Stereoselective Conjugate Addition of Alkyl Groups to (*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-phenylsulfonyl-2-cyclopentenone by Means of Trialkylaluminum Reagents

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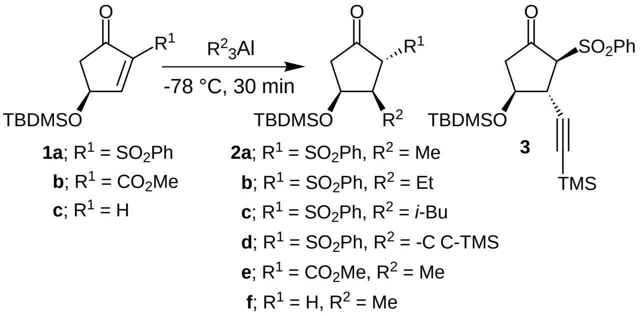
Received 11 May 1999

Abstract: Reaction of (*S*)-4-(*tert*-butyldimethylsilyloxy)-2-phenylsulfonyl-2-cyclopentenone with 2.2 equiv of R_3Al (R = Me, Et, *i*Bu) in toluene at -78 °C stereoselectively afforded the corresponding (2*R*,3*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-alkyl-2-phenylsulfonyl-cyclopentanones as a single diastereoisomer.

Key words: aluminum, conjugate addition reaction, cyclopentanone, stereoselectivity, sulfone

Conjugate addition reactions[1] of alkyl groups to α,β-unsaturated ketones have been one of the most important carbon-carbon bond forming reactions. Such reactions are usually carried out using organocopper or organozinc reagents. It would be useful, if organoaluminum reagents could be used for this purpose, as they have some advantages over other reagents in terms of availability of lower alkyl ligands, easy handling, and low toxicity.[2] However, trialkylaluminums are less reactive than are organocopper reagents in conjugate addition reactions to the α,β-unsaturated ketones, so that the reactions require an additive such as a radical initiator,[3] transition metal,[4] or Cu(I) salt.[5] Alkynyl and alkenylaluminum reagents are exceptions; they react with α,β-unsaturated ketones without additives.[6,7] We anticipated that even trialkylaluminums can react with the α,β-unsaturated ketones if the enones are doubly activated by introduction of an additional electron-withdrawing group. In connection with our studies on the synthesis of polyfunctionalized cyclopentanes,[8] we now examined the conjugate addition reaction of alkyl groups to (*S*)-4-[*tert*-butyldimethylsilyl(TBDMS)oxy]-2-phenylsulfonyl-2-cyclopentenone (**1a**)[9] using trialkylaluminum reagents and found that the reaction proceeded cleanly with high stereoselectivity to give (2*R*,3*S*,4*S*)-4-TBDMSoxy-3-alkyl-2-phenylsulfonylcyclopentanes (**2a-c**).



A solution of 2.2 equiv of trimethylaluminum (Me_3Al) in hexane was added to a solution of **1a** in toluene at -78 °C, and the mixture was stirred at the same temperature for 30 min to give (2*R*,3*S*,4*S*)-4-TBDMSoxy-3-methyl-2-phenylsulfonylcyclopentanone (**2a**) in 86% yield as a sole diastereoisomer (Table 1, entry 1).[10,11] The stereochemistry of **2a** was determined by its conversion through treatment with samarium(II) iodide (SmI_2)[12] to **2f** (72%).[8a] When 1 equiv of Me_3Al was used, the reaction was not completed even after stirring for 1.5 h; **2a** was obtained in 49% yield along with 49% of unreacted **1a** (Table 1, entry 2). Solvent effects were observed: the reaction in dichloromethane gave **2a** in a slightly lower yield (74%), but ether was not effective; only unreacted **1a** (81%) was recovered (Table 1, entries 3 and 4).

Table 1 Reaction of aluminum reagents with 1a and 1b.

Entry	1	Reagent (equiv)	Solvent	Total yield (%)	Products (Ratio)
1	a	Me_3Al (2.2)	toluene	86	**2a**
2	a	Me_3Al (1)	toluene	49 [b]	**2a**
3	a	Me_3Al (2.2)	CH_2Cl_2	74	**2a**
4	a	Me_3Al (2.2)	Et_2O	0 [c]	-
5	a	Et_3Al (2.2)	toluene	65	**2b**
6	a	*i*Bu_3Al (2.2)	toluene	32	**2c**
7	a	$Et_2Al\text{-}C\equiv CTMS$ (2.2)	toluene	quant.	**3+2d+2b** (51:31:18)[d]
8	b	Me_3Al (2.2)	toluene	22 [e]	**2e**
9	b	Me_3Al (4)	toluene	51	**2e**

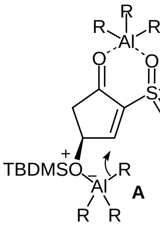
a) Reactions were carried out at -78 °C for 30 min. *b*) Unreacted **1a** was recovered in 49% yield after 1.5 h. *c*) Unreacted **1a** was recovered in 81% yield after 3 h. *d*) Determined by ^1H NMR spectroscopy. *e* Unreacted **1b** was recovered in 22% yield.

A similar reaction of **1a** with 2.2 equiv of triethylaluminum proceeded stereoselectively to provide **2b** in 65% yield (Table 1, entry 5). The reaction of **1a** with triisobutylaluminum gave **2c** in 32% yield with high stereoselectivity (Table 1, entry 6). The stereochemistry of the products **2b** and **2c** was determined by a comparison of the chemical shifts and coupling constants of H-2 and H-4 protons in the ^1H NMR spectra with those of **2a**.[13] In contrast, a similar reaction of diethyl(trimethylsilylethynyl)aluminum[14] in toluene gave an inseparable 51:31:18

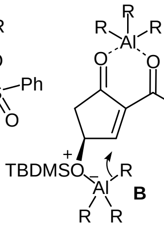
mixture of **3**, **2d** and **2b** in quantitative yield (Table 1, entry 7).[15]

The ester congener **1b**,[8c,9] upon treatment with 2.2 equiv of Me_3Al in toluene at -78 °C for 30 min, gave the 3,4-*cis* adduct **2e** as a sole diasteroisomer but only in 22% yield, along with 22% of unreacted **1b** (Table 1, entry 8). The spectroscopic data of **2e** were identical to those of a racemic authentic sample.[8a] Use of 4 equiv of Me_3Al increased the yield to 51% (Table 1, entry 9). As expected, no reaction took place when the cyclopentenone **1c** was treated with Me_3Al under the same conditions.

One possible rationalization for the high diastereoselectivity obtained in the reaction of **1a** or **1b** with R_3Al is based on the assumption of 1:2 complex **A** or **B**, respectively. Thus, the first alane combines with the keto and sulfonyl or ester groups as a Lewis acid to activate the enone **1a** or **1b**. The second R_3Al makes the chelation between R_3Al and an oxygen atom of the TBDMSO group at C-4 to form the intermediate **A** or **B**.[16] The alkyl group is then transfered intramolecularly from the coordinated R_3Al to give the 3,4-*cis* adducts **2a**–**e**.[17] The nucleophilicity of the alkyl group of the resulting ate-complex is known to be higher than for a noncoordinated R_3Al.[2a,18] A bulky alane such as triisobutylaluminum would retard the formation of the intermediate **A** to reduce the yield of the conjugate addition. The high reactivity of diethyl(trimethylsilylethynyl)aluminum to the enones would allow the reaction to proceed through non-chelated intermediate **C**, in which the nucleophile attacked from the less-hindered side to afford the 3,4-*trans* isomer **3**. In ether, complexation of R_3Al with ether would make it unable to form the intermediate **A**.



A



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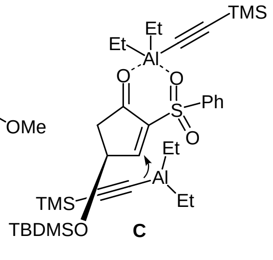

C

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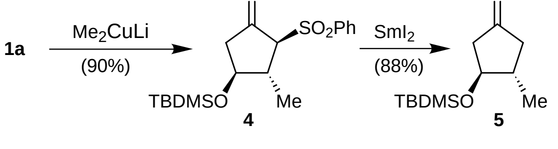
(10) A typical procedure for the conjugate addition of trialkylaluminum: A 1.0 M solution of Me_3Al in hexane (0.63 mL, 0.63 mmol) was added to a solution of **1a** (100 mg, 0.28 mmol) in toluene (6 mL) at -78 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min and quenched with sat. aq. NH_4Cl. The mixture was allowed to warm to room temperature and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc, 10:1) to give **2a** (89 mg, 86%) as colorless crystals: mp 111-113.5 ¡C (from hexane); $[\alpha]_D^{24}$ -96.9 (*c* 1.08, $CHCl_3$); IR (CCl_4) ν 1760, 1320, 1140 cm^{-1}; ^1H NMR δ: 0.02, 0.05 (both 3H, s, SiMe), 0.82 (9H, s, *t*-Bu), 1.30 (3H, d, *J* = 6.8 Hz, 3-Me), 2.31 (1H, dt, *J* = 16.8. 1.0 Hz, one of 5-H_2), 2.54 (1H, dd, *J* = 16.8, 3.9 Hz, one of 5-H_2), 2.96 (1H, dqd, *J* = 10.0, 6.8, 3.5 Hz, 3-H), 3.48 (1H, d, *J* = 10.0 Hz, 2-H), 4.31 (1H, t, *J* = 3.7 Hz, 4-H), 7.54-7.61 (2H, m, ArH), 7.65-7.71 (1H, m, ArH), 7.86-7.91 (2H, m, ArH). *Anal.* Calcd for $C_{18}H_{28}O_4SSi$: C, 58.66; H, 7.66. Found: C, 58.87; H, 7.51.

(11) In contrast, treatment of **1a** with lithium dimethylcuprate gave the 2,3-*trans*-3,4-*trans* isomer, (2*S*,3*R*,4*S*)-4-(TBDMSoxy)-3-methyl-2-phenylsulfonylcyclopentanone (**4**), in 90% yield as a single diastereoisomer. Desulfonylation of **4** with SmI_2 produced **5**.[8a]



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(13) The ^1H NMR data of H-2 and H-4 protons of **2a-d**, **3**, and **4**.

Compound	H-2	H-4
2a	3.48 (1H, d, *J* = 10.0 Hz)	4.31 (1H, t, *J* = 3.7 Hz)
2b	3.48 (1H, br d, *J* = 9.6 Hz)	4.50 (1H, t, *J* = 3.6 Hz)
2c	3.46 (1H, d, *J* = 9.8 Hz)	4.43 (1H, t, *J* = 3.5 Hz)
2d	3.95 (1H, d, *J* = 9.3 Hz)	-[a]
3	3.84 (1H, d, *J* = 9.7 Hz)	4.23 (1H, ddd, *J* = 10.1, 7.9, 6.8 Hz)
4	3.40 (1H, br d, *J* = 10.5 Hz)	3.79 (1H, ddd, *J* = 10.3, 8.5, 6.6 Hz)

a) The signal overlapped with that of **2b**.

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(15) The ratio of **3**, **2d** and **2b** was estimated to be 51:31:18 by an integrated intensity of the peak heights of the signals due to the protons of the *tert*-butyl group appeared at δ 0.90, 0.84 and 0.81, respectively.

(16) For the chelation of metals with TBDMSoxy ketones, see: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. For other examples, see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(17) An intriguing alternative to this mechanism would involve the formation of the chelated intermediate **D**. Unfortunately, the *cis*-selectivity of the ester **1b** cannot be explained through a similar intermediate **E**.

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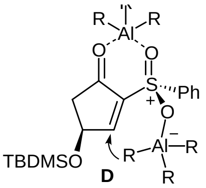
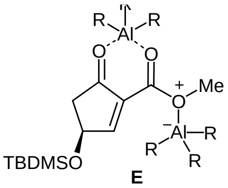


D



E

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1437-2096,E;1999,0,08,1313,1315,ftx,en;Y10099ST.pdf