

THE HIGHLY REGIOSELECTIVE COUPLING REACTION OF ALLYLIC ALCOHOLS WITH LITHIUM ENOLATE OF DITHIOESTERS USING 1-CHLORO-2-METHYL-*N,N*-TETRAMETHYLENEPROPENYLAMINE

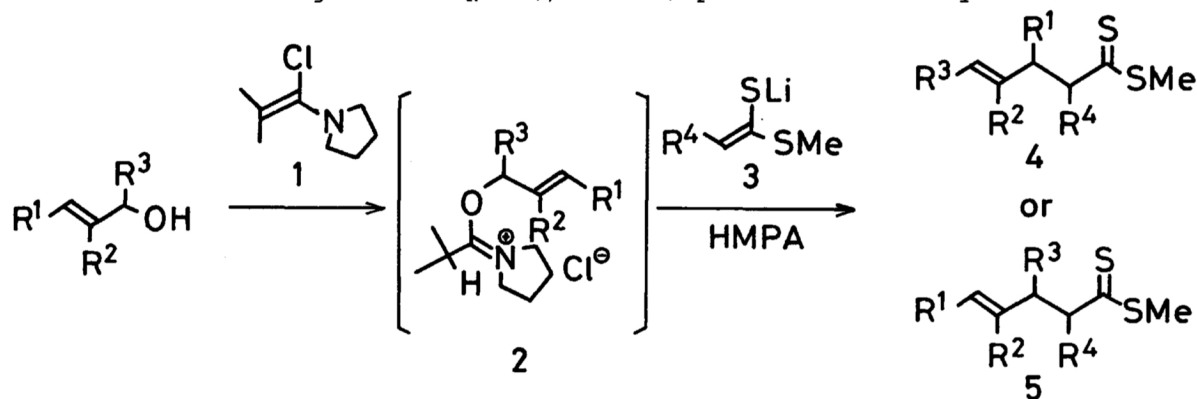
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1-Chloro-2-methyl-*N,N*-tetramethylenepropenylamine was found to be a good condensation reagent for the regioselective coupling reaction of allylic alcohols with lithium enolate of dithioesters under mild conditions to afford γ,δ -unsaturated dithioesters, which proceeds by a thio-Claisen rearrangement of *S*-allylic ketene dithioacetals initially formed.

The coupling reaction of allylic alcohol derivatives with organometallics as a carbon nucleophile provides a useful method for the synthesis of olefin accompanied by new carbon-carbon bond formation.¹⁾ The coupling of allylic esters with active methylene compounds assisted by a palladium catalyst has been well documented so far.²⁾ However, the reaction with rather hard nucleophile such as enolate or its equivalent is limited to a few cases such as the reaction of allylic acetate with boron enolate,³⁾ tin enolate in the presence of a palladium catalyst,⁴⁾ and enol silyl ether in the presence of a Lewis acid,⁵⁾ or the reaction of β -alkynyl- β -propiolactones with lithium enolate of dithioesters.⁶⁾ We wish to describe here the direct and regioselective reaction of allylic alcohols with lithium enolate of dithioesters using 1-chloro-2-methyl-*N,N*-tetramethylenepropenylamine as a condensation reagent to give olefinic products.⁷⁾

α -Chloroenamine **1**, prepared easily from *N,N*-tetramethyleneisobutanamide, oxalyl chloride, and triethylamine,⁸⁾ was subjected to the reaction with crotyl alcohol in THF-CH₂Cl₂ at 0 °C for 15 min. Then the mixture was treated with a THF solution of lithium thioenolate **3** (R⁴ = H) (2.2 equiv.) of methyl ethanedithioate⁹⁾ at -30 °C for 20 h to give the S_N2' (γ -attack) product **4** in 63% yield without any



Scheme 1.

Table 1. Yields of γ,δ -Unsaturated Dithioester 4 or 5 by the Reaction of Various Allylic Alcohols with Lithium Thioenolate 3 using 1-Chloro-2-methyl-*N,N*-tetramethylenepropenylamine [a)]

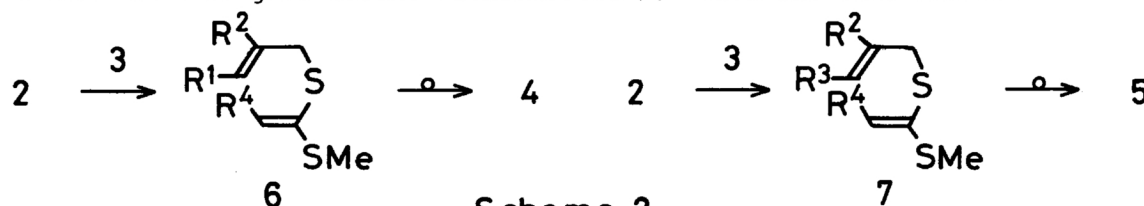
Entry	R ¹	R ²	R ³	R ⁴	Product ^{b)}	Yield/%
1	H	H	H	H	4(=5)	82
2	H	H	H	CH ₃	4(=5)	64
3	H	CH ₃	H	H	4(=5)	88
4	H	CH ₃	H	CH ₃	4(=5)	50
5	CH ₃	H	H	H	4	74
6	<i>n</i> -C ₃ H ₇	H	H	H	4	50
7	C ₆ H ₅	H	H	H	4	46
8	H	H	CH ₃	H	5	54
9	H	H	C ₂ H ₅	H	5	41
10	H	H	<i>n</i> -C ₈ H ₁₇	H	5	45
11	H	CH ₃	CH ₃	H	5	42

a) All reactions were performed on 1 mmol scale with the same procedure as described in the text.

b) All products were identified by NMR and IR spectra.

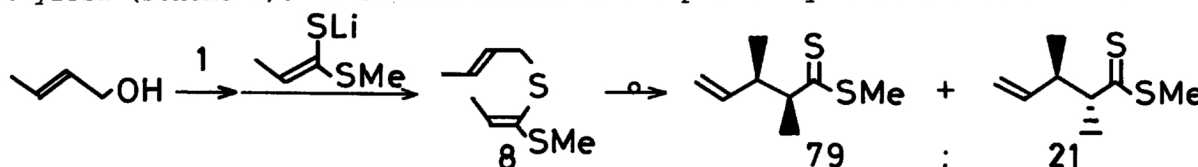
formation of the S_N2 (α -attack) product 5. Addition of hexamethylphosphoric triamide (HMPA) to the mixture was remarkably effective to increase the yield of the coupling product to 74% for a short reaction time of 30 min, and even slightly excess use of the enolate (1.3 equiv.) to the alcohol with an acidic hydrogen was enough to complete the reaction. Although in the coupling reaction of allylic alcohols with Grignard reagents using α -chloroenamine 1^{7b)} a copper catalyst increased the ratio of S_N2' product rather than S_N2 product, the addition of copper (I) iodide (10 mol%) in the present reaction decreased the yield of the S_N2' product to 68%. The result of the reaction of various kinds of allylic alcohols with lithium enolate of dithioesters using α -chloroenamine 1 was summarized in Table 1.

Primary allylic alcohols gave only the S_N2' products 4 (entries 5, 6, and 7), while secondary allylic alcohols with the terminal vinyl group gave only the S_N2 product 5 (entries 8, 9, 10, and 11). The regioselectivity in the reaction seems to be unusual, since the enolate attacked the more hindered site of the allyloxyiminium salts 2 formed initially. The lithium enolate of dithioester, however, has been known to be an ambident nucleophile of carbon and sulfur atoms.¹⁰⁾ Thus the regioselectivity can be reasonably explained by assuming that the sulfide ion in the enolates attacks the less hindered α -carbon of 2 in the case of the primary allylic alcohols (R³ = H) to give initially *S*-allylic ketene dithioacetal 6. On the other hand, in the case of the secondary ones (R³ = alkyl) it attacks terminal vinyl carbon of 2 to give ketene dithioacetal 7. Then the thio-Claisen



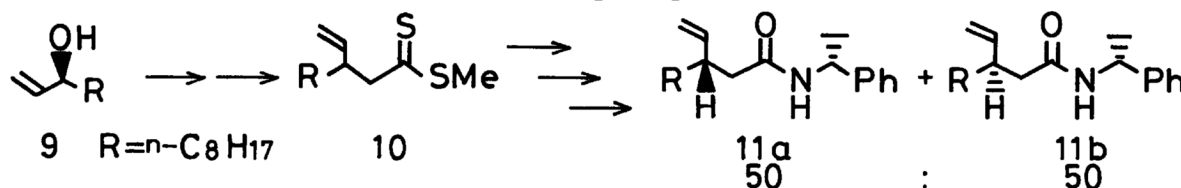
rearrangement of the ketene dithioacetals¹¹⁾ 6 and 7 proceeds to give the products 4 and 5, respectively (Scheme 2).

This reaction path was proved by the following two control experiments. The reaction of crotyl alcohol with the lithium thioenolate of methyl propanedithioate initially showed the formation of *S*-crotyl ketene dithioacetal 8 confirmed by the NMR and IR spectra. Ketene dithioacetal 8 rearranged gradually to the *threo*- and *erythro*- γ,δ -unsaturated dithioesters in a ratio of 79 : 21 at room temperature in 44% yield (Scheme 3). A similar result was reported by Beslin et al.¹²⁾ in the



Scheme 3.

reaction of the same thioenolate with crotyl chloride *via* 8. In addition, the reaction of (*S*)-(+)-1-undecen-3-ol 9¹³⁾ with the lithium thioenolate of methyl ethanedithioate in the presence of the α -chloroamine gave racemic methyl 3-vinylundecanedithioate 10 in 40% yield. The optical purity of the product was confirmed by the transformation of the dithioester into the diastereomeric *N*-[(*R*)- α -methylbenzyl]-3-vinylundecanamide (11a and 11b) (Scheme 4). This indicates that the sulfide ion of the enolate attacks the less hindered terminal vinyl carbon of the iminium salt 2 in the case of the secondary allylic alcohol ($R^1 = H$, $R^3 = \text{alkyl}$),



Scheme 4.

then the thio-Claisen rearrangement occurred resulting in the formation of the racemic product.

A typical procedure is described for the preparation of methyl 3-methyl-4-pentenedithioate: To a solution of 1-chloro-2-methyl-*N,N*-tetramethylenepropenylamine (1.2 ml of 0.993 M CH₂Cl₂ solution, 1.20 mmol) was added a solution of crotyl alcohol (1.0 mmol) in THF (3 ml) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 15 min at the same temperature. Then into a solution of the lithium thioenolate prepared from methyl ethanedithioate (1.30 mmol) and lithium diisopropylamide (1.56 mmol) in THF (10 ml) at -30 °C for 1.5 h, were added HMPA (1 ml) and the solution of the iminium salt at -30 °C. After stirring the reaction mixture at -30 °C for 30 min, the reaction was quenched by adding a saturated aqueous ammonium chloride solution. The organic layer was extracted with ether, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica-gel (hexane, *R_f* = 0.6) to give methyl 3-methyl-4-pentenedithioate in 74% yield.

In conclusion, 1-chloro-2-methyl-*N,N*-tetramethylenepropenylamine is a useful condensation reagent for the regioselective coupling reaction of allylic alcohols

with lithium enolate of dithioester to give γ,δ -unsaturated dithioesters¹⁶⁾ under mild reaction conditions.

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