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Yield and Selectivity Enhancement by Trimethylsilyl Chloride in the Conjugate Addition of Stabilized Organolithiums

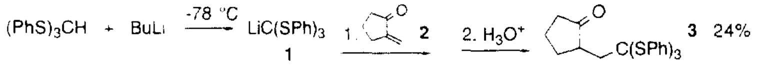
Hong Liu and Theodore Cohen*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Abstract: The yield and selectivity in the conjugate addition of some stabilized organolithiums to α,β-unsaturated carbonyl compounds, especially easily polymerized ones, are increased in the presence of trimethylsilyl chloride, alone or in combination with hexamethylphosphoric triamide. *E*-silyl enol ethers bearing the versatile phenylthio group are obtained prior to hydrolysis. Some synthetic uses are demonstrated.

Over 10 years ago it was reported that trimethylsilyl chloride (TMSCl) increases the rates and yields in the conjugate addition of cuprates to unsaturated carbonyl compounds.[1,2] This technique has become widely used[3] and has stirred controversy about the mechanism of this effect and the mechanism of cuprate conjugate additions in general.[2,3a,4] We now report what appears to be the first examples[5,6] of yield and selectivity enhancements due to the presence of TMSCl in the conjugate additions of organolithiums.

A new one-pot procedure for constructing five- and six-membered rings by the conjugate addition of a dilithiomethane synthon to two different enones followed by either the oxidative connection of the α-positions or an intramolecular aldol reaction of the two resulting enolates was developed in these laboratories.[7] Following the synthesis of the linear triquinane hirsutene, we attempted to extend this strategy to angular triquinanes by executing the conjugate addition of tris(phenylthio)methyllithium (**1**) to 2-methylenecyclopentanone (**2**). However, in contrast to the high yields in the conjugate addition of **1** to 2-cyclopentenone and 2-cyclohexenone, the yield in the conjugate addition of **1** to **2** is only 24% (eq. 1). Unreacted tris(phenylthio)methane and oligomeric by-products were isolated upon workup. After the reaction had been quenched with CH_3OD, the isolated conjugate adduct **3** was fully deuterated at the α-position and the recovered tris(phenylthio)methane was mainly deuterated indicating that enolization is not a factor.

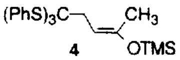


(1)

A dramatic yield enhancement was observed when **1** was treated with an equimolar mixture of **2** and TMSCl (Table 1, entry 1). The yellow color of **1** was quenched immediately upon the addition of this mixture. The yield was 75% in less than 1 min.

To explore the scope and limitations of the enhancement effect of TMSCl on the 1,4-addition of tris(phenylthio)methyllithium (**1**), we have undertaken a screening of various α, β-unsaturated carbonyl compounds using this new procedure and have compared the results with those obtained by the conventional procedure in the absence of TMSCl. The results of these side-by-side reactions are summarized in Table 1.

With unsubstituted enones the yields in the conjugate addition of **1** were significantly improved in the presence of TMSCl (Table 1, entries 2 and 4). Silyl enol ether **4** was isolated in quantitative yield from the conjugate addition of methyl vinyl ketone (MVK) in the presence of TMSCl. NOE experiments established the exclusive *E*-configuration. For an α-substituted noncyclic enone the yields were similar by both procedures (entry 5). For a β-substituted enone, TMSCl caused an inferior yield (entry 6). A β,β-disubstituted enone such as mesityl oxide was absolutely unreactive even in the presence of hexamethylphosphoric triamide (HMPA) or tetramethylethylenediamine (TMEDA).[8] 3-Methylene-2-norbornanone gave a result similar to MVK (entry 7). In the case of conjugate addition to methyl vinyl ketone, it is noteworthy that when TMSCl is added before workup instead of being premixed with the enone the yield is lower (Table 1, entry 3), indicating that the function of TMSCl is not only to prevent product loss that occurs during workup due to condensation reactions.[9] Silylation presumably also deactivates the enolates anion toward polymerization.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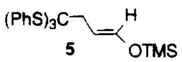
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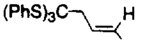
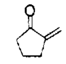
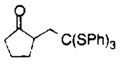
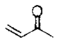
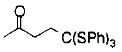
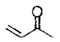
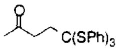
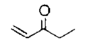
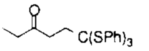
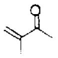
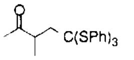
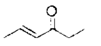
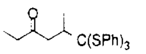
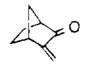
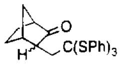
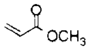
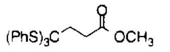
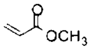
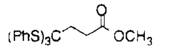
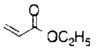
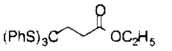

6

For unsubstituted α,β-unsaturated esters, the effect of TMSCl is very prominent. Without TMSCl, the reactions do not afford the desired 1,4-adducts. The esters are consumed to produce unidentified polymers; most of the tris(phenylthio)methane is recovered. In sharp contrast, with TMSCl present, good yields of 1,4-adducts are obtained, although the reaction appears to be slower than with enones (Table 1, entries 8-10). However, the silylation of the adduct enolate was found to be far from complete. Adding HMPA reverses the effect of TMSCl, nearly all starting tris(phenylthio)methane being recovered. Only polymerized material was found when an α-substituted unsaturated ester was subjected to either reaction condition. A β-substituted ester is unreactive toward **1** in the absence or presence of TMSCl. Replacing TMSCl with the more reactive trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave an intractable complex mixture.

Table 1. Conjugate Addition of Tris(phenylthio)methyllithium to α, β-unsaturated Ketones and Esters [a]

Entry	Enones	Adducts	% Yields with TMSCl	% Yield without TMSCl
1			75	24
2			96	65
3[b]			76	65
4			83	70
5			68	72
6			40	80
7			82	58
8			66	0
9[c]			69	0
10			60	0

[a] The reaction time is 1.5-2 h; unless otherwise indicated, 1.0 molar equiv. of TMSCl was used. [b] TMSCl was added before workup instead of being premixed with the enone. [c] 6 equiv. of TMSCl were used.

The reaction of **1** with acrolein gave the 1,2- and 1,4-adducts in a 3:5 ratio (Table 2, entry 1). In the presence of TMSCl, 1,2-addition is greatly suppressed without much impact on the yield of 1,4-adduct (entry 2). HMPA alone totally blocks the 1,2-addition pathway, but leads to an extremely low yield of 1,4-adduct (entry 3). *However, in the presence of both HMPA and TMSCl, the reaction proceeds exclusively in a 1,4-fashion in nearly quantitative yield.* No 1,2-adduct is detectable (entry 4). Thus, in the case of acrolein, the use of TMSCl allows one to take advantage of the known[10] ability of HMPA to promote conjugate addition. Unfortunately, this salutary effect does not extend to the α-substituted enal methacrolein (entries 7 and 8) and the β-substituted enal *trans*-2-pentenal (entries 9 and 10). Replacing the carcinogenic HMPA with *N,N'*-dimethylpropyleneurea (DMPU)[11] or 4-dimethylaminopyridine (DMAP)[1b], while blocking the 1,2-addition pathway, only has a marginal effect on the yields of conjugate addition (entries 5 and 6).

The proximate product from acrolein, enol silyl ether **5** and the analog **6** obtained by the use of *tert*-butyldimethylsilyl chloride (TBDMSCl), were shown to have the *E*-configuration exclusively according to the ^{1}H NMR coupling constants and NOE experiments.

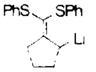
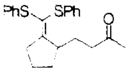
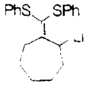
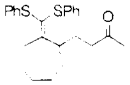
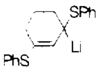
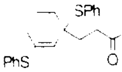
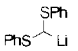
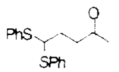
Table 2. Conjugate Addition of Tris(phenylthio)methyllithium to Enals[a]

Entry	Enals	Additive	% Yield of 1,4-adduct	% Yield of 1,2-adduct
1	acrolein	none	54	32
2	acrolein	TMSCl	56	6.5
3	acrolein	HMPA	2.3	0
4	acrolein	TMSCl/HMPA	97	0
5	acrolein	TMSCl/DMPU	68	0
6	acrolein	TMSCl/DMAP	62	0
7	methacrolein	none	78	10
8	methacrolein	TMSCl/HMPA	30	3
9	*trans*-2-pentenal	none	76	12
10	*trans*-2-pentenal	TMSCl/HMPA	intractable mixture	

[a] 2 equiv. TMSCl and 4 equiv. HMPA. DMPU or DMAP were used.

Some synthetic applications of the present discovery have been explored. Typical examples are summarized in Scheme 1. Coupled with the sulfur-lithium exchange reaction,[12] some useful 1,7-dicarbonyl compounds which are potential tricarbonyl compounds, having a masked carbonyl group at 4-position, were produced in one-pot (yields are calculated based on tris(phenylthio)methane). The trimethylsilyl enol ether **5** did not undergo clean sulfur-lithium exchange with *sec*-BuLi, presumably because the trimethylsilyl enol ether does not survive this reaction. Replacing TMSCl with triisopropylsilyl chloride (TIPSCl) or TBDMSCl gave good results due to the stability of these silyl enol ethers. Unfortunately, the organolithium species derived from **5** and **6** by sulfur-lithium exchange gave low yields upon reaction with electrophiles such as methyl iodide, benzaldehyde, and methyl vinyl ketone .

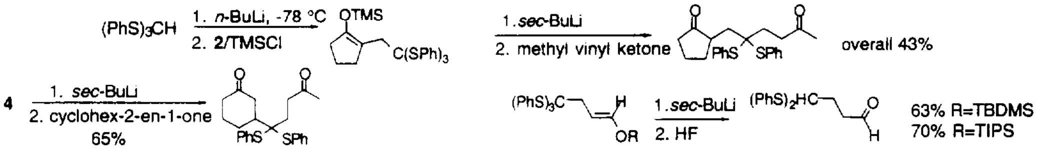
Table 3. Conjugate Addition of other Organolithiums

Entry	Organolithiums	Electrophiles	Products	Additives	% Yield
1	 **7**	MVK		none TMSCl HMPA/TMSCl	12[a,b] 45[b] 60 (93)[c]
2	 **8**	MVK		none TMSCl HMPA/TMSCl	35[a,b] 51[b] 64 (98)[c]
3	 **9**	MVK		none HMPA/TMSCl	27[a,b] 50 (91)[c]
4	Ph_3CLi **10**	acrolein	$Ph_3CCH_2CH_2CHO$	none TMSCl	15[a] 45[a]
5	 **11**	MVK		none HMPA/TMSCl	22 + 56[d] 52[e]

[a] Appreciable amounts of oligomerized products were found. [b] A small amount of 1,2-adduct was formed. [c] The yield in parenthesis is based on consumed organolithium precursor. [d] Yield of 1,2 adduct. [e] 18% of **11** was found to be silylated.

Table 3 summarizes the results of conjugate additions of some other stabilized organolithiums.[13] It is noteworthy that in entries 1-3, when TMSCl/HMPA is used, the reactions were very clean; only conjugate adducts and starting materials were found. The isolation of the silylation product of **11** approximately defines the scope of the technique; the use of less stabilized organolithiums than **11** will probably not be feasible.[14]

In summary, the yield and selectivity enhancement effect of TMSCl and TMSCl/HMPA on conjugate addition of some stabilized organolithiums have been studied. The TMSCl/HMPA assisted conjugate addition reveals its highest potentiality in the reaction with easily polymerized α,β-unsaturated carbonyl compounds, presumably due to the prevention of 1,2-addition and polymerization.[15]



Scheme 1

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14. Butyllithium gave mainly silylation product when exposed to methyl vinyl ketone and TMSCl.
15. A representative experimental procedure is as follows. To a solution of tris(phenylthio)methane (417 mg, 1.2 mmol) in THF (7 mL) at -78 °C was added *n*-BuLi (0.75 mL, 1.6 M in hexanes, 1.2 mmol). The yellow solution was stirred for 30 min after which HMPA (0.7 mL, 4 mmol) was added. Then a mixture of acrolein (0.07 mL, 1 mmol) and TMSCl (0.26 mL, 2.0 mmol) in THF (3 mL) was added dropwise and the solution was stirred for 1 h. The reaction was quenched with 1 N HCl. After workup purification by column flash chromatography (10% ethyl acetate / hexanes, R_f 0.17) afforded 382.8 mg (97%) of 4,4,4-tri(phenylthio)butanal. IR (neat) 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1 H), 7.20 - 7.80 (m, 15 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.08 (t, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 200.2, 136.2, 131.2, 129.4, 128.7, 75.5, 40.0, 32.0; MS (EI) *m/z* (relative intensity) 287 (M^+ - SPh, 70), 257 (43), 218 (70), 110 (100), 77 (40); HRMS (EI) calcd for $C_{16}H_{15}OS_2$ 287.0564, found 287.0550.

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