was recovered in quantitative yield. \(^{c}\) \(7a\) was recovered in 41% yield. eq: equivalent.
entry 10). However, we selected the condition described in entry 7 as the optimized condition to avoid the use of highly toxic and expensive benzeneselenol.

Having established the deprotection conditions, we prepared a series of protected N-benzyl amino alcohols 7a–7i (see Supplementary Materials for more detail), which were subjected to optimized deprotection conditions to investigate the generality and the functional-group compatibility (Chart 4). The treatment of unsubstituted five- to seven-membered substrates 7b, 7a, and 7c with PhSH in MeOH smoothly provided corresponding 1,2-, 1,3-, and 1,4-amino alcohols 6b, 6a, and 6c in good yields. We observed that the geminal methyl groups on the C1 position reduced the reaction rate owing to the steric hinderance around the sulfur atom, whereas the addition of AcOH effectively accelerated the deprotection to provide 6d and 6e, respectively. The cyano group (6f), the bromo group (6g), and the nitro group (6h), which would likely be damaged by our previous deprotection condition using LiAlH₄, could survive under the PhSH-mediated deprotection condition.

Next, we synthesized the diastereomers of cyclic sulfamidite 9a from N-tertiary-butoxycarbonyl (Boc) serine methyl ester (8a) using the Tewson’s method, and which were subjected to the optimized deprotection conditions. The attempted deprotection through PhSH in MeOH was extremely slow, and unreacted cyclic sulfamidite 9a was recovered even after 12 h. However, here, we found that the addition of Et₃N generating thiolate effectively promoted the deprotection to provide N-Boc serine methyl ester with an 92% yield. It should be noted that we did not confirm the loss of enantiopurity in 8a during the protection and deprotection sequences or the large reactivity bias between the diastereomers during the deprotection sequences.

To further investigate the functional-group compatibility, we synthesized N-Boc and N-benzyloxycarbonyl (Cbz) cyclic sulfamidites 9b–9f (see Supplementary Materials for more detail), which were subjected to the optimized conditions established in Chart 5 (Chart 6). The primary tertiarbutyldimethylsilyl (TBS) ether (9b), the acetyl (9c) group, and the azide group (9e) can be compatible providing corresponding amino alcohol 8 in high yield. In the case of sulfamidite 9d with the primary bromo group, amino alcohol 8d was the major product (65%), whereas a considerable amount of sulfide 10 was obtained (18%) through an undesired S₄N₂ reaction. Regarding substrate 9f bearing α,β-unsaturated ester, which would easily accept thiolate by Michael addition, trace amount of such byproduct was observed.

Finally, we conducted a model study imitating the final stage of the total synthesis of (−)-HTX (5) (Table 2). Under an aerobic atmosphere, thiols generate thyl radicals that easily isomerize alkenes through addition/elimination sequences. Therefore, to examine the feasibility of this protecting group for a substrate with alkene moiety, we conducted a model study using a radical-sensitive enyne substrate in view of its application to the total synthesis of (−)-HTX (5) (Table 2). The test substrate 11 with a Z-enzyme side chain was carefully treated with PhSH in freshly degassed MeOH. However, as anticipated, the reaction provided the desired amino alcohol 12 alongside a small amount of amino alcohol 13.

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**Chart 4. Substrate Scope of the Deprotection Condition Using Benzenethiol**

**Chart 5. Protection and Deprotection of the N-Boc Serine Methyl Ester**

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*a) Yields are of isolated products. b) AcOH (10 eq) was added.*
Table 2. Deprotection of Amino Alcohol Bearing a Z-Enyne Structure

| Entry | Thiol          | Time (h) | 12 (%) | 13 (%) | 14 (%) | Recovery of 11 (%) |
|-------|----------------|----------|--------|--------|--------|---------------------|
| 1     | phenyl SH      | 31       | 82a    | 5a     | 0      | 9b                  |
| 2     | 4-MeC6H4 SH    | 31       | 84a    | 7a     | 0      | 6b                  |
| 3     | 4-OMeC6H4 SH   | 31       | 80b    | 0      | 0      | 13b                 |
| 4     | 4-ClC6H4 SH    | 31       | 75a    | 3a     | 0      | 5                   |
| 5     | 4,5-Cl2C6H4 SH | 5        | 91b    | 0      | 0      | 0                   |
| 6     | 4,5-Cl2C6H4 SH | 31       | 34a    | 6a     | 8a     | 34a                 |

*a* Obtained as inseparable mixture of E/Z isomers. *b* Yields are of isolated products.
with an isomerized E-enyne side chain. We then optimized the structure of the thiol with the expectation that the steric and electronic nature of PhSH would affect the isomerization process. PhSH with an electron-donating methoxy group and an electron-withdrawing Cl group at the para-position demonstrated almost the same results as with unsubstituted PhSH. In contrast, PhSH with both methoxy and Cl groups at the ortho-position completely suppressed the generation of amino alcohol 13, suggesting that the steric bulkiness of the ortho-substituent prevented the addition of the thiol radicals to the enyne moiety. Although the best yield of 12 was obtained when 11 was treated with o-chlorothiophenol in MeOH (91%), more sterically hindered o-dichlorothiophenol lowered the yield of 12 and, in fact, promoted the isomerization of the enyne structure to provide E-enynes 13 and 14.

In summary, deprotection conditions for the simultaneous protection of amino alcohols by cyclic sulfamidite were investigated. In the optimization process, we found that PhSH serves as a suitable deprotection reagent, allowing a wide-ranging substrate scope and good functional-group compatibility. The model study imitating a Z-enyne structure of (−)-HTX revealed that the sterically hindered o-chlorothiophenol completely suppressed the isomerization of the enyne stereochemistry during the deprotection process. The application of the established deprotection protocol to the total synthesis of (−)-HTX is currently ongoing.

Acknowledgments This work was financially supported by KAKENHI (JP16H01127, JP16H00999, JP26253001, JP18H02549, JP18H04379, JP18K18462) and Platform Project for Supporting Drug Discovery and Life Science Research (BINDS) from AMED under Grant Number JP18am0101100. The authors great thank Yoshiharu Iwabuchi for helpful discussion.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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36) During the preparation of 11, we confirmed that the cyclic sulfamidite can tolerate a variety of reaction conditions including, ester formation using DCC and DMAP, alkyne reduction by diimide, Sonogashira coupling. For the preparation of 11, see Supplementary Materials. In addition, we also observed that PDC oxidation of cyclic sulfamidite 7b and acid (PPTS, MeOH) or base (K2CO3, MeOH) treatment with cyclic sulfamidite 7d resulted in completely recovery of the starting materials. Further functional-group compatibility of the cyclic sulfamidite are under investigating.