

Generation of silyl group stabilized amide homoenolates by utilizing the complex-induced proximity effect (CIPE)

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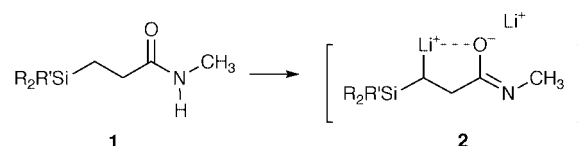
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Generation of silyl group stabilized amide homoenolates from 3-trimethylsilyl- and 3-dimethylphenyl-propanamide with Bu^tLi-TMEDA at -78 °C and their reactions with chlorosilanes, diphenyldisulfide and alkyl halides were carried out.

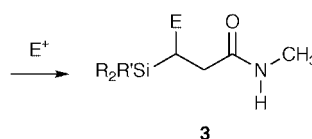
In connection with our studies on the chemistry of amide homoenolates,¹ we planned to investigate silyl group stabilized amide homoenolates, since silicon substituted carbanions have attracted considerable interest because of their multiple synthetic utilities. One of the important properties of silicon-carbon bonds is that carbanions α to silicon are favoured. However, when there are no additional electron withdrawing groups on the carbon attached to the silicon, high yield generation of the corresponding silicon stabilized carbanion by abstracting a hydrogen α to the silyl group is accompanied with difficulties.² We envisioned the generation of silyl group stabilized carbanions *via* hydrogen abstraction, by utilizing the complex-induced proximity effect (CIPE).³ Thus, we have chosen *N*-methyl-3-(trimethylsilyl)propanamide **1a** as a substrate.

When **1a** was treated with 2.2 equivalents of BuLi at -78 °C in THF for 1.5 h and the reaction was quenched with chlorotrimethylsilane, only a trace amount of **3** (E = Me₃Si, Table 1, entry 1) was obtained (Scheme 1). Treatment of **1a** with 2.2 equivalents of BuLi and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) under the same conditions and subsequent quenching with chlorotrimethylsilane gave the silylated product **3** (E = Me₃Si) in 61% yield (entry 2).

In a similar manner, chlorodimethylphenylsilane (entry 3), diphenyldisulfide (entry 4), and allyl bromide (entry 7) gave the corresponding **3** in good yields. However, benzyl bromide gave alkylated product **3** in lower yield (entry 6). When the solvent was changed from THF to ether no reaction occurred (entry 5). Carbanion generation from *N*-methyl-3-(dimethylphenylsilyl)propanamide **1b** and its reactions with chlorotrimethylsilane, allyl bromide and diphenyldisulfide also proceeded successfully (entries 8–10). However, generation of a trimethylsilyl group stabilized carbanion from the homologue of **1a**, *N*-methyl-4-(trimethylsilyl)butanamide, under similar reaction conditions resulted in no reaction, presumably due to its insufficient CIPE.

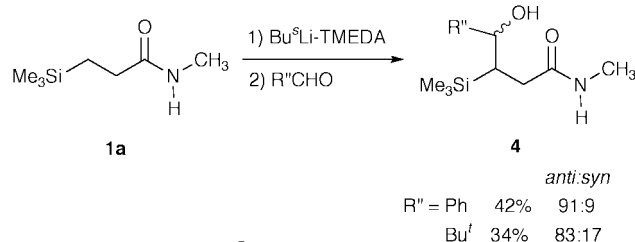


a: R, R' = CH₃
b: R = CH₃, R' = Ph

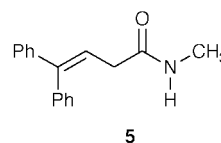


Scheme 1

Reaction of the homoenolate derived from **1a** with benzaldehyde gave a mixture of diastereoisomers (*anti*:*syn* = 91:9), which are chromatographically separable, in 42% combined yield (Scheme 2). 2,2-Dimethylpropanal also gave the corresponding adduct **4** (*anti*:*syn* = 83:17) in a moderate yield



anti:*syn*
R'' = Ph 42% 91:9
Bu^t 34% 83:17



Scheme 2

Table 1 Reaction of **1** with several electrophiles

Entry	1	Base	Solvent	Electrophile	Yield (%) 3
1	1a	BuLi	THF	Me ₃ SiCl	trace
2	1a	Bu ^t Li-TMEDA	THF	Me ₃ SiCl	61
3	1a	Bu ^t Li-TMEDA	THF	Me ₂ PhSiCl	83
4	1a	Bu ^t Li-TMEDA	THF	PhSSPh	86
5	1a	Bu ^t Li-TMEDA	Et ₂ O	PhSSPh	0
6	1a	Bu ^t Li-TMEDA	THF	PhCH ₂ Br	33
7	1a	Bu ^t Li-TMEDA	THF	CH ₂ =CHCH ₂ Br	52
8	1b	Bu ^t Li-TMEDA	THF	Me ₃ SiCl	51
9	1b	Bu ^t Li-TMEDA	THF	CH ₂ =CHCH ₂ Br	67
10	1b	Bu ^t Li-TMEDA	THF	PhSSPh	67

(Scheme 2). When benzophenone was used, the corresponding adduct was found to be unstable under even slightly acidic conditions such as chromatography on silica gel, and acid treatment (2 M HCl, at rt for 5 min) of the crude reaction mixture gave condensed product **5** in 78% yield (Scheme 2).

In conclusion, silyl group stabilized amide homoenolates are successfully generated and reacted smoothly with some electrophiles. Some of the products are prospective synthetic intermediates since elimination of the silyl groups β to the carbonyl group is possible⁴ and the dimethylphenylsilyl group can be converted to a hydroxy group.⁵

Applications of the above type of silyl group stabilized carbanions for asymmetric reactions are currently underway.

Experimental

Typical procedure for the reaction of **1a**

To a solution of **1a** (159 mg, 1 mmol) and TMEDA (340 μ l, 2.2 mmol) in THF (5 cm³), Bu^tLi (2.2 mmol) was added dropwise at -78 °C. After 1.5 h, diphenyldisulfide (262 mg, 1.2 mmol) was added. The reaction mixture was stirred for 0.5 h at -78 °C, after which aq. NH₄Cl was added. The reaction mixture was extracted with ethyl acetate and the extract was dried and concentrated under reduced pressure to afford a crude product,

which was purified by flash chromatography with hexane–ethyl acetate (2:1 v/v) as eluent to give **3a** [E = PhS, 230 mg, 86%].

References

- 1 T. Houkawa, T. Ueda, S. Sakami, M. Asaoka and H. Takei, *Tetrahedron Lett.*, 1996, **37**, 1045; M. Asaoka, M. Tanaka, T. Houkawa, T. Ueda, S. Sakami and H. Takei, *Tetrahedron*, 1998, **54**, 471.
- 2 E. W. Colvin, *Silicon Reagents in Organic Synthesis*, Academic Press, London, 1988, ch. 1; E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, 1981, ch. 4; W. P. Weber, *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983, ch. 6; I. Fleming, *Comprehensive Organic Chemistry*, ed. D. N. Jones, Pergamon Press, Oxford, 1979, vol. 3, part 13.
- 3 P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356; P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; D. J. Pippel, M. D. Curtis, H. Du and P. Beak, *J. Org. Chem.*, 1998, **63**, 2.
- 4 I. Fleming and D. A. Perry, *Tetrahedron*, 1981, **37**, 4027; M. Asaoka, T. Aida, S. Sonoda and H. Takei, *Tetrahedron Lett.*, 1989, **30**, 7075; M. Asaoka, M. Sakurai and H. Takei, *Tetrahedron Lett.*, 1991, **32**, 7567.
- 5 I. Fleming, *Chemtracts: Org. Chem.*, 1996, **9**, 1.

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