Bulky Thiols and Their Coordination Compounds. An Improvement of the Removal Method of Tetrahydropyranyl Group from Thiols and Its Application for Ligand Syntheses

Hideaki Watanabe, Seiji Ogo,† and Takeshi Yamamura*
Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo 162
†*Department of Applied Molecular Science, Institute for Molecular Science, Myodaiji, Okazaki 444*

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The route for the syntheses of alkanthiols having bulky groups at the neighborhood of sulfur atoms was improved, and applied for the preparation of thiol ligands that mimic the cysteine containing metal binding sites in proteins. The new method developed the deprotection of tetrahydropyranyl group from α,α-diphenylalkyl 2-tetrahydropyranyl sulfides.

Models for the active sites of metalloenzymes are effectively achieved using the coordination compounds in which the inorganic centers are placed in the cavities that mimic the pockets of the enzymes. However, this strategy confronts with significant difficulties for the cases of cysteine containing active sites of proteins. For this purpose we need to confine thiols to the cavities made of large organic skeletons, or to cover the sulfur atoms with bulky groups at their neighborhoods. Although several papers have so far been reported on the syntheses of bioinorganic models with bulky thiol ligands,[1, 2] little is known for those involving multidentate types of bulky thiol ligand.

Berg and Holm introduced diphenylmethanethiol[3] protected by 2-tetrahydropyranyl (THP) group[4] in order to obtain a tridentate NS_2 type of bulky thiol ligand for the modeling of the active site of a molybdenum enzyme.[5] Although they achieved a good yield of THP deprotection for their system (in situ, 92 %), we found that their method using $AgNO_3/H_2S$ for the removal of THP[3,4] was not available to the other multidentate cases shown later, giving low yields (less than 30 %) and a lot of byproducts such as olefinic and alkoxy compounds, or giving indefinable mixtures of more than 10 species. Trials by other known methods[4,6,7] were also unsuccessful. Thus, we searched for several acids considering that thiols protected by THP are classified into hemithioacetal (see the scheme), and that C-O bonds in acetals are easily cleaved by acids.[7] By this search, we found that the combination of boron trifluoride (BF_3), 2-mercaptoethanol ($HSCH_2CH_2OH$), and triethylamine (NEt_3)

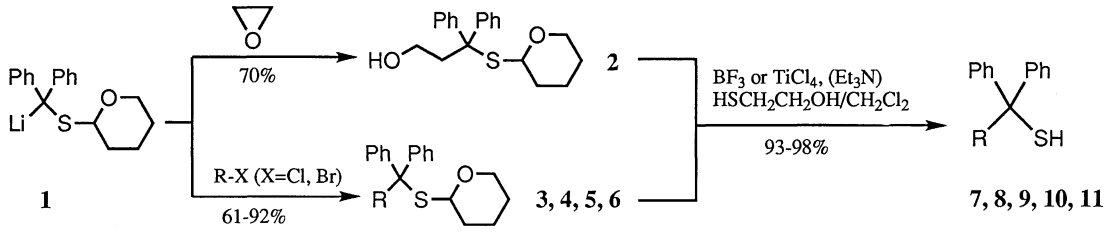
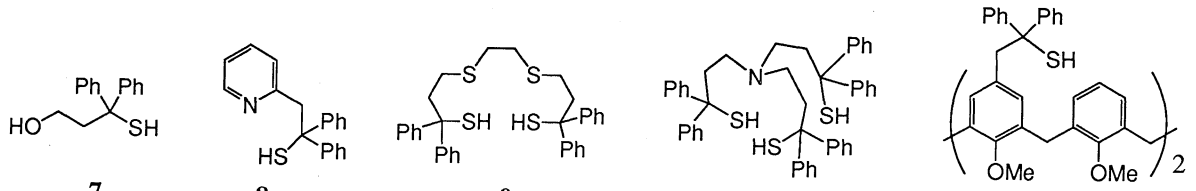


Figure 1. Synthetic scheme for bulky thiol ligands

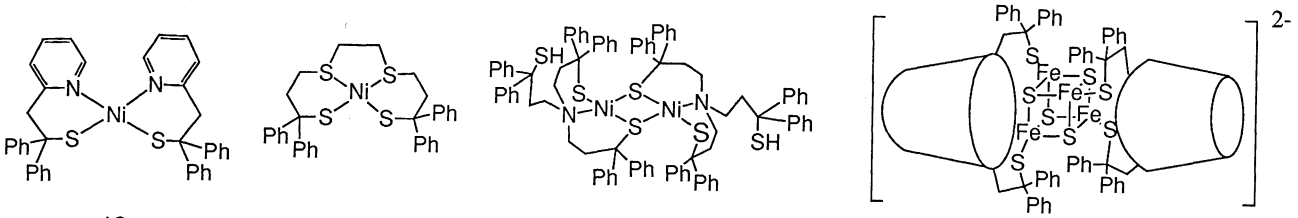
Table 1. Reaction conditions examined for the removal of 2-tetrahydropyranyl group from **6**

entry No	condition[a]	solvent	time (h)	precursor	product	yield (%)[b, c]
1	$AlCl_3$=1.0	toluene	0.1	**6**	**11**[d]	12[b]
2	$AlCl_3/HSCH_2CH_2OH$=2/10	toluene	24	**6**	**11**[e]	5[b]
3	$AlCl_3/HSCH_2CH_2OH/NEt_3$=2.0/50/2.6	toluene	14	**6**	---[f]	12[b]
4	BF_3=1.9	$CHCl_3$	0.5	**6**	**11**[g]	31[b]
5	BF_3=1.9	THF	39	**6**	---[f]	---
6	BF_3=1.8	$THF/CHCl_3$=5/95	17	**6**	**11**[h]	12[b]
7	BF_3/NEt_3=2/5	CH_2Cl_2	17	**6**	---[f]	---
8	$BF_3/HSCH_2CH_2OH$=2/10	CH_2Cl_2	0.5	**6**	**11**	93[b]
9	$BF_3/HSCH_2CH_2OH/NEt_3$=2.0/50/2.6	CH_2Cl_2	1	**6**	**11**	97[c]
10	$TiCl_4$=1.8	CH_2Cl_2	0.2	**6**	**11**[i]	32[b]
11	$TiCl_4/NEt_3$=2/5	CH_2Cl_2	2.5	**6**	---[j]	---
12	$TiCl_4/HSCH_2CH_2OH$=2/10	CH_2Cl_2	1.2	**6**	**11**[d]	69[b]
13	$TiCl_4/HSCH_2CH_2OH/NEt_3$=1.9/50/2.5	CH_2Cl_2	17	**6**	**11**	98[c]

[a] The numbers represent the molar ratio of the reagents per 2-tetrahydropyranyl group. [b] Conversion yield by HPLC. [c] Isolation yield. [d] Many byproducts were observed. [e] 61% of **6** was recovered. 26% yield for half deprotected compound. [f] No reaction. [g] 53% yield for bis-olefinic compound. [h] 18% of **6** was recovered. 31% yield for half deprotected compound. No olefinic compound. [i] No olefinic compound. [j] 8% yield for olefinic compound with many other byproducts.



7 8 9 10 11



12 13 14 15

effectively works for THP deprotection yielding almost equimolar amount of target thiols. Titanium (IV) tetrachloride ($TiCl_4$),[8] was also available instead of BF_3. This success owes to the use of $HSCH_2CH_2OH$, which prevents the sulfur elimination, whereas NEt_3 suppresses the generation of fine concomitants observed in HPLC charts. BF_3 was 5 to 10 times superior to $TiCl_4$ in reaction time. On the contrary, $AlCl_3$, which achieved small yields by itself, was almost quenched by $HSCH_2CH_2OH/NEt_3$. For example, the deprotection of 3,3-diphenyl-3-[(2-tetrahydropyranyl)thio]propanol, **2**, to 3,3-diphenyl-3-mercapto-1-propanol, **7**, was performed at room temperature adding dropwise $TiCl_4/CH_2Cl_2$ to $2/CH_2Cl_2$ in the presence of $HSCH_2CH_2OH$ and NEt_3. The reaction was continued 15 hr and quenched by 1M HCl aq. solution. The target compound was extracted from $CHCl_3$.

Figure 1 schematically exhibits the reactions we performed for the syntheses of the OS, NS, S_2, NS_3, and S_4 ligands of our bioinorganic use. Table 1 summarizes the reaction conditions for the deprotection of **6** as the representative. The analytical data, ^1H NMR assignments, mass numbers, purities, and yields of **7**, **8**, **9**, **10**, and **11** are given in the note.[9]

12-**15** are the coordination compounds prepared from **8**- **11**, respectively. Among these, **13** was previously prepared by our group via $AgNO_3/H_2S$ deprotection.[2b] The details for **12**, **14**, and **15** will be published elsewhere.

References and Notes

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9 **7** Found: C, 72.65; H, 6.98; N, 0%. M^+, 251 and 267. Calcd for $C_{15}H_{16}OS \cdot 1/4H_2O$: C, 72.40; H, 6.68; N, 0%. $[M{\cdot}Li]^+$ and $[M{\cdot}Na]^+$, 251 and 267. ^1H NMR (270 MHz; $CDCl_3$) δ 7.20-7.39 (10H, m, ArH), 3.64 (2H, t, CH_2) , 2.79 (2H, t, CH_2), 2.37 (1H, s, SH), and 1.62 and 1.66 (2H, OH+H_2O). putrity > 99%. yield 98%.
8 Found: C, 67.72; H, 5.96; N, 4.27%. M^+, 292. Calcd for $C_{19}H_{17}NS \cdot HCl \cdot 1/2H_2O$: C, 67.74; H, 5.69; N, 4.16%. $[M{\cdot}H]^+$, 292. ^1H NMR (270 MHz; $CDCl_3$): δ 8.69 (1H, d, py-6-H) , 7.94 (1H, t, py-4-H), 7.73 (1H, t, py-5-H), 7.24-7.37 (10H, m, ArH), 6.47 1H, d, py-3-H), 4.51 (2H, s, CH_2), and 3.48 (1H, s, SH). purity > 99%. yield 93%.
9 Found: C, 68.84; H, 6.69; N 0%. M^+, 546. Calcd for $C_{32}H_{34}S_4 \cdot 1/2H_2O$: C, 69.14; H, 6.35; N 0%. M^+, 546. ^1H NMR (270 MHz; $CDCl_3$): δ 7.12-7.27 (10H, m, ArH) , 2.61-2.64 2.30-2.34 (4H, m, $SCH_2CH_2CPh_2$), 2.49 (2H, s, SCH_2CH_2S), and 2.15 (1H, s, SH). purity>99%. yield 97%.
10 Found: C, 71.96; H, 6.64; N, 1.85%. M^+, 696. Calcd for $C_{45}H_{45}NS_3 \cdot HCl \cdot H_2O$: C, 72.01; H, 6.45; N, 1.87%. $[M{\cdot}H]^+$, 696. ^1H NMR (270 MHz; $CDCl_3$): δ 7.16-7.34 (10H, m, ArH), 2.66 (1H, s, SH), and 2.25-2.46 (4H, m, CH_2). purity > 95%. yield 93%.
11 Found: C, 76.90; H, 6.34; N, 0%. M^+, 927. Calcd for $C_{60}H_{56}O_4S_2 \cdot 2H_2O$: C, 76.56; H, 6.45; N, 0%. $[\mathbf{11}{\cdot}Na]^+$, 927. ^1H NMR (500 MHz; $CDCl_3$): δ 7.4-6.4, 6.03, 5.34 (30H, ArH), d 4.15, 3.86, 3.73, 2.88, 2.80 (8H, $ArCH_2Ar$), d 3.73, 3.56, 6.69 (12H, OMe), d 3.51, 3.46 (4H, $ArCH_2$), and d 2.34, 1.93 (2H, SH). purity > 98%. yield 98%.