Allylic Dithioacetal as a Propene-1,3-Zwitterion Synthon. Regioselective Conversion of C-S Bonds in Allylic Dithioacetals into C-C Bonds

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Abstract: Reaction of allylic dithioacetals with organocuprate or organolithium reagent followed by treatment with a variety of alkyl electrophiles gives the corresponding \( E \) and \( Z \) isomeric mixture of vinyl sulfides in good yield. Further cross coupling with a Grignard reagent in the presence of \( \text{NiCl}_2(\text{dppe}) \) affords the corresponding alkylation products in good yield. In general, the Grignard reagent having the same alkyl group as the \( R_2 \) substituent in \( 1 \) is employed so that the stereochemical problem in coupling products can be lifted.

Key words: allylic dithioacetals, organocuprate, electrophiles, cross coupling, zwitterion synthon

Regioselective replacement of a carbon-heteroatom bond in an unsymmetrical allylic system by a carbon-carbon bond is important in organic synthesis. The \( \alpha \)- versus \( \gamma \)-selectivity depends on the nature of the substrates, reagents, stoichiometry and reaction conditions.\(^1,2\) Lewis acids as well as organometallic catalysts occasionally play a pivotal role in directing the regioselectivity. A decade ago, we reported the geminal dimethylation of allylic dithioacetals \( 1 \) with \( \text{MeMgI} \) in the presence of \( \text{NiCl}_2(\text{dppe}) \) (eq 1).\(^3\) No 1,3-dimethylation product was observed at all. On the other hand, propargylic dithioacetal \( 3 \) can serve as an allene 1,3-dication synthon \( 5 \) leading to 1,3-dimethylation product \( 4 \) under similar conditions (eq 2).\(^4\) More recently, we found that \( 3 \) can also behave as an allene 1,3-zwitterion synthon \( 6 \) (eq 3). The interesting feature for this reaction involves an umpolung of one of the two carbon-sulfur bonds in the dithioacetal functionality.\(^6\) The organocopper intermediate \( 7 \) can react with a number of electrophiles leading to either allenyl or alkynyl product \( 8 \) or \( 9 \). The regioselectivity of the latter reaction depends on the nature of the electrophile. The remaining carbon-sulfur bond in \( 8 \) or \( 9 \) can be further displaced by the nickel-catalyzed cross coupling reaction.\(^7\) It is envisaged that the reaction of \( 1 \) under similar conditions would generate a substituted allylcopper intermediate \( 10 \) which might behave differently from that of the allenyl/propargylic counterpart 7. We have tested this viewpoint and now wish to report our findings on using allylic dithioacetal as a propene-1,3-zwitterion synthon \( 11 \).
In a typical procedure, reaction of 1 with 0.6 equiv of Bu₂CuLi in THF at -78 °C followed by treatment with an alkyl halide afforded regioselectively an E/Z mixture of the corresponding vinyl sulfide 12 in good yield (eq 4). Representative examples are summarized in Table 1. Organic lithium reagent (1.2 equiv) behaved similarly (entries 5 and 8-10) and there was no apparent discrepancy in regio- and stereoselectivities whether organocopper reagent or organolithium reagent was employed.

Equation 4

As can be seen from Table 1, a range of alkyl halides can be used for this purpose. The alkyl electrophile reacted regioselectively at the position away from the sulfur substituent of the corresponding unsymmetrical allyl organometallic species 10. This regioselectivity is just opposite to that observed for the propargylic substrates (eq 3). Presumably, the anionic electron density might be higher at the benzylic position due to resonance. It is interesting to note that, when both C₁ and C₃ positions have ary1 substituents, alkylation occurred preferentially at the position having thioether substituent (entry 3). The proton electrophile, however, gave a mixture of regioisomers (entry 6).

The alkylation in general gave a mixture of E and Z isomeric 12. Surprisingly, when R² was a methyl group and TMSCH₂Cl was employed as the electrophile, only E isomer was isolated (entry 2). The stereoisomers of 12 can sometimes be separated by column chromatography. By using Wenkert-Takei procedure,⁷ vinyl carbon-sulfur bond can readily be converted into the corresponding carbon-carbon bond. Accordingly, a mixture of E/Z isomeric 12 was treated with the Grignard reagent in the presence a catalytic amount of NiCl₂(dppe) to afford the corresponding coupling product 13 in good yield (eq 4).⁸

In general, the Grignard reagent having the same alkyl group as the R² group in 1 was employed so that the stericchemical problem in 12 can be lifted. The results are tabulated in Table 2. It is noteworthy the reaction of a mixture of 12c and 14 afforded 13c in good yield (entry 13). Our earlier work showed that the NiCl₂(dppe)-catalyzed cross coupling of 1b with MeMgI yields the geminal dimethylation product 17 exclusively.³c The regioselectivity in this study just complements with those of the literature procedures to afford 1,3-dimethylation product 13c from the same allylic dithioacetal.
The reaction can also proceed in one-pot. Thus, treatment of 1c with BuLi at -78 °C followed by (PrO)Me₂SiCH₂Cl gave the corresponding alkylation product 18 which was allowed to react with MeMgI to yield the organosilicon product 19. Without purification, the crude 19 was oxidized under Tamao conditions⁹ to afford the corresponding alcohol 20 in 44% overall yield (eq 5).

![Equation 5](image)

In summary, we have demonstrated a useful regioselective transformation involving allylic dithioacetals. A variety of electrophiles and alkyl nucleophiles can be used in this strategy. Further investigation on the synthetic applications of this reaction is in progress in our laboratory.

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References and Notes

8. ¹H NMR (400 MHz, CDCl₃) data (δ, J) for selected 13, b: -0.09 (s, 9 H), 0.94-1.04 (m, 2 H), 1.68 (s, 3 H), 3.62 (m, 1 H), 5.25 (br, J = 9.2 Hz, 1 H), 7.12-7.28 (m, 5 H), δ: 0.86 (t, J = 7.2 Hz, 3 H), 1.12-1.34 (m, 4 H), 1.62-1.81 (m, embodied a doublets at 1.68, J = 1.2 Hz and a singlet at 1.7 for the two Me group, 8 H), 3.59 (dt, J = 9.2, 7.6 Hz, 1 H), 5.35 (br, d, J = 9.2 Hz, 1 H), 7.34-7.45 (m, 3 H), 7.60 (s, 1 H), 7.75-7.79 (m, 3 H). e: 1.49 (d, J = 1.2 Hz, 3 H), 1.75 (s, 3 H), 2.00 (dd, J = 13.2, 8.4 Hz, 1 H), 3.13 (dd, J = 13.2, 6.4 Hz, 1 H), 3.93 (m, 1 H), 5.48 (dd, J = 9.2, 1.2 Hz, 1 H), 7.11-7.23 (m, 5 H), 7.39-7.49 (m, 3 H), 7.63 (s, 1 H), 7.77-7.83 (m, 3 H). h: -0.08 (s, 9 H), 0.92 (t, J = 7.2 Hz, 3 H), 0.99 (s, J = 7.2 Hz, 3 H), 1.04 (dd, J = 14.4, 8.8 Hz, 1 H), 1.12 (dd, J = 14.4, 6.8 Hz, 1 H), 2.00 (dq, J = 7.2, 1.2 Hz, 2 H), 2.07-2.20 (m, 2 H), 3.82 (m, 1 H), 5.30 (br, d, J = 9.6 Hz, 1 H), 7.35-7.43 (m, 3 H), 7.60 (s, 1 H), 7.73-7.77 (m, 3 H). i: 0.88 (t, J = 7.2 Hz, 3 H), 1.23-1.42 (m, embodied a doublet at 1.75, J = 7.2 Hz for a Me group, 7 H), 1.67 (d, J = 1.2 Hz, 3 H), 2.00 (br, t, J = 7.6 Hz, 2 H), 3.81 (dq, J = 9.2 Hz, J = 7.2 Hz, 1 H), 5.35 (dd, J = 9.2 Hz, J = 1.2 Hz, 1 H), 7.36-7.45 (m, 3 H), 7.64 (s, 1 H), 7.75-7.77 (m, 3 H). j: -0.06 (s, 9 H), 0.90 (t, J = 7.2 Hz, 6 H), 1.05 (dd, J = 14.4, 8.0 Hz, 1 H), 1.15 (dd, J = 14.4, 6.8 Hz, 1 H), 1.24-1.41 (m, 8 H), 1.96-2.00 (m, 2 H), 2.08-2.12 (m, 2 H), 3.84 (m, 1 H), 5.38 (br, d, J = 9.2 Hz, 1 H), 7.38-7.46 (m, 3 H), 7.62 (s, 1 H), 7.75-7.80 (m, 3 H). 20: 1.72 (d, J = 1.2 Hz, 3 H), 1.78 (d, J = 0.8 Hz, 3 H), 3.74-3.93 (m, 3 H), 5.44 (br, q, J = 9.2 Hz, 1 H), 7.36-7.48 (m, 3 H), 7.67 (s, 1 H), 7.77-7.81 (m, 3 H).

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