Tetrahedron Letters 54 (2013) 1264–1267

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regio- and stereoselective preparation of (*Z*)-silyl enol ethers by three-component coupling using α,β-unsaturated acylsilanes as core building blocks

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ARTICLE INFO

Article history:
Received 12 November 2012
Revised 17 December 2012
Accepted 21 December 2012
Available online 2 January 2013

Keywords:
Copper(I) *tert*-butoxide
Conjugate addition
Silyl enol ethers
Silyl migration
Three-component coupling

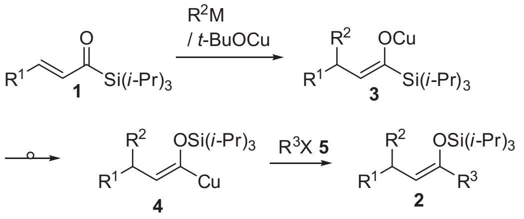
ABSTRACT

Based on the conjugate addition–silyl migration–alkylation strategy, (*Z*)-silyl enol ethers possessing a stereocenter at the γ-position were prepared with complete regio- and stereoselectivity by three-component coupling of α,β-unsaturated acylsilanes, Grignard reagents (or cuprates)/copper(I) *tert*-butoxide, and organic halides.

Silyl enol ethers are important intermediates in organic synthesis, being employed for a number of stereocontrolled synthetic processes.[1] Reflecting these trends, a variety of methods have been developed for the regio- and stereoselective preparation of silyl enol ethers. Most of conventional methods rely on selective formation of kinetic and thermodynamic enolates by deprotonation of carbonyl compounds. It is difficult, however, to control the regiochemistry in enolization of unsymmetrical internal ketones having similar substituents in steric and electronic effects.

As an alternative to the above process, the Brook rearrangement[2]-based strategy for the preparation of silyl enol ethers has been developed.[3] This strategy consists of the following processess:[4] (1) generation of α-silylalkoxide intermediates having a leaving group at the β-position, (2) the 1,2-Csp^3-to-*O* silyl migration, and (3) β-elimination to form the C–C double bond of silyl enol ethers. Despite these studies, only limited methods have been developed for the preparation of silyl enol ethers of acyclic internal ketones in a regio- and stereoselective manner.[3e,f,s]

In the course of our studies[5a,b,d–f,j] on synthetic application of silyl migration from sp^2 carbon to oxygen atom,[5] we have recently reported a stereoselective preparation of α,β-disubstituted silyl enol ethers by the reaction of acylsilanes with copper(I) *tert*-butoxide and organic halides.[6] This transformation involves 1,2-silyl migration in copper(I) enolates of the acylsilanes and alkylation of the resulting 1-siloxy-1-alkenylcopper species with organic halides. To extend this synthetic strategy to regio- and stereoselective preparation of fully substituted silyl enol ethers, we designed a 1,3-silyl migration based three-component coupling by the use of α-silyl-α,β-unsaturated ketones, organocopper reagents, and organic halides.[7] We envisioned that, if the above multi-component process could be extended to α,β-unsaturated acylsilanes **1**, the process would furnish the α,β-disubstituted silyl enol ethers **2**. This process involves three steps: (1) the conjugate addition of organometallic reagents to **1**,[8] (2) the 1,2-silyl migration in the copper(I) enolates **3** giving the alkenylcoppers **4**, and (3) the coupling of **4** with organic halides **5** (Scheme 1). Here we describe the synthesis of (*Z*)-α,β-disubstituted silyl enol ethers **2** having a γ-stereocenter by three-component coupling of α,β-unsaturated acylsilanes **1**, the



R^1 = Me (**1a**), Ph (**1b**), H (**1c**); R^2 = Me, n-Pr, *i*-Pr, Bn, TMSCH$_2$;
R^3 = methallyl (**5a**), allyl (**5b**), cinnamyl (**5c**), phenyl (**5d**)

Scheme 1. Reaction pathway.

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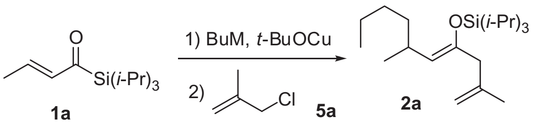
http://dx.doi.org/10.1016/j.tetlet.2012.12.089

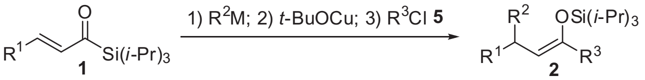
Table 1
Reaction under various conditions

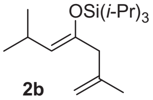
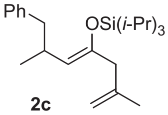
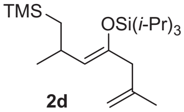
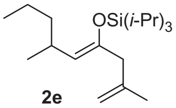
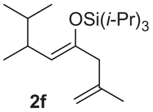
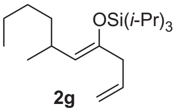
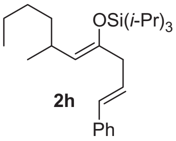
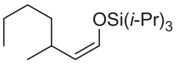
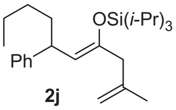


Entry	Conditions	Yield (%)
1	1) BuCu/*t*-BuOCu, THF, −30 to 25 °C, 2 h, then DMF was added, 50 °C, 30 min 2) 50 °C, 4 h	31[a]
2	1) BuMgCl, THF, −78 °C, 30 min, *t*-BuOCu, DMF, 25 °C 2) 50 °C, 1.5 h	74
3	1) $Bu_2CuMgCl$, THF, −78 °C, 30 min, then 25 °C, 30 min, *t*-BuOCu, DMSO, 25 °C 2) 50 °C, 1.5 h	71

[a] Triisopropyl(3-methylheptanoyl)silane was produced in 35% yield as a by-product.

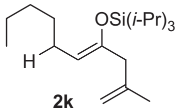
Table 2
Formation of silyl enol ethers by three-component coupling[a]



Entry	Acylsilane	R^2M	R^3X	Product	Yield (%)
1	**1a**	MeMgCl	**5a**	 **2b**	46
2[b]	**1a**	BnMgCl	**5a**	 **2c**	58
3	**1a**	$(TMSCH_2)_2CuMgCl$	**5a**	 **2d**	73
4[c]	**1a**	$Pr_2CuMgBr$	**5a**	 **2e**	70[d]
5	**1a**	*i*-$Pr_2CuMgBr$	**5a**	 **2f**	50
6	**1a**	BuMgCl	**5b**	 **2g**	74
7	**1a**	Bu_2CuLi[e]	**5c**	 **2h**	37
8	**1a**	BuMgCl	–[f]	 **2i**	73[d]
9	**1b**	BuMgCl	**5a**	 **2j**	62

(*continued on next page*)

Table 2 (*continued*)

Entry	Acylsilane	R^2M	R^3X	Product	Yield (%)
10	**1c**	Bu_2CuLi[e]	**5a**	 **2k**	46[g]

[a] The reactions were performed under the conditions described in Table 1, entry 2 for the Grignard reagents and entry 3 for magnesium cuprates unless otherwise noted.
[b] Reaction of the alkenylcopper **4** with **5a** was carried out at 70 °C.
[c] Reaction of the alkenylcopper **4** with **5a** was carried out for 2.5 h.
[d] Contaminated with a trace amount of *E*-isomer.
[e] Conditions: 1) −78 °C, 30 min then 25 °C, 30 min, 2) DMF, 50 °C, 1 h, 3) 25 °C, 1 h.
[f] The alkenylcopper **4** was protonated without the treatment with organic halide **5**.
[g] Contaminated with 1-(triisopropylsiloxy)-1-heptene. The yield was determined by NMR analysis.

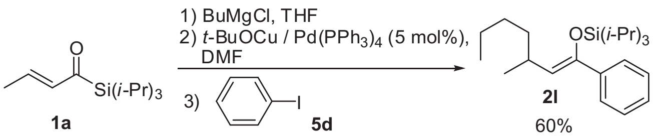
Grignard reagents (or cuprates), and allylic and aryl halides **5** in a regioselective manner.

The treatment of **1a** with the organocopper reagent, (BuCu/*t*-BuOCu),[7] prepared by mixing of copper(I) *tert*-butoxide and butylcopper in THF, followed by the addition of DMF and then methallyl chloride (**5a**) gave the silyl enol ether **2a** in 31% yield (Table 1, entry 1). To improve the yield of **2a**, we investigated a series of organometallic compounds in the conjugate addition process. When **1a** was treated with butylmagnesium chloride in THF prior to the successive addition of copper(I) *tert*-butoxide and **5a** in DMF, an efficient increase in the yield was observed (entry 2). The magnesium cuprate $Bu_2CuMgCl$ can also be employed for this reaction by the use of DMSO as a polar aprotic co-solvent (entry 3).

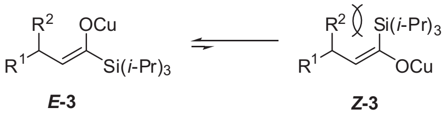
Encouraged by these results, we explored the use of other Grignard reagents and allylic chlorides **5** (Table 2). The (*Z*)-silyl enol ethers **2** possessing various substituents at the γ-position were obtained with complete regio- and stereoselectivity. These unconjugate 1,4-pentadienic silyl enol ethers **2** are difficult to prepare from the corresponding β,γ-unsaturated ketones.[9] Although the yields of **2h** and **2k** were less than 10% in the reactions using the Grignard reagent, the use of the Gilman reagent resulted in a substantial increase in the yields of **2** in these reactions (entries 7 and 10).

When the alkenylcopper species **4**, generated from **1a** and BuMgCl, was trapped with H_2O, (*Z*)-β-monosubstituted silyl enol ether **2i** was stereoselectively obtained (entry 8). Its stereochemistry was confirmed by the coupling constant (5.9 Hz)[10] between two vinyl protons. It has been reported that (*E*)-silyl enol ethers were favorably produced by the silylation of enolates generated by conjugate addition of organometallic reagents to unsaturated enals.[11] Therefore, the present reaction is a useful complementary to the conventional method with respect to the stereochemistry.

Furthermore iodobenzene can be employed as an alkylating reagent in the three-component coupling (Scheme 2). The reaction was carried out in a similar manner in the presence of 5 mol % of $Pd(PPh_3)_4$ (see Supplementary data).



Scheme 2. Palladium(0)-catalyzed cross-coupling.



Scheme 3. Stereochemistry of the copper enolates.

The configuration of the disubstituted silyl enol ethers **2a**, **c–g**, **j**, and **k** was confirmed by NOE or NOESY experiments (see Supplementary data). The stereochemistry of other silyl enol ethers **2b**, **2h**, and **2l** was deduced from the above results.

The stereochemistry of **2** can be explained by the exclusive formation of thermodynamically more stable (*E*)-enolates ***E*-3** rather than (*Z*)-enolates ***Z*-3**, which are destabilized by the steric repulsion between the triisopropylsilyl group and the secondary alkyl substituent (R^1R^2CH) at the β-position (Scheme 3).[12] The (*E*)-enolates undergo 1,2-silyl migration with retention of the geometry of double bond, followed by the alkylation of resulting alkenylcoppers to afford the (*Z*)-silyl enol ethers **2** stereoselectively.

In conclusion, regio- and stereoselective preparation of silyl enol ethers of unsymmetrical internal ketones has been achieved by the three-component coupling.[13] It has also been demonstrated that α,β-unsaturated acylsilanes are efficient linchpins in introducing a stereocenter into the silyl enol ethers as well as construction of the unconjugated dienol ether structure. Studies on the scope of this reaction and synthetic application of the silyl enol ethers are currently underway.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 23550118) from the Ministry of Education, Culture, Sports, Science, and Technology (Japan).

Supplementary data

Supplementary data (experimental procedures and full characterization of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.089.

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13. *Typical procedure*: A solution of the unsaturated acylsilane **1a** (45 mg, 0.20 mmol) in THF (0.85 mL) was added to butylmagnesium chloride (2.0 M in THF, 0.12 mL, 0.24 mmol) at −78 °C under Ar. After stirring for 30 min, the temperature was raised to 25 °C and then the mixture was stirred for additional 30 min. To this mixture were successively added a solution of *t*-BuOCu (0.48 mmol) in DMF, prepared by the reaction of CuI (91 mg, 0.48 mmol) and *t*-BuOLi (0.98 M in THF, 0.49 mL, 0.48 mmol) in DMF (1.8 mL), and then a solution of methallyl chloride (**5a**) (54 mg, 0.60 mmol) in DMF (1.0 mL) at 25 °C. The mixture was heated at 50 °C for 1.5 h and then the reaction was quenched by addition of 3.5% aqueous NH_3. The product was extracted with diethyl ether and the extract was washed with H_2O, and dried over K_2CO_3. The solvent was evaporated under reduced pressure and the residue was purified by PTLC (hexane) to give the silyl enol ether **2a** (50 mg, 74%) as a single isomer.