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A CONVENIENT COUPLING REACTION OF ALLYL ALCOHOLS WITH GRIGNARD REAGENTS USING 1-CHLORO-2-METHYL-N,N-TETRAMETHYLENEPROPENYLAMINE

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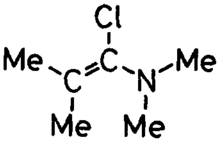
Summary: *1-Chloro-2-methyl-N,N-tetramethylenepropenylamine was found to be a good condensation reagent for a regioselective coupling reaction of allyl alcohols with Grignard reagents under mild conditions to afford olefinic products.*

The allylic unit is a common structural feature of many natural compounds. The coupling reaction of various derivatives of allyl alcohols with organometallics is the most important synthesis for allylic units.[1] Generally the reaction was completed by two-step procedure *via* the corresponding halides,[2] tosylate,[3] acetate,[4] mesitoate,[5] and carbamate.[6] Recently some reports have appeared on the direct coupling of free alcohols with various organometallics such as the Grignard reagents in the presence of nickel catalyst[7] or 2-fluoropyridinium salts,[8] alkyllithium using *N*-methyl-*N*-phenylaminotriphenylphosphonium iodide,[9] or alkylcopper-Lewis acid.[10] However, these methods require excess use (∿ 3 eq) of the organometallics, because the active hydrogen of allyl alcohols reacts with organometallics. Regiochemistry (either S_N2' or S_N2) of the reaction is also a serious problem in allylic system. We now wish to describe here a regioselective coupling of free allyl alcohols with slightly excess Grignard reagents using 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine (2) under mild conditions.



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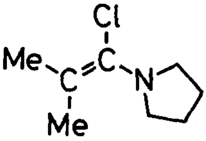

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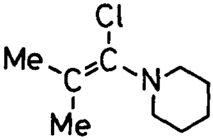

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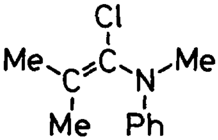

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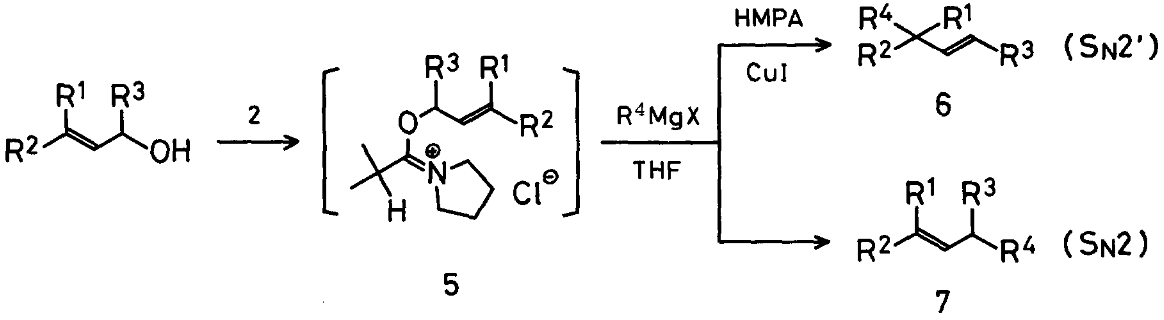
1-Chloro-*N*,*N*,2-trimethylpropenylamine (1) as α-chloroenamine, prepared easily from *N*,*N*-dimethylisobutanamide, oxalyl chloride and triethylamine,[11] was subjected to the reaction with crotyl alcohol in THF (3 ml)-CH_2Cl_2 (1 ml) at 0 °C. Then, a solution of β-phenethylmagnesium bromide was added into the reaction

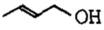
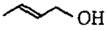
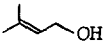
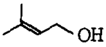
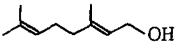
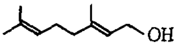
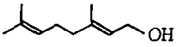
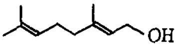
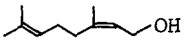
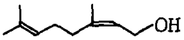
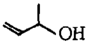
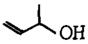


mixture at -30 °C to give the S_N2' and S_N2 reaction (γ- and α-attack) products, 3-methyl-5-phenyl-1-pentene and 6-phenyl-2-hexene, in the ratio of 60:40 in 94% yield. Addition of hexamethylphosphoric triamide (HMPA) (1 ml) or copper(I) iodide (10 mol%) increased the S_N2' product to the ratio of 80:20 or 86:14, respectively. Addition of both HMPA and copper(I) iodide gave predominantly the S_N2' product (96:4). Next, the following α-chloroenamines[11] were subjected to the reaction with crotyl alcohol and β-phenethylmagnesium bromide in the presence of HMPA and copper(I) iodide. The use of 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine (2), 1-chloro-2-methyl-*N*,*N*-pentamethylenepropenylamine (3) and 1-chloro-*N*,2-dimethyl-*N*-phenylpropenylamine (4) gave the desired olefins in the ratio of 99.5:0.5, 97:3, and 56:44 in 98%, 97%, and 18% yields, respectively. Thus, α-chloroenamine 2 was found to be the most effective condensation reagent.

The result of the reaction of various kinds of allyl alcohols with the Grignard reagents using α-chloroenamine 2 in the presence of HMPA and copper(I) iodide was summarized in Table I. The reaction course, giving either olefin 6 or 7, was influenced by the structure of both alcohols and Grignard reagents. Primary alkyl Grignard reagents selectively alkylated at the γ carbon of allyl alcohols in the presence of HMPA and copper(I) iodide (S_N2' reaction) (entries 2, 4,6,8,10,12, and 13). However, the reaction of ethyl Grignard reagent with cinnamyl alcohol selectively produced the S_N2 product (entry 14). On the other hand, phenyl and vinyl Grignard reagents reacted regioselectively at the α carbon in the absence of HMPA and copper(I) iodide (S_N2 reaction) (entries 3,5,7, 9, and 11), except the case of the reaction with 3-buten-2-ol (entry 13). The use of two equiv of Grignard reagents increased the yields of olefins (entries 6, 10, and 11).

The high reactivity of the allyloxyiminium salt 5,[12] formed initially by the reaction of allyl alcohols with α-chloroenamine 2, toward Grignard reagents makes possible the chemoselective coupling of allyl alcohol and Grignard reagent in the co-existence of ketone, ester, nitrile, or halide. When a 1:1 mixture of crotyl alcohol and propiophenone was treated with β-phenethylmagnesium bromide using 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine 2, the desired olefins were obtained in 86% yield and propiophenone was recovered in 98% yield. The similar

Table I. The Cross Coupling Reaction of Allyl Alcohols and Grignard Reagents[a]

Entry	Alcohol	R^4	Yield/%[b]	Ratio[c]		
				6	:	7
1		$PhCH_2CH_2$-	87			
2		$PhCH_2CH_2$-	98	99.5	:	0.5
3		Ph-[d]	100[c]	0.5	:	99.5[e]
4		$PhCH_2CH_2$-	93	91	:	9
5		Ph-[d]	86[c]	0	:	100
6		$PhCH_2CH_2$-	88 (96)[h]	99	:	1
7		Ph-[d]	83 (88)[h]	0.5	:	99.5[e]
8		CH_3CH_2-	85	99	:	1
9		CH_2=CH-[d]	80	9	:	91[e]
10		$PhCH_2CH_2$-	86 (100)[h]	98	:	2
11		Ph-[d]	82 (93)[h]	1	:	99[e]
12		$PhCH_2CH_2$-	78	99[f]	:	1
13		Ph-	77	91[g]	:	9
14		CH_3CH_2-[d]	46	10	:	90[e]

[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. [c] Determined by glc. [d] In the absence of HMPA and copper(I) iodide. [e] The geometry of double bond is reserved. [f] E:Z = 60:40. [g] E:Z = 66:34. [h] Two equiv of RMgBr were used.

reaction in co-existence of ethyl laurate, benzonitrile or octyl bromide instead of the ketone gave the olefins in 84 ∿ 95% yields with recovery of them in over 95% yields.

A representative procedure for the present reaction of crotyl alcohol with β-phenethylmagnesium bromide is as follows. To a solution of 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine (1.3 ml of 0.923 M CH_2Cl_2 solution, 1.2 mmol)[11] was added a solution of crotyl alcohol (1.0 mmol) in THF (3 ml) at 0 °C under an argon atomosphere, and the reaction mixture was stirred for 15 min at the same temperature. Then the mixture was cooled to -30 °C, and hexamethylphosphoric triamide (1 ml), copper(I) iodide (10 mol%) and a solution of β-phenethylmagnesium bromide (1.50 ml of 0.865 M THF solution, 1.3 mmol) was subsequently added to the reaction mixture. After stirring for 30 min, the reaction was quenched by the addition of 2 M HCl aq solution. The organic layer was extracted with ether and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica-gel TLC (hexane, Rf = 0.8) to give 3-methyl-5-phenyl-1-pentene and 6-phenyl-2-hexene in the ratio of 99.5:0.5 in 98% yield.

In conclusion 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine is an effective condensation reagent for the coupling reaction of allyl alcohol with Grignard reagents in good yields with high regioselectivity and chemoselectivity under mild conditions and in one-pot operation.

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12. It has been known that the reaction of alcohols with α-chloroenamine give the corresponding alkyl chlorides (L. Ghosez and J. Marchand-Brynaera, "α-Haloenamines and Keteniminium Salts," in H. Bohme and H. G. Viehe, Eds., "Iminium Salts in Organic Chemistry," Part 1, Vol. 9, in the series "Advances in Organic Chemistry," 1976, P. 498). In the present reaction, although the reaction path *via* allyl chloride from allyl alcohol was presumable, the following fact seemed to exclude the formation of allyl chloride. The reaction of crotyl chloride with β-phenethylmagnesium bromide in the presence of HMPA and copper(I) iodide afforded a mixture of 3-methyl-5-phenyl-1-pentene and 6-phenyl-2-hexene in 85% yield in the ratio of 70:30, respectively, which was much inferior to the selectivity (99.5:0.5) of the reaction of crotyl alcohol using α-chloroenamine 2.

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