Chemo-, regio- and stereoselective preparation of silyl enol ethers from thiol esters and bis(iodozincio)alkane†

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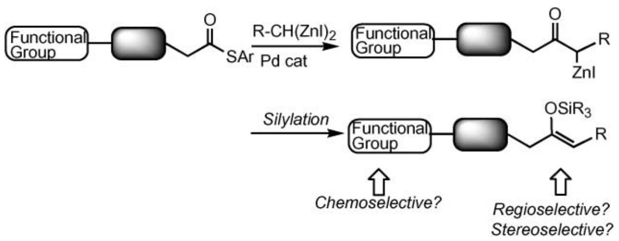
Treatment of thiol ester with bis(iodozincio)alkane in the presence of palladium catalyst followed by silylation affords *Z*-silyl enol ether chemo-, regio- and stereoselectively.

While silyl enol ethers have been important reagents especially for cross-aldol reactions,[1] the selective preparation of those compounds are still challenging. For example, their regioselective preparations from 2-hexanone can be performed easily by adapting thermodynamic or kinetic control.[2] On the contrary, it is not so easy to realize the regioselective preparation from an internal ketone, such as 3-hexanone. An alternative route to get the corresponding product may provide a solution in one case,[3] but a more general method, which would also lead to further selectivities such as chemo- and stereoselectivities possible, is desirable. We had reported a series of synthetic applications of a *gem*-dizinc reagent. As the *gem*-dizinc reagent can achieve zincioalkylation by a single cross-coupling reaction, it gives a route to prepare an organozinc reagent through homologation of an electrophile.[4] We had also shown that the palladium-catalyzed cross-coupling reactions of bis(iodozincio)methane with several thiol esters affords the zinc enolate selectively which corresponds to the terminal enolate of methyl ketone.[5,6] In this communication, we report on the chemo-, regio- and stereoselective preparation of silyl enol ethers based on the cross-coupling reaction of *gem*-dizincioalkane and various thiol esters (Scheme 1).

As shown in Table 1, thiol ester **1** was treated with *gem*-dizincioalkanes **2**[7] in the presence of palladium catalyst and the mixture were quenched with various silylation reagents. The palladium catalyst was prepared from Pd_2dba_3 and tris(2-furyl)phosphine in THF. The molar ratio of phosphine to palladium was tuned to 2 : 1.‡ Silyl triflate gave the best yield among the used silylation reagents. The reactions of 1,1-bis(iodozincio)ethane (**2b**)[7] caused some interest in the *E*/*Z*-selectivities of the formed enolate **3**. Use of *tert*-butyldimethylsilyl chloride, cyanide and triflate gave the *Z*-enolate more diastereoselectively (runs 2, 7, 9 and 11).



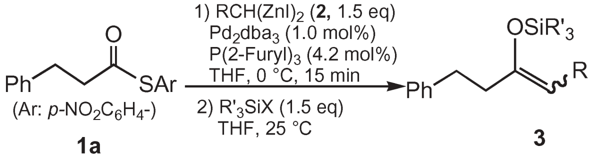
Scheme 1 Selective preparation of silyl enol ether based on cross-coupling of *gem*-dizinc reagent with thiol ester.

As shown in Table 2, various thiol esters were examined for the preparation of silyl enol ethers as starting materials. Thiol esters carrying terminal alkyne (run 2), ester (runs 5, 9), or aryl bromide (runs 8, 10), were transformed into the corresponding silyl enol ethers in good yields. When 1,1-bis(iodozincio)ethane was used, the produced silyl enol ethers had *Z*-configuration exclusively.[8]

The preparation of a silyl enol ether which carries a keto group in the same molecule is one of the most difficult applications of this method. As shown in Scheme 2, several thiol esters carrying keto groups were treated with bis(iodozincio)methane and the palladium catalyst in the presence of chlorotrimethylsilane. The thiol esters[9] were converted into the corresponding silyl enol ethers.

The reaction pathway can be explained as shown in Scheme 3. The palladium-catalyzed cross-coupling reaction of thiol ester and *gem*-dizinc will afford an α-zincioketone regio- and chemoselectively. The isomerization of the α-zincioketone to zinc enolate may give the sterically less hindered *Z*-enolate stereoselectively, which will be trapped with silylation reagent.

Table 1 Use of various silylation reagents[a]



1a **3**

Run	$RCH(ZnI)_2$	R'_3SiX	Yield[b] (%)	*Z* : *E*
1	$CH_2(ZnI)_2$	Me_3SiCl	96	—
2	$CH_3CH(ZnI)_2$	Me_3SiCl	93	79 : 21
3	$CH_2(ZnI)_2$	Me_3SiCN	92	—
4	$CH_2(ZnI)_2$	Me_3SiOTf	>99	—
5	$CH_2(ZnI)_2$	$PhMe_2SiCl$	34	70 : 30
6	$CH_2(ZnI)_2$	t-$BuMe_2SiCl$	32	—
7	$CH_3CH(ZnI)_2$	t-$BuMe_2SiCl$	34	96 : 4
8	$CH_2(ZnI)_2$	t-$BuMe_2SiCN$	92	—
9	$CH_3CH(ZnI)_2$	t-$BuMe_2SiCN$	60	93 : 7
10	$CH_2(ZnI)_2$	t-$BuMe_2SiOTf$	89	—
11	$CH_3CH(ZnI)_2$	t-$BuMe_2SiOTf$	72	93 : 7

[a] Thiol ester (2.0 mmol), dizinc (0.5 M in THF, 3.0 mmol), R'_3SiX (3.0 mmol), Pd_2dba_3 (0.02 mmol) and phosphine (0.84 mmol) were used. [b] Yields were determined by ^1H NMR using bromoform as an internal standard. The product was also isolated by bulb-to-bulb distillation in runs 1–4, and by short silica gel column chromatography in runs 5–11.

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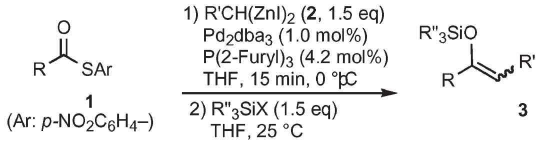
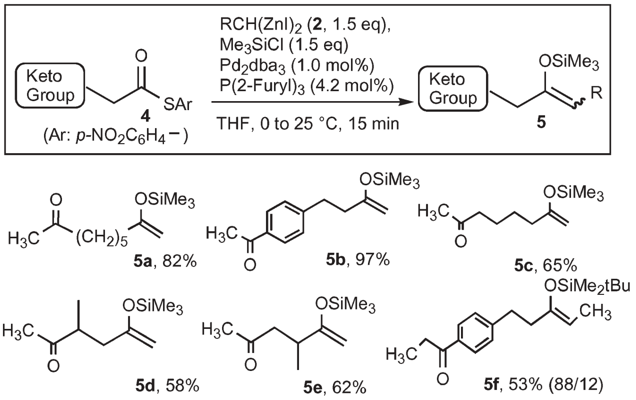
Table 2 Preparation of silyl enol ethers from various thiol esters[a]

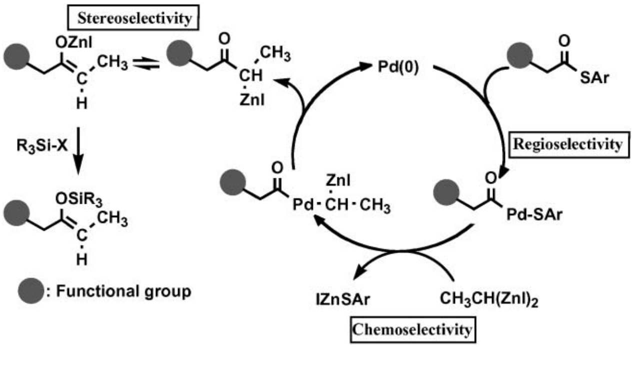


Run	R	$R'CH(ZnI)_2$	R''_3SiX	Product[b,c]
1	$H_2C{=}CH(CH_2)_3$–	$CH_2(ZnI)_2$	Me_3SiCl	94 (**3c**)
2	$HC{\equiv}C(CH_2)_3$–	$CH_2(ZnI)_2$	Me_3SiCl	94 (**3d**)
3	Ph–	$CH_2(ZnI)_2$	Me_3SiCl	70 (**3e**)
4	$PhCH_2SCH_2$–	$CH_2(ZnI)_2$	Me_3SiCl	79 (**3f**)
5	$EtO_2C(CH_2)_5$–	$CH_2(ZnI)_2$	Me_3SiCl	96 (**3g**)
6	$PhO(CH_2)_{10}$–	$CH_2(ZnI)_2$	Me_3SiCl	79 (**3h**)
7	$Br(CH_2)_7$–	$CH_2(ZnI)_2$	Me_3SiCl	88 (**3i**)
8	*p*-$BrC_6H_4(CH_2)_2$–	$CH_2(ZnI)_2$	Me_3SiCl	76 (**3j**)
9	$EtO_2C(CH_2)_5$–	$CH_3CH(ZnI)_2$	*t*-$BuMe_2SiOTf$	67 (**3k**, 93 : 7[d])
10	*p*-$BrC_6H_4(CH_2)_2$–	$CH_3CH(ZnI)_2$	*t*-$BuMe_2SiOTf$	65 (**3l**, 93 : 7[d])
11	$CH_3CH_2CH_2$–	$CH_3CH(ZnI)_2$	*t*-$BuMe_2SiOTf$	58 (**3m**, 95 : 5[d])
12	$H_2C{=}CH(CH_2)_3$–	$CH_3CH(ZnI)_2$	*t*-$BuMe_2SiOTf$	66 (**3n**, 90 : 10[d])

[a] Thiol ester (2.0 mmol), dizinc (0.5 M in THF, 3.0 mmol), R''_3SiX (3.0 mmol), Pd_2dba_3 (0.02 mmol), and phosphine (0.84 mmol) were used. [b] Yields (%) were determined by ^1H NMR using bromoform as an internal standard. The product was also isolated by bulb-to-bulb distillation in runs 1–8 and by short silica gel column chromatography in runs 9–12. [c] The reaction period after an addition of R''_3SiX was as follows: 15 min for runs 1–8; 6 h for runs 9–12. [d] *Z* : *E* Ratio of the product.



Scheme 2 Preparation of silyl enol ether carrying keto group.



Scheme 3 Plausible pathway of the reaction.

The method mentioned above is quite an easy and efficient procedure to produce silyl enol ethers regio-, chemo- and stereoselectively. The synthetic utility of silyl enol ethers has already been emphasized.[1–3] The cross-coupling reaction by a *gem*-dizinc reagent is a convenient method to introduce C–metal bonding highly selectively. Such an introduction is not easily performed by conventional halogen–metal exchange or deprotonation reactions.

Notes and references

‡ *Gem*-dizinc reagents **2** were prepared as a THF solution following the procedure of ref. 7. The thiol esters were obtained from a mixed anhydride and a thiol following the reported procedure.[9]

Preparation of **3**: Tri(2-furyl)phosphine (0.082 mmol) in THF (1.0 mL) was added at 25 °C to a solution of Pd_2dba_3 (0.02 mmol) in THF (1.0 mL) and the mixture was stirred for 15 min. 1,1-Bis(iodozincio)ethane in THF (**2b**, 0.40 M, 3.0 mmol) and *p*-nitrobenzene thiol ester of carboxylic acid (**1**, 2.0 mmol, 0.18 g) in THF (1.0 ml) were added subsequently at 0 °C. The resulting mixture was stirred for 15 min at the same temperature. Silylation reagent (3.0 mmol) was added to the reaction mixture. The resulting mixture was stirred for 6 h at 25 °C. Et_3N (1.0 mL) was added to the mixture. A saturated aqueous solution of sodium bicarbonate (5.0 mL) was added to the reaction mixture and the mixture extracted with diethyl ether. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, and dried over anhydrous sodium sulfate. After rapid column chromatography on silica gel with hexane–ethyl acetate as the eluent, **3** was obtained.

Preparation of **5**: To a solution of Pd_2dba_3 (0.02 mmol) in THF (1.0 mL), tri(2-furyl)phosphine (0.082 mmol) in THF (1.0 mL) was added at 25 °C. The mixture was stirred for 10 min. To this solution, chlorotrimethylsilane (3.0 mmol, 0.4 mL) and *p*-nitrobenzene thiol ester of keto acid (2.0 mmol) in THF (2.0 mL) were added subsequently at 0 °C and a solution of bis(iodozincio)methane in THF (**2a**, 0.40 M, 3.0 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 5 min at the same temperature and then stirred for an additional 15 min at 25 °C. Et_3N (1.0 mL) was added to the mixture. A saturated aqueous solution of sodium bicarbonate (5.0 mL) was added to the reaction mixture and the mixture extracted with diethyl ether. The combined organic layers were washed with brine, and dried over anhydrous sodium sulfate. The product was isolated by bulb-to-bulb distillation.

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