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The reaction of 1-chloro-2-methyl-1-propenyllithium with a selection of organolithiums. The development and synthetic utility of novel base/nucleophile combinations

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Abstract

The title compound was generated by and reacted with (1) a series of reagents which have basic as well as nucleophilic properties and (2) a series of base/nucleophile combinations. Product yields of the isobutenyl derivative were generally low to very good, and the best results (89%) were obtained by using a 1:2 ratio (3 equiv total) of ^{n}BuLi:LiPPh$_2$. Synthetic utility of the reaction is optimized as it approaches a situation in which the base/nucleophile combination is composed of one compound which is both a strong base and a poor nucleophile and another compound which is both a weak base and a good nucleophile.

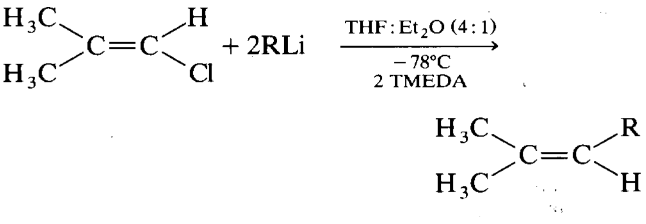
1. Introduction

Many biologically active compounds, such as prostaglandins and insect pheromones, have trisubstituted alkenes in their molecular systems [1]. A particularly intriguing route to such alkenes is via α-haloalkenylmetals [2–8,10–15], intermediates which are known as carbenoids and which are capable of undergoing ambiphilic reactions [9]. Examples of these reactions include a wide range of metals; lithium, [2–8,10–13], boron [10l,n,12], magnesium [2], aluminum [10m], silicon [12,13], copper [10f,g], germanium [10j], silver, [2,10a,b], tin [10h–j], and mercury [2,3,10e]. Reactions of α-haloalkenylmetals with nucleophiles are relatively unexplored and more interesting mechanistically [9,11]. In several studies [2,12–15] of the reactions of 1-chloro-2-methyl-1-propenyllithium, it is generated by reacting an alkyllithium with 1-chloromethylpropene. However, the synthetic utility of the intermediate is not fully developed, and there is little comparison of the reactivities of the precursor or intermediate with various bases and nucleophiles. This reactivity is an extremely important aspect of the reaction, since once of the major hindrances to its development has been the rapid nucleophilic attack upon the carbenoid by a second equivalent of the base or by a second equivalent of itself rather than by the intended nucleophile [14].

The present work describes the metallating abilities and nucleophilic activities of some organolithium compounds towards 1-chloromethylpropene, both individually and combined. It also reports the development of novel base/nucleophile combinations, which are each composed of an alkyllithium and a heteroanion and which will facilitate the general synthetic utilization of the reaction of these carbenoids with nucleophiles.

2. Results and discussion

The reaction of organolithiums with 1-chloromethylpropene is general (eqn. (1)), and the yields are low to very good.



R = Me, ^{n}Bu, ^{t}Bu, ph, PhCH$_2$ (1)

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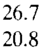
The results of treatment of 1-chloromethylpropene with various alkyllithiums (2 equiv) in the presence of tetramethylethylenediamine (TMEDA) and with ^{n}BuLi in the absence of TMEDA with tetrahydrofuran (THF):ether (4:1) as solvent at −78°C are given in Table 1. The use of ^{n}Butyllithium gives 2-methyl-2-heptene in 46% yield (entry 1), and treatment with methyllithium gives a 23% yield of adduct (entry 7). Phenyllithium and benzyllithium are intermediate in reactivity and produce 31.5% (entry 6) and 39% (entry 8) of the corresponding alkenes respectively. The order of product yields of the alkyllithiums is ^{n}BuLi > PhCH$_2$Li > PhLi > ^{t}BuLi > MeLi. Though a detailed mechanistic study of this metallation has not been reported [17,18], metallating abilities of organolithiums without TMEDA nevertheless gave results similar to ours. The yield is slightly higher when an amount of TMEDA equivalent to that of ^{n}BuLi was used (entries 1 *vs.* 2), and this is probably due to the well-known ability of TMEDA to coordinate with lithium [20] and to increase the kinetic basicity [13] of organolithiums. The use of ^{t}BuLi instead of ^{n}BuLi gives much lower yields (entries 4 *vs.* 1 and 5 *vs.* 3). Increasing the temperature from −78 to −65°C decreases the yield slightly (entries 1 *vs.* 3 and 4 *vs.* 5). Although the study has not been extended to all organolithium compounds, this trend is generally expected since the intermediate carbenoids are unstable at higher temperature, and these reactions must therefore be carried out at low temperatures.

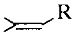
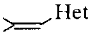
The reactions of 1-chloromethylpropene with 2 equiv of Et$_2$NLi or Ph$_2$PLi were carried out in order to include reactions with heteroanions in the study. The functionalized alkene yield increases with these anions. Using 2 equiv of lithium diethylamide gives diethylisobutenylamine in 43% yield (entry 3), and the reaction with lithium diphenylphosphide (2 equiv) yields 16.3% of isobutenyldiphenylphosphine (entry 5). Reaction with EtOLi (entry 4) or EtSLi (entry 6) is very sluggish and does not give the desired product in good yield. The use of EtONa or EtSNa gives even slightly lower yields.

TABLE 1. The effect of TMEDA and temperature upon the reactions of 1-chloro-2-methylpropene with organolithiums (RLi) in THF:ether (4:1)

entry	organolithium (RLi)	TMEDA (equiv)	temperature (°C)	yield (%) [a] 
1	^{n}BuLi	2	−78	46.0
2	^{n}BuLi	no	−78	38.3
3	^{n}BuLi	2	−65	42.8
4	^{t}BuLi	2	−78	26.7
5	^{t}BuLi	2	−65	20.8
6	PhLi	2	−78	31.5
7	MeLi	2	−78	23.0
8	PhCH$_2$Li	2	−78	39.0

[a] Typical deviations are ±1.76.

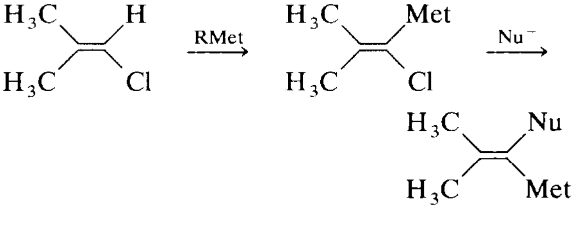
TABLE 2. Yields of reactions of 1-chloro-2-methylpropene with bases and nucleophiles (1 equiv each) run in the presence of TMEDA (2 equiv) in THF:Ether (4:1) at −78°C

entry	RLi or HetLi		yield (%) [a]	
q	base	nucleophile		
1	^{n}BuLi	^{n}BuLi	46.0	–
2	^{t}BuLi	^{t}BuLi	26.7	–
3	Et$_2$NLi	Et$_2$NLi	–	43.0
4	EtOLi	EtOLi	–	2.6
5	Ph$_2$PLi	Ph$_2$PLi	–	9.3
6	EtSLi	EtSLi	–	1.5
7	^{n}BuLi	Et$_2$NLi	14.6	27.5
8	^{n}BuLi	EtOLi	18.8	3.2
9	^{n}BuLi	Ph$_2$PLi	16.7	69.0
10	^{t}BuLi	Ph$_2$PLi	1.2	58.0
11	^{n}BuLi	Ph$_2$PLi (2 equiv)	10.5	86.7
12	^{t}BuLi	Ph$_2$PLi (2 equiv)	0.7	78.0
13	^{n}BuLi	EtSLi	24.1	8.7
14	^{t}BuLi	EtSLi	17.0	4.2
15	^{n}BuLi	PhSLi	29.6	34.6
16	^{t}BuLi	PhSLi	5.0	21.7

[a] Typical deviations from the average yields are ±1.07 and ±2.1 for alkenes and heteroalkenes respectively.

Reported general basicity orders [19] of these heteroanions are R$_3$C$^-$ > R$_2$N$^-$ > RO$^-$ > RS$^-$; and R$_2$N$^-$ > R$_2$P$^-$. Reported nucleophilicity orders [19] are R$_3$C$^-$ > R$_2$N$^-$ > RO$^-$; R$_2$P$^-$ > R$_2$N$^-$; and RS$^-$ > RO$^-$. Although these may not hold in all cases and may depend upon various other conditions, they are consistent with most results. In accord with the above orderings, the results of this study can be rationalized that (1) Bu$^-$ and Et$_2$N$^-$ are good bases but not good enough nucleophiles, (2) Ph$_2$P$^-$ is a good nucleophile but a poor base and (3) EtOLi and EtSLi are not good enough as bases or as nucleophiles. Thus, the low yields (Table 2) of the reactions of 1-chloromethylpropene with 2 equiv of the various hetero-anions could result because none of these is a good base as well as a good nucleophile.

It has been reported [2,11] that the primary step in the reaction is α-lithiation by an organolithium to give the carbenoid and that in the second step, nucleophile substitution takes place to give the product.



(2)

Thus, in these reactions, at least two equiv of organolithiums were used; it was reasoned [2,11] that one equiv serves as a base in the metallation, and one equiv as a nucleophile in the ensuing nucleophile attack. The report [2,11] that the first step, leading to the reactive carbenoid, would be slow and the second, nuclophilic attack, would be fast seems reasonable. In view of the reported mechanism [2,11], a greater ability of the organolithium to metallate the substrate and an increased nucleophilicity of the desired nucleophile should each increase the yield of the overall reaction.

In order to explore this reasoning, we also studied the reactions of 1-chloromethylpropene with a selection of heteroanions, which serve as both base and nucleophile, as well as with base/nucleophile combinations composed of heteroanions plus n- or ^{t}Butyllithium (Table 2). Reactions using base/nucleophile mixtures were devised based on the proposed mechanism [2,11] (eqn. 2). By using the base/nucleophile combinations, we expected that a solution composed of such mixed reagents could furnish one reagent which would function predominantly as a base and the other reagent would function predominantly as a nucleophile, in the presence of each other (eqn. (2)). This should take advantage of the differing dependencies of the mechanistic steps upon basicity and nucleophilicity. It also provided us a comparison of the effects of nucleophilicity of the heteroanions in the second step, since the base is always BuLi. With ^{n}Butyllithium and EtOLi (entry 8), production of 2-methyl-2-heptene rather than the vinylic ether is dominant. Using ethylthiolate (entries 13 and 14) offers little improvement. However, switching to lithium phenylthiolate or lithium diethylamide gives slightly higher yields. As hoped, use of one of the strongest nucleophiles ($LiPPh_2$) in a 1:1 combination with the strongest base (either ^{n}BuLi or ^{t}BuLi), increases the yield to 66 or 58.2% respectively (entries 9 and 10). The improved results using Ph_2PLi in the base/nucleophile combination are in accord with the proposed mechanism [2,11], and the concept that ^{n}BuLi functions as the metallating agent and Ph_2P^- functions as the nucleophile [16*].

In each reaction of 1-chloromethylpropene with a base/nucleophile mixture, the stronger base was added first, followed by the better nucleophile. If addition of the nucleophile was delayed, the product incorporating the base was increased at the expense of that incorporating the nucleophile. This supports the concept that the intended base and the intended nucleophile compete for the carbenoid.

As a final optimization of yields, we increased the concentration of the nucleophile (Ph_2PLi) expecting the more basic BuLi would be even less competitive as nucleophile. As expected, not only is the yield of diphenylisobutenylphosphine increased (to 89.2 from 66.0%) by this, but also the yield of 2-methyl-2-heptene is reduced (to 9.5 from 20.9%).

3. Conclusion

The reaction of 1-chloromethylpropene with various organolithium compounds gives the isobutenyl products in low to moderate yields. The use of an organolithium as a base with a lithium alkoxide as a nucleophile yields predominantly the alkene rather than the vinyl ether. The vinyl amine is obtained in moderate yield by using 2 equiv of Et_2NLi, and the vinyl phosphine is obtained in very good yield by using a base/nucleophile combination of ^{n}BuLi/Ph_2PLi. In order for the reaction to be synthetically useful, one needs a base/nucleophile mixture which consists of a good base with relatively low nucleophilicity and a good nucleophile with relatively low basicity.

4. Experimental section

4.1. General Data

Standard techniques for handling air- and moisture-sensitive compounds were used [21]. The alkene was purchased from Aldrich Chemical Co., distilled under nitrogen from a small amount of calcium hydride, and then stored under nitrogen. THF and ether were distilled over LAH and stored under nitrogen. The alkanes used as internal standards were obtained from the Humphrey Chemical Co. and were used as received. ^{n}BuLi, ^{t}BuLi, MeLi, and PhLi were purchased from Aldrich Chemical Co. Benzyllithium [22] lithium diethylamide [23], diphenylphosphinolithium [24], sodium thiophenoxide [25], lithium thiophenoxide [26], lithium ethoxide [27], and sodium ethoxide [28] were prepared according to the reported methods. Diethylamine, chlorodiphenylphosphine, benzylether, ethanethiol, thiophenol, and lithium were purchased from Aldrich Chemical Co. Ethanethiol, thiophenol, chlorodiphenylphosphine, and benzyl ether were distilled before use. Diethylamine was dried with LAH, refluxed, and distilled from KOH under nitrogen [29].

4.2. Instruments

The GC analyses were carried out on a Hewlett-Packard 5890 gas chromatograph equipped with a flame ionization detector and connected to a Hewlett-Packard 3390A integrator. A 6 m, 3.2 mm o.d. column packed with 10% SE-30 on 100/200-mesh Chromosorb-W was

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* Reference number with an asterisk indicates a note in the list of references.

used. Mass spectral data were obtained on a Hewlett-Packard 5895 gas chromatograph/mass spectrometer data system equipped with a 15 m, 0.25 mm i.d. J&W DB-1 capillary column.

4.3. Reaction of 1-chloromethylpropene with organolithiums

In all cases, the reactions were carried out on a 5 mmol scale in 15 ml of THF:Et_2O (4:1) solvent. The procedure used was similar to that reported previously [13,14]. The chloroalkene, the n-alkane used as internal standard, THF, ether, and TMEDA were transferred via syringes to a 50 ml round bottom flask equipped with a magnetic stirring bar. The solution was then cooled to the desired temperature by the use of dry ice/acetone. Two equiv of the organolithium were added via syringe to the reaction flask. The reaction mixture was stirred at the desired temperature for 6 h and allowed to warm to room temperature. Then, 5 ml of water were added, and the reaction mixture was extracted with ether. The ether layer was washed with water and dried over anhydrous $MgSO_4$. Yields were determined by GC and reported as the averages of at least three runs.

As reported in our initial study of these systems [14a], several different sets of reaction conditions were explored before the above conditions were adopted. Modifying various conditions, such as times of various steps and quenching with water at a lower temperature had little effect on the yield. The above conditions gave the best results. Quenching with D_2O did not result in incorporation of deuterium in recovered alkene.

4.4. Reactions of 1-chloromethylpropene with heteroanions

The reactions were carried out as described above with the following exceptions. An appropriate number of equivalents of the organolithium, heteroanion, or both was used; the substance which was considered to be the base was added first, followed by the substance which was considered the nucleophile. If addition of the nucleophile was delayed, the product incorporating the base was increased at the expense of that incorporating the nucleophile.

4.5. Product identification

Products 2-methyl-2-butene, 2-methyl-2-heptene, 2-methyl-1-propenylbenzene, and 2,4,4-trimethylpent-2-ene were identified by GC coinjection with authentic samples purchased from Aldrich Chemical Co. Some (< 10%) of the recovered material is 1-chloro-2-methylpropene, as reported in earlier studies [24d]. As reported previously, significant and varying amounts of products resulting from dimerization and, in some cases, trimerization of the carbenoid were observed in the GC/MS.

3-Methyl-1-phenyl-2-butene, obtained in the reactions using either 1 or 2 equivalents of benzyllithium, was identified by comparison with previously-reported spectral data [30]. The ^1H NMR data were: (300 MHz, $CDCl_3$) d 7.05 (5H, s), 5.25 (1H, t), 3.2 (2H, d) and 1.7–1.6 (6H, m). The GC/MS data were: m/z (relative intensity) 146 $[M]^+$ 52; 131 $[M-CH_3]^+$ 100; 91 $[C_7H_7]^+$ 48; 77 $[C_6H_5]^+$ 8.

1-*N*,*N*-Diethylaminomethylpropene was obtained by an alternate route by reacting isobutyraldehyde with diethylamine and xylene in the presence of anhydrous potassium carbonate for 4 h at 100°C as reported previously [31]. Its identity was confirmed by GC/MS data: m/z (relative intensity) 127 $[M]^+$ 63; 112 $[M-CH_3]^+$ 100; 98 $[M-C_2H_5]^+$ 15; 82 $[Et_2N]^+$ 12; 42 $[C_3H_6]^+$ 28.

Diphenyl(2-methylpropenyl)phosphine was prepared by an alternate synthesis reported in the literature [32], in which the Grignard of 1-bromomethylpropene was reacted with chlorodiphenylphosphine in THF. The product diphenyl(2-methylpropenyl)phosphine from our reaction was identified by GC coinjection with the sample obtained from this synthesis. The GC/MS data confirmed its identity; m/z (relative intensity) 240 $[M]^+$ 100; 225 $[M-CH_3]^+$ 8; 185 $[PPh_2]^+$ 18; 108 $[PPh]^+$ 30; 91 $[C_7H_7]^+$ 22.

2-Methylpropenylthiobenzene was purified by column chromatography and the GC/MS data were compared to those previously reported [16]: m/z (relative intensity) 164 $[M]^+$ 100; 149 $[M-CH_3]^+$ 40; 110 $[C_6H_6S]^+$ 24; 77 $[C_6H_5]^+$ 13.

The other products of reactions with heteroanions were identified by comparison of spectroscopic data with that of authentic samples.

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