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THE STEREOCHEMISTRY OF ADDITIONS OF GRIGNARD REAGENTS TO ALKYNOLS

Frederick W. Von Rein and Herman G. Richey, Jr.

Department of Chemistry, The Pennsylvania State University
University Park, Pennsylvania 16802

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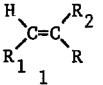
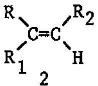
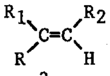
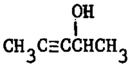
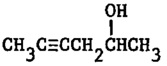
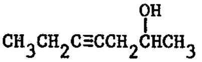
Additions, promoted by the hydroxyl[1] function, of Grignard reagents to alkynols were reported in two recent communications.[2,3] The configurations (cis-trans) of the hydrolysis (H replacing Mg) products obtained from the vinyl Grignard reagents that result from such additions are particularly important, since they could indicate the stereochemistry of addition of the addends (R and MgX) derived from the Grignard reagent.[4] However, a stereochemical pattern was not established; configurations were assigned only to two products, one[2] corresponding to a cis and the other[3] to a trans addition. The results of studies of a larger number of additions reported in this communication suggest that additions of Grignard reagents to alkynols often are trans and that products corresponding to cis additions arise at least in part from a side reaction.

The assignment of configuration to each product reported in the Table is discussed in the following communication.[5] All products resulting from addition of the organic group (R) of the Grignard reagent (RMgX) to that alkyne carbon nearer to the hydroxyl function have the configuration (**1**) expected to result from trans addition. In some reactions, addition of the organic group to that alkyne carbon furthest from the hydroxyl function also results only in production of that product with the configuration (**2**) expected to result from a trans addition; however, in other reactions this product is accompanied by the isomer (**3**) expected from a cis addition. Formation of **3** apparently is favored by the use of tetrahydrofuran (THF) instead of ether, by a methyl rather than an ethyl substituent at the terminal alkyne carbon, and by an α-methyl substituent. The formation in some reactions of both **2** and **3** probably is not caused by accidental impurities; the relative amounts of **12**-**14** formed from **11** in ether did not alter significantly when high purity

Table. Addition Products from Reactions of Grignard Reagents with Alkynols.[a]

alkynol $R_1C{\equiv}CR_2$	solvent	time (hr)	reaction procedure[b]	hydrolysis products[c,d] (approximate % yield)  1	  2	  3	ratio 1:2+3	rati 2:3
$CH_3C{\equiv}CCH_2OH$ 4	ether	24	A	85	--	--		
	THF	48	A	79	--	--		
	THF	12	B	26[c] (5)	--	--		
 $CH_3C{\equiv}CCH(OH)CH_3$ 6	THF	54	A	22[d]	--	--		
$CH_3C{\equiv}CCH_2CH_2OH$ 7	ether	120	A	50 (8)	25 (9)	--[e]	2.0	
	THF	120	A	43	10	2 (10)	3.7	4.1
 $CH_3C{\equiv}CCH_2CH(OH)CH_3$ 11	ether	48	A	45 (12)[d]	14 (13)[d]	16 (14)[d]	1.5	0.9
	THF	48	A	32	8	4	2.6	1.8
$CH_3CH_2C{\equiv}CCH_2CH_2OH$ 15	ether	48	B	46[d]	22[d]	--	2.1	
	THF	48	A	35	13	--	2.5	
 $CH_3CH_2C{\equiv}CCH_2CH(OH)CH_3$ 16	ether	72	B	3[d]	24[d]	--[e]	0.11	
	THF	168	A	12	13	11[d]	0.5	~1.2
$CH_3C{\equiv}CCH_2CH_2CH_2OH$ 17	THF	72	B	--	7[d]	--		

[a] The molar ratio of Grignard reagent (allylmagnesium or vinylmagnesium chloride) to alkynol was 3.

[b] Procedure A: the reaction, carried out at 50°, was followed by glc and nmr analysis of hydrolyzed aliquots (the same reactants using procedure B gave qualitatively similar results, though, of course, somewhat lower yields). Procedure B: the reaction, carried out at reflux, was hydrolyzed, the reaction mixture distilled, and the composition of the distillate determined by glc and nmr analysis.

[c] R- = $CH_2{=}CHCH_2$- for all compounds except 5 in which it is $CH_2{=}CH$-.

[d] The spectral properties of each new compound are in accord with the structural assignment.

[e] Since a sample was available and its properties were known, the failure to detect this isomer indicates that it was not present in an amount exceeding 3% of its cis-trans isomer.

rather than "Grignard grade" magnesium or allyl bromide rather than allyl chloride was used to form the Grignard reagent, or when excess magnesium bromide was added to a Grignard reagent prepared from allyl bromide. Neither does it seem likely that the presence of both **2** and **3** is due to *cis-trans* isomerization of one of these stereoisomers after its formation. Slow isomerization is ruled out by the failure to observe significant changes with time of product ratios in those reactions for which product composition was monitored at intervals. Equilibration so rapid that only equilibrium mixtures are observed seems unlikely; the very different compositions of the product mixtures obtained in ether and THF from **7** or **16** cannot be attributed to isomerization in THF but not in ether, since addition of a large amount of THF to an ether reaction solution after Grignard addition to **7** was complete did not lead to the production of **10**.

The suggestion that formation of a product (**3**) expected for a *cis* addition may result at least in part by addition to an allenol formed by isomerization of the alkynol reactant is in accord with several observations: (1) allenols **18**, **19**, **20**, and **21** actually were isolated from reactions of **7**,[6]

$CH_2{=}C{=}CHCH_2CH_2OH$

18

$CH_2{=}C{=}CHCH_2\overset{OH}{\overset{|}{C}}HCH_3$

19

$CH_3CH{=}C{=}CHCH_2CH_2OH$

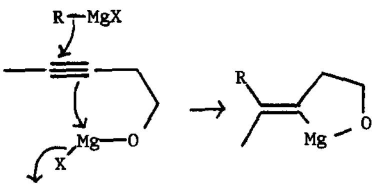
20

$CH_3CH{=}C{=}CHCH_2\overset{OH}{\overset{|}{C}}HCH_3$

21

11, **15**, and **16**, respectively, that furnished both **2** and **3**, but were isolated only in much smaller amounts or not at all from reactions in which only **2** was noted; (2) some deuterium was found in the vinyl methyl group of **14** upon hydrolysis with D_2O of a reaction mixture of **11** in ether;[7] (3) as reported in a following communication,[8] it was observed that Grignard reagents add readily to some allenols, reaction in THF of allylmagnesium chloride and **18** leading to formation of **10** as *the major product*. The results of experiments in which hydrolysis was effected by D_2O indicate that the alkyne-allene isomerization could be initiated by metalation of the alkyne, the Grignard reagents that result from addition serving at least in part as bases. For example, in a reaction of **7** in THF at 50°, significant amounts of deuterium (0.25 D after 12 hr, a time which only about one-half of the mixture of addition products had formed) were found in recovered **7** and only small amounts (0.14 and 0.16 D, respectively, after 12 hr) in **8** and in a mixture of **9** and **10**. By contrast, similar experiments in ether showed only negligible incorporation of deuterium into recovered **7** and almost complete monodeuteration of the vinyl positions of the addition products, even at times at which the addition products had formed almost completely.

The conclusion that additions of Grignard reagents to alkynols often (and perhaps always) are preferentially *trans* accords with the conclusion, based on the composition of a mixture of diastereoisomers, that additions to alkenols are preferentially *trans*.[9] *Trans* addition is expected for mechanisms in which addition of one addend held by the oxygen and another from an external molecule is concerted,[9-11] for example, the mechanism illustrated in **22**, but not for a concerted



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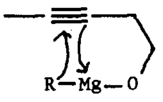
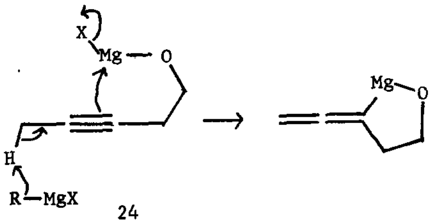


23



24

addition of R and Mg held, as illustrated in **23**, in proximity to the double bond by their attachment to the oxygen.[2,12] The isomerization of alkynols to allenols also may be promoted by the hydroxyl group, perhaps as shown in **24** — control experiments showed no isomerization or significant incorporation of deuterium following hydrolysis with D_2O when 2-heptyne was heated with allylmagnesium chloride in THF with or without 1-propanol.

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REFERENCES

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4. Vinyl Grignard reagents (lacking hydroxyl[1] substituents, however) are configurationally stable under conditions similar to those used in this work [H. G. Richey, Jr., in "The Chemistry of Alkenes," Vol. 2, J. Zabicky, Ed., Wiley-Interscience, London, 1970, Chapter 2].
5. H. G. Richey, Jr., and F. W. Von Rein, *Tetrahedron Lett.*, p. 3781, 1971.
6. Small amounts of 5-hexyn-1-ol also were isolated from reactions of **7** in THF.
7. The experimental error was considerable because less than 1.0 D was incorporated and the analysis was of a mixture of **13** and **14**. It is not certain if any significant amount of deuterium was present in the vinyl position.
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10. H. Felkin and C. Kaeseberg, *Tetrahedron Lett.*, 4587 (1970).
11. In one possible variant, R (from a species such as **23**) could add internally and MgX come from an external molecule (RMgX, MgX_2, etc.).
12. J. J. Eisch and G. R. Husk, *J. Amer. Chem. Soc.*, **87**, 4194 (1965).