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A new strategy for chemoselective O-acylation of β-mercapto alcohols via alkylsilyl and stannyl protection

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ABSTRACT

Chemoselective preparation of O-acylated derivatives from bis-protected mercapto alcohols was described. Trialkylsilyl and trialkylstannyl chloride are used to generate an intermediate with O- and S-protection. The intermediates from β-mercapto alcohols are reactive toward acylating agents and selective to provide O-acylated derivatives. The present preparation involves the direct conversion of alcohol to the corresponding O-acylated compounds without deprotection.

1. Introduction

Protection of functional groups is one of the most important and widely carried out synthetic transformations in preparative organic chemistry.[1] We sought to prepare functional methacrylate and acrylate polymers used in a large number of applications[2a] including attachable of metal or semiconductors nanoparticle.[2b,c] Molecules bearing free-SH are considered important protectors against radiation-induced damage to DNA[3a] by gamma[3b] and fast neutron radiation.[3c] If tumor cells absorb fewer drugs than the normal ones, thiol compounds can be used in cancer radiotherapy.[3d]

Moreover, these compounds are also employed in cosmetic preparations to reduce actinic damage to human skin due to over-exposure to sunlight.[3e] The thiol group can involve in a radical reaction so that chemical protection is often required during acrylic polymerization.[3f] The selective O- or S-acylation of mercapto alcohols is synthetically important but there are few examples in the literature.[4a–m] The typical example of selective O-acylation involves acid-catalyzed esterifications of alcohols with thiolcarboxylic acids.[4a,b] Selective O-acylation of mercaptoethanol with moderate yield was achieved with acetic acid in the presence of yttria-zirconia-based Lewis acid as a heterogeneous catalyst.[4c] In general, proton and Lewis acid-catalyzed thioesterifications are disfavored by lower equilibrium constants between carboxylic acids and thioesters as well as a higher energy transition state.[4d] Sometimes, S- or O-acylation via carbodiimide couplings selectively occurred depending on carboxylic acids.[4e,f] Lipase-catalyzed acylations of β-mercapto alcohols also reported.[4g,h] The chemoselectivity of these reactions is probably enzyme-specific as lipase-catalyzed esterifications and transesterifications have been successfully in the selective acylation of various kinds of polyfunctional compounds such as sugars and aminoalcohols.[4i–m] However, many of these selective methods present low yields depending on alcohols, poor regioselectivity, and harsh catalytic conditions. Therefore, the development of convenient, mild, and high yielding approaches to the selective O-acylation was still desirable and much in demand.

2. Results and discussion

In this Letter, we wish to report a new strategy and simple procedure for chemoselective O-acylation of mercaptoethanol and mercaptophenol using protective groups such as trialkyl/triphenyl silyl and stannyl groups. To begin with, we studied β-mercaptoethanol that was simply treated with one equivalent of acrylating agents in the presence of Et_3N and it was found that S-acrylation preferentially occurred (Scheme 1). The acrylation proceeded inefficiently to afford low isolating yields and it was partly due to further thiol reaction such as olefinic addition. The similar reaction of acetic anhydride with β-mercaptoethanol exhibited O-acetylation in major with minor S-acetylation. While opposite selectivity of β-mercaptoethanol was resulted according to acylating agents, the selectivity was not high as shown in Scheme 1.[5]

Alkylsilyl protection groups of alcohols are stable under conventional basic reaction conditions. Recently, we observed

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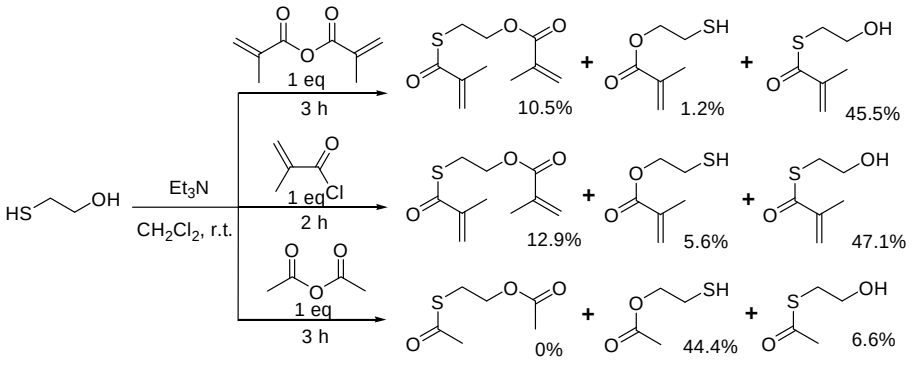
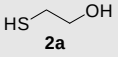
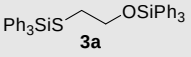
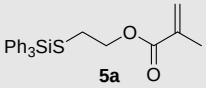
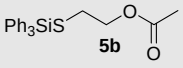
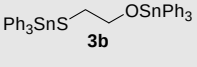
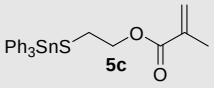
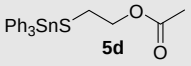
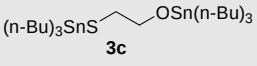
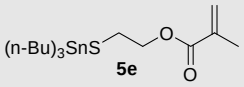
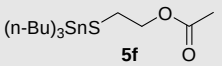
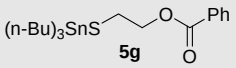
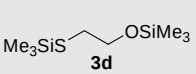
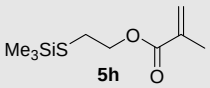


Scheme 1.

that protected β-mercaptoethanols were found to be reactive and selectively converted into O-acylated products. When triphenylsilyl protected mercaptoethanol was treated with methacrylic anhydride, it converted to O-acrylated product in high yield. S-acrylation product was not detected. Similar selective results were found with methacrylic chloride and acetic anhydride with quantitative yields. The reaction presumably involves nucleophilic attack of protected alkoxy groups. Thus, our attention shifts to stannyl protection which increases the attacking reactivity of alkoxy group. We prepared bis-(O,S-triphenylstannyl)-2-mercaptoethanol (**3b**) from β-mercaptoethanol (**2a**) and triphenylstannyl chloride in the presence of Et_3N with 99% conversion within 1 h. The resultant compound **3b** was in situ O-acylated with methacrylic anhydride (**4a**), methacrylic chloride (**4b**), and acetic anhydride (**4c**) with excellent yields at room temperature as shown in Table 1 (entries 4–6). This method involves the direct conversion to corresponding O-acylated compounds without deprotection. High selectivity and conversions are summarized in Table 1.

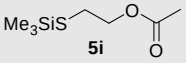
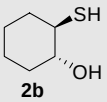
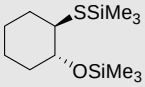
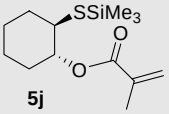
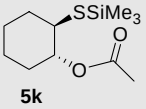
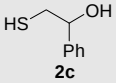
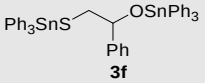
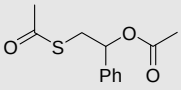
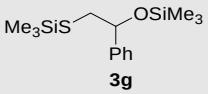
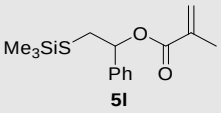
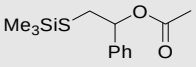
To study the applicability of this new method, we have prepared several bis-protected β-mercaptoethanol including tributyl-

Table 1
Selective O-acylation of several β-mercapto alcohols with acylating agents

Entry	Mercapto alcohols	Intermediate	Acylating agent[a]	Product	Time (h)	Yield[b] (%)
1	 **2a**	 **3a**	**4a**	 **5a**	3	97
2	**2a**	**3a**	**4b**	**5a**	1	99
3	**2a**	**3a**	**4c**	 **5b**	2	98
4	**2a**	 **3b**	**4a**	 **5c**	3	99
5	**2a**	**3b**	**4b**	**5c**	1	98
6	**2a**	**3b**	**4c**	 **5d**	2	97
7	**2a**	 **3c**	**4a**	 **5e**	3	90
8	**2a**	**3c**	**4b**	**5e**	1	93
9	**2a**	**3c**	**4c**	 **5f**	4	97
10	**2a**	**3c**	**4d**	 **5g**	3	97
11	**2a**	 **3d**	**4a**	 **5h**	12	16
12	**2a**	**3d**	**4b**	**5h**	6	18

(*continued on next page*)

Table 1 (*continued*)

Entry	Mercapto alcohols	Intermediate	Acylating agent[a]	Product	Time (h)	Yield[b] (%)
13	**2a**	**3d**	**4c**	 **5i**	12	21
14	 **2b**	 **3e**	**4a**	 **5j**	8	27 (35)
15	**2b**	**3e**	**4b**	**5j**	6	30 (30)
16	**2b**	**3e**	**4c**	 **5k**	8	32 (30)
17	 **2c**	 **3f**	**4c**	 **6**	2	45 (36)
18	**2c**	 **3g**	**4a**	 **5l**	6	34 (40)
19	**2c**	**3g**	**4b**	**5l**	5	38 (30)
20	**2c**	**3g**	**4c**	 **5m**	6	35 (33)

The structures of the products were determined from spectral (IR and ^{1}H NMR) data.

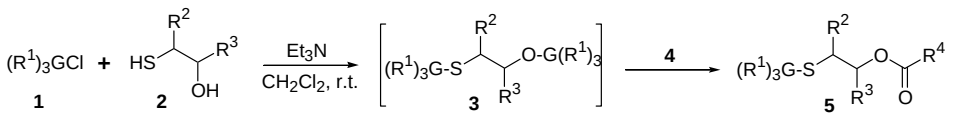
[a] Compounds **4a**, **4b**, **4c,** and **4d** represent methacrylic anhydride, methacrylic chloride, acetic anhydride, and benzoyl chloride, respectively.

[b] Isolated yield after purification by flash column chromatography. The parentheses contain recovered intermediate yield.

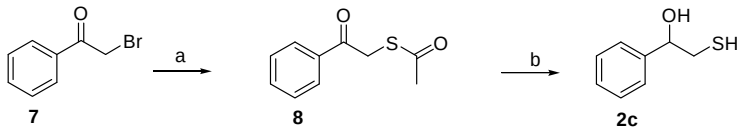
stannyl (**3c**) and trimethylsilyl (**3d**) groups. By treating with **4a**, **4b,** and **4c** they generated only O-acylated products (Scheme 2). Tributylstannyl chloride produced quantitatively O-acylation products, but trimethylsilyl chloride afforded low yields of O-acylated products even in prolonged reaction times in Table 1 (entries 11–13). The reaction of benzoyl chloride with **3c** also yielded O-benzoyl compound **5g** (entry 10). Furthermore, *trans*-1-mercaptocyclohexane-2-ol (**2b**), prepared from cyclohexene oxide and sulfurated sodium borohydride,[6] underwent selective O-acylation via corresponding bis-trimethylsilyl derivative **3e**, which was recovered to give low conversion yield after acylation.

In continuation, we have prepared a substituted mercaptoethanol, 2-mercapto-1-phenylethanol (**2c**) prepared through $LiAlH_4$ reduction of thioacetyl acetophenone (**8**) derived from phenacyl bromide in Scheme 3. Mercaptoethanol (**2c**) was easily converted to bis-triphenylstannyl (**3f**) and bis-trimethylsilyl derivatives (**3g**). The reaction of stannyl derivative (**3f**) in situ with acetic anhydride resulted in the formation of diacetylated product (**6**) as shown in Table 1 (entry 17) with no expected O-acetylated product. This was overcome with trimethylsilyl chloride (entries 18–20). In spite of low product yields, mono-S-acylation derivative was not found.

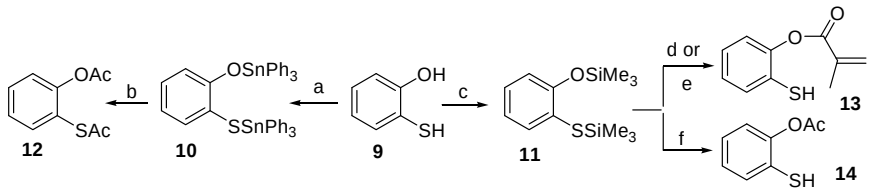
Finally, we studied the selective reaction with aromatic mercapto alcohol. *o*-Mercapto phenol (**9**) was prepared from the reaction of a diazotization product of *o*-aminophenol and potassium ethylxanthate.[7] Triphenylstannyl derivative **10** formed a diacetylated product (**12**) with acetic anhydride, while trimethylsilyl derivative (**11**) underwent selective O-acylation. Deprotection



Scheme 2.



Scheme 3. Reagents and conditions: (a) thioacetic acid, DMF, K_2CO_3, rt, 2 h, 71%; (b) $LiAlH_4$, Ether, rt, 1 h, 62%.



Scheme 4. Reagents and conditions:[8] (a) Ph_3SnCl, CH_2Cl_2, Et_3N, rt, 1 h, 95%; (b) **4c**, 3 h, 30%; (c) Me_3SiCl, CH_2Cl_2, Et_3N, rt,1 h, 95%; (d) **4a**, 5 h, 40%; (e) **4b**, 4 h, 50%; (f) **4c**, 6 h, 46%.

occurred during isolation to give free –SH of O-acylated products (**13** and **14**) with moderate yields (Scheme 4). Unreacted intermediate (**11**) was recovered with 30–40%.

The acylation of triphenylsilyl alcohol was unique for β-mercapto alcohol and did not occur with 6-mercaptohexyl alcohol or 4-mercaptomethylbenzyl alcohol of remote functionalities. Thus, the exceptional reactivity and selectivity of β-mercapto alcohol seem to be due to the assistance of a neighboring sulfur.

3. Conclusion

We have developed a simple and efficient method for the chemoselective O-acylation of several mercapto alcohols via bis-protective derivatives using alkyl/arylsilyl and stannyl groups. The reaction underwent only with β-mercapto alcohols to give O-acrylated or O-acetylated products. One-step synthesis, high conversion, and impressive chemoselectivity are the noteworthy advantages of present protocol.

Acknowledgments

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5. The reason of the opposite selectivity is not clear. The possibility of intramolecular acyl rearrangement was excluded because isolated two products of *O*-acetyl and *S*-acetyl did not interconvert in methylene chloride containing triethylamine.
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8. *General procedure for the preparation of O-acylation derivatives*: To a solution of a mercapto alcohol (**2**, **9**) (1.0 mmol) in CH_2Cl_2 (3.0 mL), triphenylsilyl chloride (2.2 mmol) and Et_3N (2.1 mmol) were added and stirred for appropriate time at room temperature. After complete disappearance of starting material as indicated by TLC, a solution of acylating agent (**4**) (1.0 mmol) was added. The progress of the reaction was monitored by TLC, and upon completion the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2. The organic portion was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography to give the corresponding O-acylated product in moderate to high yields. The spectral (IR and ^1H NMR) data of some of the representative compounds are given below.
Compound **5a**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.97 (s, 3H), 3.19 (t, 2H, J = 6.3 Hz), 3.94 (t, 2H, J = 7.2 Hz), 5.59 (s, 1H), 6.08 (s, 1H), 7.38–7.49 (m, 10H), 7.63–7.67 (m, 5H). *Compound* **5b**: ^1H NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H), 3.12 (t, 2H, J = 6.3 Hz), 3.92 (t, 2H, J = 6.3 Hz), 7.38–7.49 (m, 10H), 7.62–7.66 (m, δ 5H). *Compound* **5c**: ^1H NMR ($CDCl_3$, 300 MHz): 1.96 (s, 3H), 2.84 (t, 2H, J = 6.9 Hz), 4.14 (t, 2H, J = 7.2 Hz), 5.53 (s, 1H), 6.05 (s, 1H), 7.42–7.48 (m, 10H), 7.65–7.69 (m, 5H). *Compound* **5d**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.85 (s, 3H), 2.81 (t, 2H, J = 6.9 Hz), 4.08 (t, 2H, J = 6.9 Hz), 7.44–7.47 (m, 10H), 7.64–7.69 (m, 5H). *Compound* **5e**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 9H, J = 7.2 Hz), 1.16 (t, 6H, J = 8.1 Hz), 1.34 (q, 7H, J = 7.5 Hz), 1.51–1.59 (m, 5H), 1.94 (s, 3H), 2.77 (t, 2H, J = 7.5 Hz), 4.17 (t, 2H, J = 7.5 Hz), 5.55 (s, 1H), 6.11 (m, 1H). *Compound* **5f**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, 9H, J = 7.2 Hz), 1.15 (t, 6H, J = 8.1 Hz), 1.34 (q, 7H, J = 7.2 Hz), 1.51–1.59 (m, 5H), 2.05 (s, 3H), 2.74 (t, 2H, J = 7.2 Hz), 4.10 (t, 2H, J = 7.2 Hz). *Compound* **5g**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.92 (t, 9H, J = 7.2 Hz), 1.19 (t, 6H, J = 6.6 Hz), 1.33 (q, 6H, J = 7.5 Hz), 1.53–1.65 (m, 6H), 2.89 (t, 2H, J = 7.2 Hz), 4.37 (t, 2H, J = 7.8 Hz), 7.41–7.47 (m, 2H), 7.53–7.59 (m, 1H), 8.04–8.08 (m, 2H). *Compound* **5h**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 9H), 1.98 (s, 3H), 3.10 (t, 2H, J = 6.6 Hz), 3.73 (t, 2H, J = 6.6 Hz), 5.59 (s, 1H), 6.09 (s, 1H). *Compound* **5k**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.09 (s, 9H), 1.34–1.49 (m, 4H), 1.81–1.89 (m, 4H), 2.08–2.12 (m, 1H), 2.31 (s, 3H), 3.42–3.49 (m, 1H). *Compound* **5m**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 9H), 2.34 (s, 3H), 3.01–3.19 (m, 2H), 4.71–4.78 (m, 1H), 7.33–7.36 (m, 5H). *Compound* **13**: IR (KBr): ν_{max} 2925, 2854, 2361, 1741, 1434, 1377, 1201, 946 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.09 (s, 3H), 2.99 (s, 1H), 5.57 (s, 1H), 6.40 (s, 1H), 7.15–7.24 (m, 2H), 7.29 (d, 1H, J = 8.7 Hz), 7.60 (dd, 1H, J = 8.1 Hz). *Compound* **14**: IR (KBr): ν_{max} 2924, 2855, 2361, 1769, 1464, 1368, 1186, 1058, 952 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.33 (s, 3H), 7.15–7.24 (m, 2H), 7.30 (d, 1H, J = 7.8 Hz), 7.59 (dd, 1H, J = 7.8 Hz).