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Preliminary communication

THE ADDITION OF THE NORMANT REAGENT ("CH_3MgBr" + CuBr) TO TERMINAL ALKYNES IN THF. CONCERNING THE NATURE OF THE REACTIVE SPECIES IN SOLUTION

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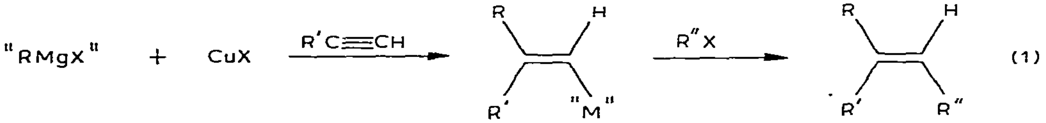
Summary

The reactive intermediates in the Normant reagent responsible for reaction with terminal alkynes in THF have been determined.

The stoichiometric mixture of Grignard reagent and cuprous salt is a versatile reagent for the stereoselective synthesis of trisubstituted alkenes from terminal alkynes (eq. 1) [1].



The importance of trisubstituted alkenes in the synthesis of isoprenoid natural products [2], and the ease with which they are formed by the transformation in eq. 1, makes an understanding of the nature of the Normant reagent highly desirable. We have now studied the solution composition of a mixture of "CH_3MgBr" and CuBr in THF to determine (1) what compounds are formed in this reaction mixture, (2) how much of each compound formed is present at a particular time under the conditions of addition to the terminal alkyne, and (3) which compounds actually add to the terminal alkyne.

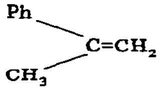
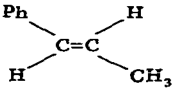
Depending on the time and temperature of reaction, a mixture of "CH_3MgBr" and CuBr in THF has been found to contain the following compounds; $CuMg(CH_3)_3$, $Cu_3Mg_2(CH_3)_7$, $Cu_2Mg(CH_3)_4$, $Cu_3Mg(CH_3)_5$, $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$. The characterization of these compounds and conditions under which they form in the reaction of "CH_3MgBr" with CuBr is reported elsewhere [3]. This report will concentrate on the determination of the exact species in the Normant reagent responsible for addition to phenylacetylene (A), used as a model system.

Entry 1 (Table 1) shows that after 24 hours at —25° C the mixture "CH_3MgBr" and CuBr (Normant reagent) gave upon hydrolysis a 36% yield of addition products [4] consisting of $Ph(CH_3)C{=}CH_2$ (B_1) and (*E*)-$PhCH{=}CH(CH_3)$ (B_2) in 2:1 ratio, respectively. $CuMg(CH_3)_3$ (entry 2), $Cu_3Mg_2(CH_3)_7$ (entry 3), and $Cu_2Mg(CH_3)_4$ (entry 4) gave no addition products under similar conditions. $Cu_3Mg(CH_3)_5$ (entry 5) and $Cu_4Mg(CH_3)_6$ (entry 6) gave small amounts of B_1 under the same conditions. Only $Cu_6Mg(CH_3)_8$ (entry 7) gave B_1 and B_2 in amounts and approximate ratio comparable to the mixture of "CH_3MgBr" and CuBr. $Cu_6Mg(CH_3)_8$ is only metastable at even —50° C and slowly decomposes to a mixture of solid methylcopper and $Cu_4Mg(CH_3)_6$. Thus reactions of (A) with $Cu_6Mg(CH_3)_8$ had to be carried out by adding (A) to a —45° C solution of $Cu_6Mg(CH_3)_8$ after which the resultant mixture was allowed to warm to —30° C over a 15 minute period. The reaction was complete in two hours or less at —30° C.

As mentioned earlier, the composition of the "CH_3MgBr"-CuBr mixture is dependent on reaction time and temperature. The preparation of this reagent in the literature is usually carried out at or below —40° C [1,4]. However, we have found that preparing this reagent at —40° C for two hours or

TABLE 1

REACTIONS OF COPPER MAGNESIUM ALKYLS WITH PHENYLACETYLENE IN TETRAHYDROFURAN[a]

Entry	Copper magnesium alkyl	$PhC{\equiv}CH{:}MgBr_2{:}$Reagent[b]	Yield product[c,d] (%)	
				
			(B_1)	(B_2)
1	CuBr + CH_3MgBr[e]		24	12
2	$CuMgMe_3$	3:0.5:1	0	0
3	$Cu_3Mg_2Me_7$	7:1;5:1	0	0
4	Cu_2MgMe_4	4:1:1	0	0
5	Cu_3MgMe_5	5:1.5:1	2.4	0
6	Cu_4MgMe_6	6:2:1	7.3	0
7	Cu_6MgMe_8[f]	8:3:1	20	8
8	$CuMgMe_3$	3:5:1	0	0
9	$CuMg_2Me_7$	7:17:1	0	0
10	Cu_2MgMe_4	4:4:1	1.5	0
11	Cu_3MgMe_5	5:5:1	6.5	1.3
12	Cu_4MgMe_6	6:6:1	10	3
13	Cu_6MgMe_8[g]	8:8:1	35	13

[a] Reactions were carried out at —25° C for 24 h. $PhC{\equiv}CH$ was added in 1:1 molar ratio per CH_3 group. [b] $PhC{\equiv}CH$ was added in 1:1 molar per CH_3. [c] These were the only addition products obtained on hydrolysis with pH_8 NH_4Cl unless otherwise noted. The remainder of the mass balance is accounted for by recovered phenylacetylene and in some cases by 1—2% of $PhC{\equiv}CCH_3$. [d] Normalized as % B_1 + % B_2 + % $PhC{\equiv}CH$ = 100%. [e] CuBr + CH_3MgBr in 1:1 ratio was stirred for either 2 h at —40° C or 1 h. at —25° C before $PhC{\equiv}CH$ was added. In either case the reaction was maintained at —25° C after the $PhC{\equiv}CH$ was added. [f] See text for reaction conditions. [g] 1% of (*Z*)-$Ph(CH_3)C{=}CH(CH_3)$ was also obtained.

at —25°C for one hour gives the same yield and distribution of addition products with (A). The mixture, "CH_3MgBr"-CuBr, does contain more free $MgBr_2$ at —25°C after one hour than do the reactions in entries 2—7. The addition of $MgBr_2$ to the reactions of $CuMg(CH_3)_3$ (entry 8) and $Cu_3Mg_2(CH_3)_7$ (entry 9) again gave no addition product. However, increasing the amount of $MgBr_2$ in the reaction of $Cu_2Mg(CH_3)_4$ (entry 10) produced a small yield of B_1. Added $MgBr_2$ increased the yields of addition of $Cu_3Mg(CH_3)_5$ (entry 11) and $Cu_4Mg(CH_3)_6$ (entry 12) significantly, producing both B_1 and B_2 as products. $MgBr_2$ added to $Cu_6Mg(CH_3)_8$ (entry 13) yielded more addition product than the mixture of "CH_3MgBr" and CuBr and produced B_1 and B_2 in a ratio of 3:1. The effect of $MgBr_2$ on the reaction is difficult to rationalize since infrared analysis of a mixture of $MgBr_2$ and (A) in THF shows no interaction and $MgBr_2$ does not appear to interact with any of the copper-magnesium compounds according to NMR analysis.

It appears that only $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$ are likely candidates as the active component(s) of the mixture of "CH_3MgBr" and CuBr. The composition of the mixture (Normant reagent) after one hour at —25°C consists of a solid containing 65% of the starting copper as a 4:1 mixture of methylcopper and cuprous bromide and a solution composed of a 6:1 mixture of $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$. While $Cu_6Mg(CH_3)_8$ gives a higher yield of addition products with (A) than does $Cu_4Mg(CH_3)_6$, the amount of $Cu_6Mg(CH_3)_8$ in the "CH_3MgBr"-CuBr mixture is smaller [3], Figure 1 shows a plot of % yield of total addition product from A by $Cu_6Mg(CH_3)_8$ + $3MgBr_2$, $Cu_4Mg(CH_3)_6$ + $6MgBr_2$ and the "CH_3MgBr"—CuBr mixture at —40°C in THF vs. time. The rate of addition by $Cu_6Mg(CH_3)_8$ + $8MgBr_2$ is significantly faster overall than the "CH_3MgBr"—CuBr mixture, but only slightly faster than $Cu_4Mg(CH_3)_6$ + $6MgBr_2$. The rate of the "CH_3MgBr"—CuBr mixture increases with time indicating an increase in concentration of the reactive intermediate as the reaction proceeds. $Cu_4Mg(CH_3)_8$ gives more addition

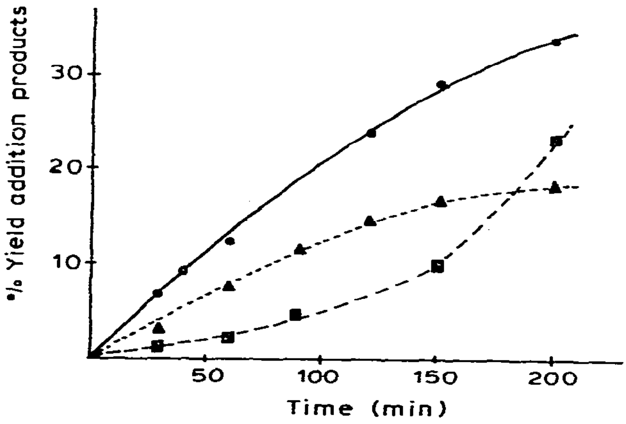


Fig. 1. Reaction of Cu_6MgMe_8+$8MgBr_2$ (●), Cu_4MgMe_6+$6MgBr_2$ (▲) and "CH_3MgBr"-CuBr (■) with phenylacetylene in THF at —40°C. The reactions were 0.1 *M* in phenylacetylene and the CH_3:PhC≡CH ratio was 1:1.

product at —40°C than at —25°C, but the rate of addition falls off at a time when the rate of the "CH_3MgBr"-CuBr mixture is increasing. These kinetic results can be attributed to a significant contribution by the more abundant $Cu_4Mg(CH_3)_6$ in the early stages of addition by the "CH_3MgBr"—CuBr mixture As the reaction proceeds the concentration of $Cu_6Mg(CH_3)_8$ in the mixture increases and the rate of addition increases. One alternative possibility is that a mixed methyl-styryl compound with the formula $Cu_6Mg(CH_3)_{8-X}(HC{=}C(CH_3)Ph)_X$ or $Cu_6Mg(CH_3)_{8-X}[C(Ph){=}C(CH_3)H]_X$ forms and is responsible for the increased rate of addition by the "CH_3MgBr-CuBr mixture.

The stereochemistry of the addition reactions by $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$ were determined to be exclusively *cis*. Deuterolysis of the reaction mixtures gave only (*E*)-Ph(CH_3)C=C(*H*)D and no (*Z*)-HC(CH_3)=CDPh was observed by either ^{1}H NMR or GLC. Exclusive *cis* addition by "RMgX"-CuX mixtures to terminal alkynes is well documented [1,4]. The appearance of B_2 in the reactions of $Cu_4Mg(CH_3)_6$ +6$MgBr_2$, $Cu_6Mg(CH_3)_8$ +8$MgBr_2$ (or 3$MgBr_2$) and the "CH_3MgBr"-CuBr mixture is unusual since only the more sterically hindered alkyl groups, e.g., isopropyl and tert-butyl, have been previously observed to give addition to the terminal end of a terminal alkyne. Kinetic analysis demonstrated that the ratio of B_1 to B_2 decreased as the reactions proceeded indicating that B_2 may arise by reaction of A with a mixed methyl styryl compound [6]. This would also explain the difference in the B_1 :B_2 ratios observed for reactions of $Cu_4Mg(CH_3)_6$ +6$MgBr_2$, $Cu_6Mg(CH_3)_8$ + 8$MgBr_2$ and the "CH_3MgBr"-CuBr mixture with A. The former two are present in high concentration vs. any mixed methyl-styryl compound that forms as the reaction proceeds giving rise to a higher B_1 to B_2 ratio. However, the concentration of $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$ in the "CH_3MgBr"-CuBr mixture is initially small and would allow more B_2 to be formed.

It seems clear from these studies that a mixture of $Cu_4Mg(CH_3)_6$ and $Cu_6Mg(CH_3)_8$ in the presence of $MgBr_2$ is the reactive intermediate when the Normant reagent is allowed to react with a terminal alkyne. Other Grignard reagent-cuprous halide mixtures react with terminal alkynes to give higher yields of addition product at faster rates than does the "CH_3MgBr"-CuBr mixture in THF. We are now actively pursuing further studies with other Grignard reagents in an attempt to broaden the scope of our results.

Although reactions of Normant reagents with alkynes proceed in higher yields when the R group of the Normant reagent is other than methyl, the present study was carried out for the reagent where R = CH_3 (singlet) due to the extreme complexity of the NMR system when the R group was other than methyl. We plan to extend our studies in the near future to include R groups other than methyl.

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6 Another possibility is that compounds of the type $Cu_4Mg(CH_3)_{6-X}(C\equiv CPh)_X$, $Cu_6Mg(CH_3)_{8-X}(C\equiv CPh)_X$ from deprotonation of $PhC\equiv CH$ are responsible for the formation of B_2. Deprotonation of $PhC\equiv CH$ was a serious side reaction and gave $PhC\equiv CH$ on hydrolysis.