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# A novel de-*O*-chloroacetylation reagent: 1-seleonocarbamoylpiperidine

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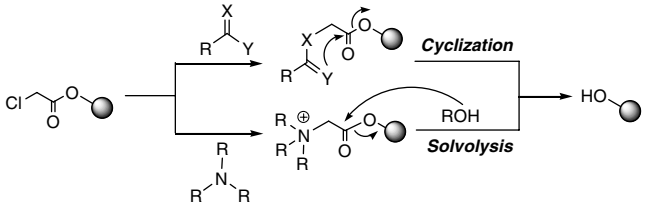
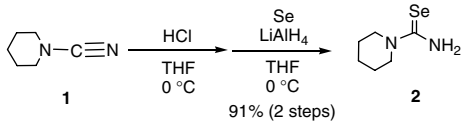
**Abstract**—1-Selenocarbamoylpiperidine **2** chemoselectively cleaves the *O*-chloroacetyl group in the presence of other acyl groups such as acetyl, pivaloyl, and Fmoc without the assistance of a base. The high lipophilicity of **2** allowed us to use 1,4-dioxane, THF, and DMF as reaction solvents, thereby enabling dechloroacetylation at high temperature. A comparative experiment with other dechloroacetyl reagents showed that selenourea **2** has a high potential as a dechloroacetylation reagent.


The chloroacetyl (CAc) group has been widely used for the protection of hydroxyl group during organic synthesis. In particular, the chemoselective deprotection of the CAc group in the presence of other acyl functionalities such as the acetyl, benzoyl, and levulinoyl groups serves as a critical method for the synthesis of complex oligosaccharides. Thus far, thiourea,[1] hydrazine dithiocarbonate (HDTC),[2] pyridine,[3] and diazabicyclo[2.2.2] octane (DABCO)[4] are representative of dechloroacetylation reagents. Thiourea and HDTC are believed to deprotect the CAc group by following the cyclization mechanism. This mechanism is illustrated in Scheme 1: the nucleophilic atom (X) of the reagent replaces the chlorine atom of the CAc group, and then another nucleophilic atom (Y) attacks the carbonyl carbon to break the C–O bond, thereby resulting in the production of free hydroxyl. In contrast, tertiary-amine-containing reagents such as pyridine and DABCO presumably attack the α-carbon to form onium salt, which is then solvolyzed by water, MeOH, or EtOH to produce naked hydroxyl group.




**Scheme 1.** Plausible mechanism of dechloroacetylation.

Among the reagents, although thiourea is most widely used, it is usually difficult to achieve complete deprotection at the hindered position. On the other hand, HDTC performs fast and with clear deprotection. However, it is critical that the HDTC be used immediately after its preparation due to it poor chemical stability. The recently reported DABCO also cleaves CAc in a fast and clean manner even at the hindered position, but the reaction media is limited to alcoholic solvents due to the solvent-assisted reaction mechanism. This limitation sometimes hampers its application to the deprotection of the CAc group installed in the fully protected lipophilic oligosaccharide. In this study, we demonstrate that 1-seleonocarbamoylpiperidine **2** serves as a new de-*O*-chloroacetylation reagent.




**Scheme 2.** Preparation of 1-selenocarbamoylpiperidine **2**.

*Keywords*: Chloroacetyl group; Selenourea; Chemoselective deprotection.
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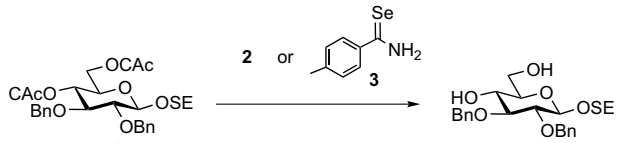
Previously, we reported the facile and high-yielding synthesis of **2** by reaction of 1-cyanopiperidine **1** with LiAlHSeH that is generated in situ by the action of $LiAlH_4$ and selenium[5,†] (Scheme 2); furthermore, we recently reported its application to selenium-containing heterocycle formation.[6] As a dechloroacetylation reagent, we expected this compound to exhibit higher reactivity than thiourea because of the high nucleophilicity of selenium and expected a higher lipophilicity because of the piperidine skeleton within **2**.

To evaluate the potential of **2** as a dechloroacetylation reagent, 4,6-di-*O*-chloroacetyl glucoside **4** (1.0 equiv) was reacted with **2** (2.4 equiv) under various conditions (Table 1). In entries 1–4, the reactions were conducted in THF with or without the presence of *N*,*N*-diisopropylethylamine (DIEA) (2.4 equiv). In the presence of DIEA, miscellaneous byproducts were accompanied with the deprotected product **5** (entries 1 and 3). On the other hand, without the use of DIEA, **2** cleaved the CAc group quantitatively (entries 2 and 4).[‡] Similarly, both the reactions conducted in 1,4-dioxane and DMF proceeded smoothly to yield 4,6-diol in high yields (entries 5 and 6). However, in less polar $CH_2Cl_2$, the yield of **5** diminished to 64% (entry 7). In entry 8, selenoamide **3**[7] was reacted with **4**. As a result, **3** did not cleave the CAc group at all; this suggests that the urea skeleton was critical for CAc group cleavage.

Next, we conducted a comparative experiment with selenourea **2** and other dechloroacetylating reagents. Thus, the dechloroacetylation of the C-2 axial position of disaccharide **6** was attempted with **2**, thiourea, DABCO, and 1-thiocarbamoylpiperidine (TCP)[8] (Table 2). Under the optimal conditions reported in the literatures,[1,4] thiourea and DABCO cleaved the CAc group in 41% and 91% yields, respectively (entries 1 and 2). Further, we confirmed that DABCO did not react with the CAc functionality in THF (entry 3). On the other hand, dechloroacetylations with selenourea **2** in refluxed THF and 1,4-dioxane proceeded smoothly to produce a monohydroxy compound **7** in 85% and 96% yields, respectively (entries 4 and 5). In the case of the corresponding thio-homolog TCP, the CAc group was cleaved in 39% yield (entry 6), suggesting that the high reactivity of **2** is endowed with a selenocarbonyl moiety.

In the next step, to examine the chemoselectivity of dechloroacetylation by selenourea **2**, several substrates bearing the CAc group with other acyl functionalities were reacted. The results are summarized in Table 3. The CAc group at the C4 hydroxyl of glucoside **8**, which was hampered by a bulky pivalate group at C6, was exclusively deprotected in high yield, and gratifyingly, a base-labile Fmoc group mounted on the C6 hydroxyl of glucoside **9** was also insusceptible to selenourea **2**, thus affording **13** in 90% yield (entries 1 and 2). Similarly, the CAc group within Fmoc-protected serine allyl

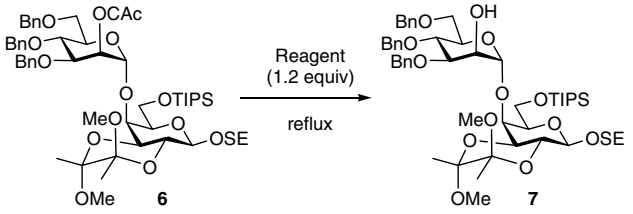
**Table 1.** Examination of dechloroacetylation of glucoside **4** with **2**




| Entry | Reagent[a] | Solvent | Base[b] | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **2** | THF | DIEA | rt | 19 | 81 |
| 2 | **2** | THF | — | rt | 24 | 99 |
| 3 | **2** | THF | DIEA | 50 | 3 | 88 |
| 4 | **2** | THF | — | 50 | 7 | 99 |
| 5 | **2** | Diox | — | 50 | 6 | 95 |
| 6 | **2** | DMF | — | 80 | 6 | 90 |
| 7 | **2** | $CH_2Cl_2$ | — | 50 | 6 | 64 |
| 8 | **3** | THF | — | 50 | 6 | 0 |

DIEA = *N*,*N*-diisopropylethylamine.
Diox = 1,4-dioxane.
[a] 2.4 equiv for compound **4**.
[b] 2.4 equiv for compound **4**.

**Table 2.** Comparative experiment on dechloroacetylation



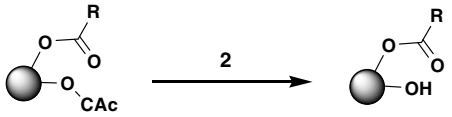

| Entry | Reagent | Solvent | Bath Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Thiourea | MeOH | 70 | 17 | 41 |
| 2 | DABCO | EtOH | 80 | 7 | 91 |
| 3 | DABCO | THF | 80 | 20 | 0 |
| 4 | **2** | THF | 80 | 8 | 85 |
| 5[a] | **2** | Diox | 110 | 7 | 96 |
| 6[a] | TCP | Diox | 110 | 15 | 39 |

SE = 2-(trimethylsilyl)ethyl.
TIPS = triisopropylsilyl.
DABCO = diazabicyclo[2.2.2]octane.
TCP = 1-thiocarbamoylpiperidine.
[a] 2.4 equiv of reagents was used.

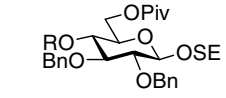
[†] Preparation of 1-selenocarbamoylpiperidine **2** (modified protocol of Ref. 5). *Step 1*: To a solution of 1-piperidinecarbonitrile (**1**; 1.5 mL, 10.0 mmol) in THF (100 mL), a 1 M solution of hydrogen chloride in diethylether (20.0 mL, 20.0 mmol) was added at 0 °C under an argon atmosphere; this mixture (mixture A) was stirred for 2 h. *Step 2*: To a suspension of black selenium powder (800 mg, 10.0 mmol) in THF (100 mL), lithium aluminum hydride (380 mg, 10.0 mmol) was added in portions at 0 °C under an argon atmosphere, and the suspension was stirred for 30 min. The suspension turned grayish. *Step 3*: To the stirred grayish suspension, mixture A was added dropwise at 0 °C. After stirring for 3 h, the reaction mixture was extracted with $CH_2Cl_2$, and the organic layer was washed with water, dried over $Na_2SO_4$, and concentrated. The resulted residue was crystallized from $CH_2Cl_2$ and $^n$Hex to give **2** as yellow crystals (~70%).

[‡] *Typical procedure of dechloroacetylation (the case of entry 4)*: To a solution of compound **4** (105 mg, 0.171 mmol) in THF (2.0 mL), **2** (78 mg, 0.410 mmol) was added, and the reaction mixture was stirred for 7 h at 50 °C and monitored by TLC (EtOAc/$^n$Hex = 2/3). The reaction mixture was filtered through Celite® and concentrated in vacuo. The resulting residue was chromatographed on silica gel (EtOAc/$^n$Hex = 1/3) to yield **5** (78 mg, 99%).

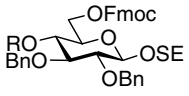
**Table 3.** Examination of chemoselective deprotection of CAc with **2**



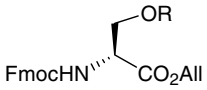

| Entry | Substrate | Equivalents of **2** | Solvent | Temp (°C) | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **8** | 1.2 | THF | 50 | 10 | **12** | 90 |
| 2 | **9** | 2.0 | Diox | 60 | 3 | **13** | 90 |
| 3 | **10** | 1.2 | THF | 70 | 8 | **14** | 99 |
| 4 | **11** | 1.2 | Diox | 100 | 5 | **15** | 99 |



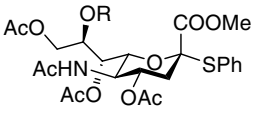

**8** R = CAc
**12** R = H




**9** R = CAc
**13** R = H




**10** R = CAc
**14** R = H

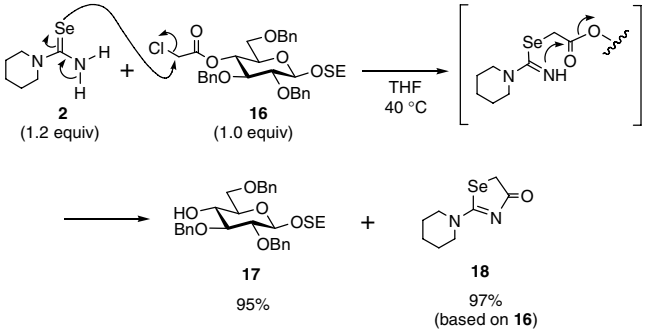



**11** R = CAc
**15** R = H

ester **10** was also cleanly deprotected to give **14** in an almost quantitative yield (entry 3). Further, CAc at the hindered C8 position of sialic acid **11** was also quantitatively cleaved in refluxed 1,4-dioxane without the cleavage and migration of acetyl groups, thereby producing 8-OH sialoside **15**, as indicated by the spectra of $^1$H NMR.[9]

Finally, we conducted the reaction of 4-*O*-CAc-glucoside **16** with **2** to discuss the reaction mechanism. This reaction concomitantly produced selenazolone derivative **18**[6] in the yield of 97%, with 4-OH glucoside **17** (95%) (Scheme 3). This result strongly suggests that dechloroacetylation by **2** proceeds via the cyclization mechanism.

In conclusion, we have demonstrated that **2** deprotects the *O*-CAc group with high chemoselectivity via the cyclization mechanism. The lipophilic piperidine moiety of **2** allowed the usage of DMF, THF, and 1,4-dioxane as reaction solvents. Moreover, **2** proved to be stable for three months when it was stored in a freezer. These features reinforce the application of **2** to the deprotection of the CAc group within lipophilic oligosaccharides.




**Scheme 3.** Proposed mechanism of dechloroacetylation with **2**.

## Acknowledgements

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9. (a) $^{1}$H NMR analysis showed the cleavage of the chloroacetyl group ($\delta$ 4.10; d, 2H) and the shift of H-8 from 5.04 to 4.10 ppm; (b) *NMR data of* **15**: $^{1}$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.51–7.32 (m, 5H, Ph), 6.10 (d, 1H, $J_{5,NH} = 9.8$ Hz, NH), 5.39 (td, 1H, $J_{3eq,4} = 4.6$, $J_{3ax,4} = J_{4,5} = 11.4$ Hz, H-4), 5.14 (dd, 1H, $J_{6,7} = 5.8$, $J_{7,8} = 1.7$ Hz, H-7), 4.66 (dd, 1H, $J_{5,6} = 10.3$ Hz, H-6), 4.10 (m, 4H, H-5, H-9, H-9, H-8), 3.56 (s, 3H, COOMe), 2.69 (dd, 1H, $J_{gem} = 13.7$ Hz, H-3eq), 2.13, 2.08, 2.04, and 1.93 (4s, 12H, 4Ac); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.2, 171.1, 171.0, 170.5, 168.0, 135.8, 129.7, 129.4, 129.0, 89.2, 72.5, 70.6, 69.2, 69.1, 65.8, 52.6, 49.5, 37.8, 23.1, 20.9.