BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(8), 2389—2390 (1975)

Effects of HMPA in the Kharasch Type Reaction of Allylic Halides

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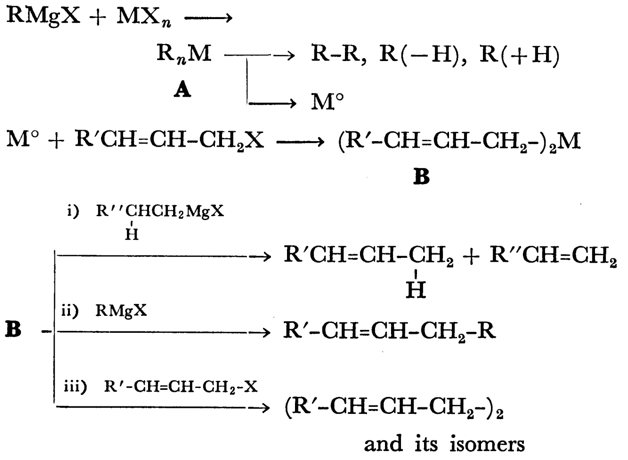
(Received December 17, 1974)

Synopsis. Addition of HMPA was found to bring about an increase of cross-coupling products in the transition metal catalyzed reaction of allylic chlorides (allyl, crotyl, and methallyl) with Grignard reagents, the effect being most significant in copper (II) chloride catalyzed reactions.

In previous papers[1,2] it was shown that the Kharasch type reaction of an allylic halide with a Grignard reagent catalyzed by a transition metal halide resulted in the formation of a product mixture which could be understood by considering the following three processes (routes i, ii and iii), relative importance of the routes depending on the nature of an intermediate organometallic species and the structure of the Grignard reagent.



Our previous studies were concerned mainly with the structure and behavior of the allylic metal intermediate (**B**).

The reactivity of a Grignard reagent can be considered as an important factor affecting the distribution of the products from allylic halide. The presence of an additive of strongly dative nature such as HMPA causes a considerable change in the reactions of Grignard reagents.[3]

We have examined the effect of HMPA in the Kharasch type reaction of allylic halides with the intention of increasing the selectivity of the reaction for obtaining cross-coupling products (route ii) by increasing nucleophilic activity of Grignard reagents.[4]

Results and Discussion

Table 1 shows the results obtained in the nickel (II) chloride catalyzed reactions of three typical allylic halides in the presence of two equivalents of HMPA to Grignard reagents, together with those without HMPA.

The effect of HMPA varies considerably with the type of halide. The product distribution from crotyl chloride was not influenced materially by the addition of HMPA except for a small increase in cross-coupling products. On the other hand, in the reaction with allyl chloride, a considerable decrease in the hydrogen transfer process (route i, formation of R(−H) and allyl (+H)) occurred accompanied by an increase in the cross-coupling product as well as R–R and homo-coupling products. A similar trend was observed with methallyl chloride to a lesser extent. The use of tetramethylethylenediamine (TMED) or dimethoxyethane (DME) produced a similar effect to that observed with HMPA, but resulted in a decrease in the total yield of products from methallyl chloride.

Dependence of the effect of HMPA on the type of catalyst was examined with methallyl chloride. The results are summarized in Table 2.

The use of one equivalent of HMPA in the presence of copper (II) chloride was found to be most effective for increasing the selectivity towards the cross-coupling process. The addition of HMPA seems to influence not only the reactivity of the Grignard reagents but also that of alkylmetal (**A**) and/or allylic metal intermediate (**B**).

It was found[5] that in the nickel(II) salt catalyzed

TABLE 1. EFFECT OF ADDITIVES IN THE NICKEL(II) CATALYZED REACTION OF ALLYLIC HALIDES[a)]

R-MgBr	*n*-Bu-	Et-	*n*-Pr-		
Allylic chloride(Ally-Cl)	Allyl-	Crotyl-	Methallyl-		
Additive	HMPA	HMPA	HMPA	TMEDA	DME
R(+H)	4(1)	29(23)	10(28)	34	19
R(−H)	37(81)	62(69)	34(60)	4	1
Ally(+H)	38(70)	8(8)	30(61)	3	1
R-R	18(7)	10(16)	20(t)	16	5
Cross-coupling(R-Ally)	21(3)	15(t)	28(8)	16	6
Homo-coupling[(Ally)$_2$]	19(3)	43(47)	15(12)	15	10

a) Values(%) are based on the theoretical amount; t: trace amount; ( ): yields without the additive. Two molar equivalents of the additives to Grignard reagent were used.

TABLE 2. EFFECT OF HMPA IN THE REACTION OF *n*-PROPYLMAGNESIUM BROMIDE (R-MgBr) WITH METHALLYL CHLORIDE(Ally-Cl)[a)]

MX_n	Non		$NiCl_2$	$CoCl_2$	$FeCl_3$	$CuCl_2$		
HMPA(×0.05 mol)	Non	2	2	2	2	2	1	0.5
R(+H)	t	10	10(28)	8(30)	48(12)	17(39)	11	23
R(−H)		9	36(60)	36(63)	6(71)	3(55)	3	19
Ally(+H)		0	30(61)	33(61)	1(46)	t (33)	t	5
R-R	0	7	20(t)	22(t)	15(t)	19(t)	4	2
Cross-coupling(Ally-R)	2	10	28(8)	27(7)	34(13)	53(12)	68	36
Homo-coupling[$(Ally)_2$]	1	2	15(12)	16(12)	16(30)	6(55)	6	28

a) Values(%) are based on the theoretical amount; t: trace amount; ( ): yields without the additive.

TABLE 3. EFFECT OF HMPA IN THE COPPER(II) CHLORIDE CATALYZED REACTIONS OF 2-CYCLOALKENYL BROMIDE (Cyclo-Br)[a)]

Cyclo-Br	Cyclo-C_6H_9		Cyclo-C_5H_7	
R-MgX	MeMgI	*i*-PrMgBr	MeMgI	*i*-PrMgBr
R(+H)	10(10)[12]	28(25)[18]	12(14)[10]	26(24)[20]
R(−H)	—(—)[—]	16(26)[21]	—(—)[—]	28(30)[22]
R-R	0(0)[0]	t (1)[4]	0(0)[0]	t (1)[5]
Cycloalkane	7(1)[7]	7(11)[8]	3(1)[4]	5(12)[6]
Cycloalkene	5(4)[3]	6(14)[4]	2(2)[4]	5(15)[4]
Cross-coupling(Cyclo-R)	88(86)[78]	52(47)[47]	80(89)[83]	55(50)[52]
Homo-coupling[$(Cyclo)_2$]	0(1)[0]	t (0)[t]	0(t)[0]	0(0)[0]

a) Values(%) are based on the theoretical amount; t: trace amount; ( ): yields without the additive.
[ ]: Results in the absence of both catalyst and HMPA.

reaction of allyl chloride with *n*-butylmagnesium bromide, the addition of triethylphosphine or use of bis(triethylphosphine)nickel bromide gave rise to a considerable increase in *n*-octane (R–R, 40 and 56%) and the homo-coupling product (12 and 59%, respectively), but scarcely influenced the yield of the cross-coupling product. The fact that a decrease in the amount of HMPA to a half equivalent, still in a large excess over the catalyst (0.02 molar equivalent), resulted in a decrease in the effect of HMPA would help exclude the possibility. However, in an uncatalyzed reaction, HMPA acts to increase to some extent both the radical process (formation of R(—H) and R(+H)) and Wurtz type coupling.

The increase of the cross-coupling products throughout the catalyzed reactions can be rationalized by assuming that HMPA acts principally to increase nucleophilic activity of alkyl groups of the Grignard reagents, but does not influence β-hydrogen transfer (route ii). The effect of HMPA was hardly seen in the reactions of 2-cyclopentenyl- and 2-cyclohexenyl bromide (Table 3) which are known to produce preferentially cross-coupling products even without catalyst.

However, it is noticeable that the presence of HMPA serves to suppress the formation of cycloalkane and cycloalkene in the reactions with isopropylmagnesium bromide which is liable to cause β-hydrogen transfer (route i).

Experimental

Materials. Commercial organic halides (*n*-BuBr, EtBr, *n*-PrBr, *i*-PrBr, allyl-Cl, crotyl-Cl and methallyl-Cl) and additives (HMPA, TMEDA, and DME) were purified by distillation.

2-Cyclohexenyl bromide and 2-cyclopentenyl bromide were prepared by bromination of the corresponding cycloalkene by *N*-bromosuccinimide in CCl_4.

Reaction Procedure. A mixture of a Grignard reagent (0.05 mol) and an additive (0.1 mol) in ether was added to a suspension of a catalytic amount (0.25 mmol) of metallic halide in anhydrous ether under nitrogen. The mixture was stirred until the evolution of gas ceased (reaction A).

To the resulting solution, an equivalent amount of allylic halide (0.05 mol) in ether was added with vigorous stirring.

The mixture was then heated under reflux until the evolution of gas stopped (reaction B). The mixture was hydrolyzed in the usual manner. For crotyl chloride[1,2)] and 2-cycloalkenyl bromide, the products were analyzed by gas chromatography with a 2 m column packed with Silicone 703 (20%)-Celite 545. For allyl chloride[1,2)] and methallyl chloride, the ethereal solution containing an internal standard (cyclohexene) was directly injected onto a Golay column HB 2000, 45 m.

2-Methyl-1-hexene(R-Ally) and 2,5-dimethyl-1,5-hexadiene ($Ally_2$) were produced from methallyl chloride and 3-alkylcycloalkenes(R-Cyclo), respectively. 3-(2′-Cycloalkenyl)-cycloalkenes($Cyclo_2$) were formed from the 2-cycloalkenyl bromides. They were identified by comparison with authentic specimens obtained by the Wurtz coupling. No other isomers and products were detected. The composition of gaseous products obtained in reactions A and B was determined with a silica gel column (2 m) for methane and ethane, and a benzyl ether column (40%, 6 m) for other gaseous hydrocarbons.

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