Pergamon

Tetrahedron Letters, Vol. 37, No. 38, pp. 6929-6930, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01519-5

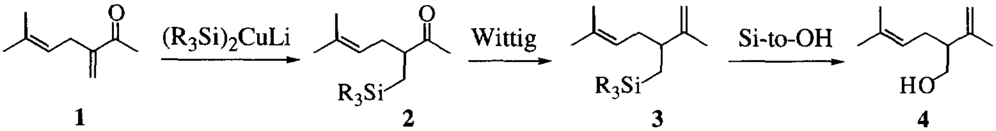
Conjugate Addition of Silyl Groups to β-Unsubstituted Enones, & Si-to-OH Conversion: a Synthesis of (±)-Lavandulol

Ian Fleming* and Duckhee Lee

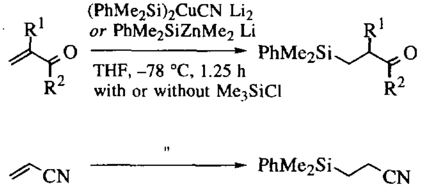
Department of Chemistry, Lensfield Road, Cambridge CB2 1EW, England

Abstract TMS chloride raises the yield in the conjugate addition of silylcuprates and zincates to β-unsubstituted enones, and Si-to-OH conversion is possible using the 2-methylbut-2-enyl(diphenyl)silyl group in the presence of highly nucleophilic alkenes. Both reactions are used in a synthesis of lavandulol. Copyright © 1996 Elsevier Science Ltd

Having established that a phenyldimethylsilyl group could be added to the β-position of enones using the silylcuprate reagent,[1] and that the silyl group could be converted into a hydroxyl in one pot,[2] we considered a synthesis of the monoterpene lavandulol **4**, from the enone **1**. However, even as uncomplicated an illustration of our ideas as this exposed us to two limitations in our methods. First, and more serious, a phenyldimethylsilyl group cannot be converted into a hydroxyl in the presence of alkene groups, because the conditions for the electrophilic removal of the phenyl group disturb the C=C double bonds. We have already reported our solution to this problem: the 2-methylbut-2-enyl(diphenyl)silyl group can be made into a cuprate, and carries a highly labile group easily removed selectively by electrophiles in the presence of alkene groups,[3] although we had not tested anything quite as challenging as the two alkene groups in an intermediate like **3**. The second problem was that the yields in some of our silylcuprate additions are not always high. The problem appears to be the subsequent Michael reaction of the intermediate enolate with a second, and even a third, molecule of the enone. We have already reported that using zincates in place of the cuprates[4] often solves this problem, but even they did not give good yields when the enone carried no β-substituents, as in the substrate **1**. We record here that the addition of trimethylsilyl chloride[5] to enones having no β-substituent, before adding them to the silylcuprate or zincate, leads to higher yields in the conjugate addition, and that the 2-methylbut-2-enyl(diphenyl)silyl group can be unmasked in the presence of di- and trisubstituted double bonds with the substitution pattern in the diene **3**, making it possible for us to synthesise lavandulol along these lines.



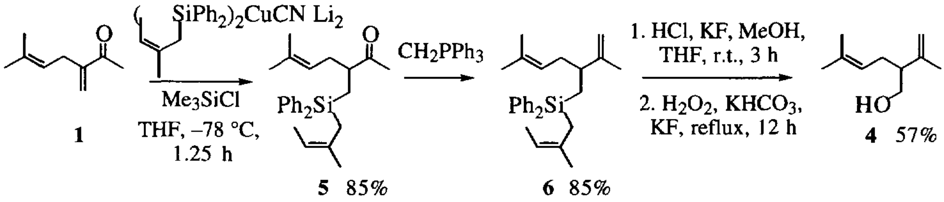
1 **2** **3** **4**



		Yield % without Me_3SiCl		Yield % with Me_3SiCl	
R^1	R^2	Cuprate	Zincate	Cuprate	Zincate
Me	H	24	36	71	78
H	OMe	29	12	80	72
Me	OMe	22	25	74	74
H	Me	42[1]	37	57	64
H	NMe_2	5	6	28	57
		29	21	50	93

As model reactions, we carried out conjugate additions of our phenyldimethylsilylcuprate and zincate reagents to methacrolein, methyl acrylate, methyl methacrylate, methyl vinyl ketone, *N,N*-dimethyl acrylamide, and acrylonitrile, and obtained in each case better yields in the presence of trimethylsilyl chloride than in its absence.[6] The addition of TMEDA, with or without the trimethylsilyl chloride, made no difference to the yields. The yields with α,β-unsaturated carbonyl compounds like methyl crotonate, which do have β-substituents, did not improve in the presence of trimethylsilyl chloride—if anything they were worse.

We prepared the starting material **1** in 60% yield from acetylacetone, prenyl bromide and formaldehyde, using the method of Amri,[7] and carried out the conjugate addition reaction using trimethylsilyl chloride and our 2-methylbut-2-enyl(diphenyl)silylcuprate, and obtained the ketone **5** in reasonable yield. Wittig reaction gave the diene **6**, and the only problem was to find conditions that would remove the 2-methylbut-2-enyl group from the silicon without disturbing the other double bonds. This was not quite as easy as we had hoped, but it was possible using methanolic hydrochloric acid in THF in the presence of fluoride ion so that we could isolate and characterise an intermediate fluoride. Tamao's conditions[8] for silyl-to-hydroxy conversion completed the synthesis of (±)-lavandulol **4**, identical (TLC, IR, ^{1}H-NMR) with an authentic sample, 3,5-dinitrobenzoate, m.p. 75-76 °C (lit.[9] 73-75 °C).



We thank the Cambridge Overseas Trust, the managers of the C. T. Taylor fund, and Professor S. V. Ley for financial help (DL).

REFERENCES and NOTES

1. Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520-2526.
2. Fleming, I.; Henning, R.; Plaut, H.; Parker, D. C.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317-337. For reviews of this reaction, see: Fleming, I. *Chemtracts, Org. Chem.* **1996**, *9*, 1-64. Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *37*, 7599-7662.
3. Fleming, I.; Winter, S. B. D. *Tetrahedron Lett.* **1993**, *34*, 7287-7290 & **1995**, *36*, 1733-1734. We have improved the preparation of the silyl chloride precursor of this reagent by carrying out the hydrosilylation of isoprene with trichlorosilane (70 °C, 7 h, 92% after distillation),[10] and treating the product with 2 equivalents of PhLi (Et_2O, –78 °C, 0.5 h, r.t., 12 h, 70% after distillation, b.p. 149-155 °C/0.09 mmHg).
4. Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701-706.
5. The usefulness of added trimethylsilyl chloride in cuprate conjugate additions is well established for carbon-cuprates: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. Bergdahl, M.; Linstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055. Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238. Nakamura, E., in *Organocopper Reagents*, ed. R. J. K. Taylor, OUP, Oxford, 1994.
6. Typically, a mixture of trimethylsilyl chloride (9 mmol) and methyl acrylate (3 mmol) in THF (5 ml) was added to the silylzincate (3.6 mmol) in THF at –78 °C under argon over 45 min, and the mixture stirred for 30 min. An aqueous workup and chromatography (SiO_2, light petroleum-EtOAc, 10:1) gave the β-silyl ester.
7. Ben Ayed, T.; Amri, H. *Synth. Commun.* **1995**, *25*, 3813-3819.
8. Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694-1696. Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37-C39. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth. (N.Y.)* **1990**, *69*, 96-105.
9. Matsui, M.; Kobayashi, A. *Agr. Biol. Chem. (Tokyo)* **1962**, *26*, 705-708; *Chem. Abstr.* **1963**, *59*, 75636b.
10. Ojima, I. *J. Organomet. Chem.* **1977**, *134*, C1-C5.

(*Received in UK* 26 *June* 1996; *revised* 26 *July* 1996; *accepted* 1 *August* 1996)