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DIMETHYLALUMINUM HALIDE INDUCED REACTIONS OF FORMALDEHYDE WITH ALKYNES. SYNTHESIS OF α-ALLENIC ALCOHOLS AND *Z*-3-CHLOROALLYLIC ALCOHOLS

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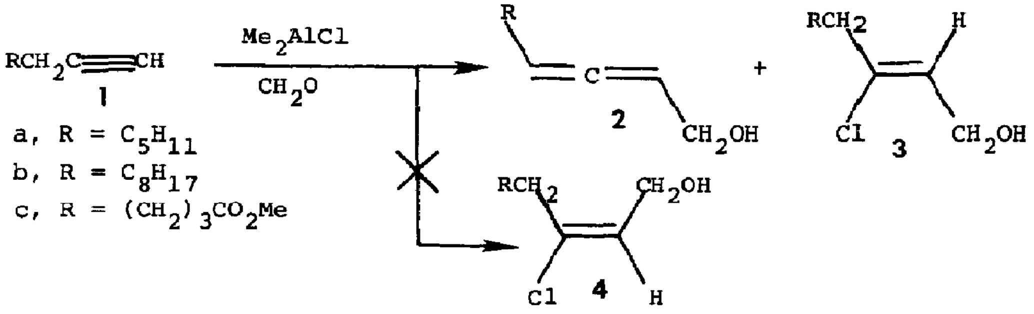
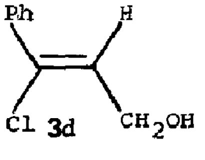
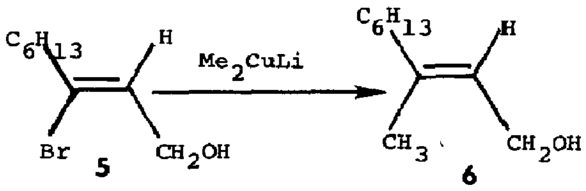
Summary: The $CH_2O{\cdot}Me_2AlCl$ complex reacts with terminal alkynes to give α-allenic alcohols via a formal ene reaction and *Z*-3-chloroallylic alcohols via a stereospecifically syn Friedel-Crafts addition.

We have recently shown that Me_2AlCl is a useful catalyst for the ene reaction of aldehydes with alkenes since it is a proton scavenger as well as a Lewis acid.[2] Terminal alkynes also undergo Me_2AlX induced reactions with formaldehyde. Treatment of 1-octyne(1a) with 2 eq of formaldehyde (as trioxane or paraformaldehyd and 2 eq of Me_2AlCl (as a 1.13 M solution in heptane) in CH_2Cl_2(0.4 M in 1a) for 15 min at 25°C gives a 2:3 mixture of allenic alcohol 2a and *Z*-chloroalcohol 3a in 56% yield.[3,4] None of the *E*-chloroalcohol 4a is obtained. Use of 6 eq of CH_2O and 6 eq of Me_2AlCl gives a 71% yield of an identical mixture of 2a and 3a. Reaction of 1-octyne with 2 eq of CH_2O and 2 eq of Me_2AlBr[6] gives a 50% yield of a 2:3 mixture of 2a and bromoalcohol 5. Unlike chloroalcohol 3a, 5 can be converted to 6[7] in 75% yield by reaction with 6 eq of lithium dimethylcuprate.[8]



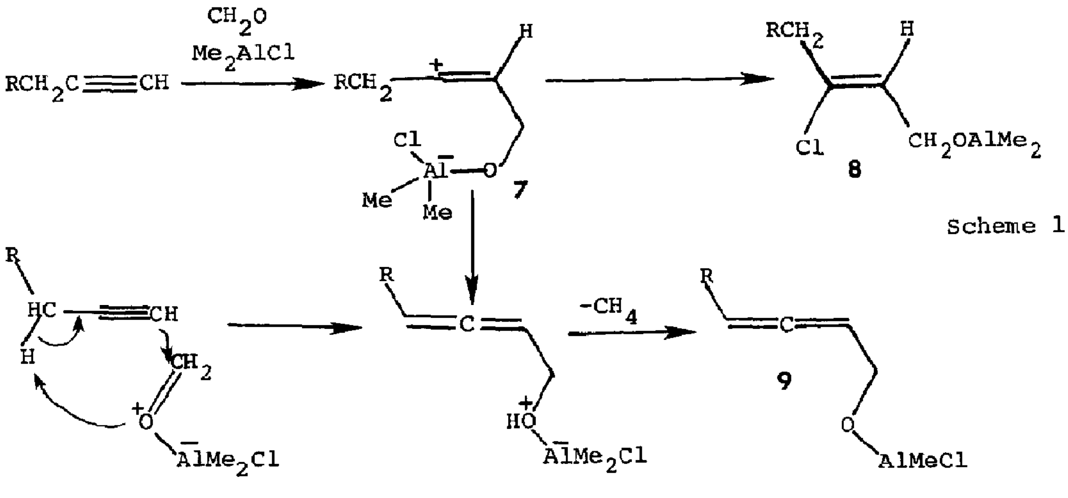




Reaction of 1-undecyne (1b) with 2 eq of CH_2O and 2 eq of Me_2AlCl gives a 45% yield of a 2:3 mixture of 2b and 3b. Allene 2b, an intermediate in Landor's synthesis of the male sex pheromone of the dried bean beetle, was previously synthesized by a multistep route.[9] Reaction of phenylacetylene with 1.5 eq of Me_2AlCl and 1.5 eq of CH_2O gives a 42% yield of Z-chloroalcohol 3d.[4]

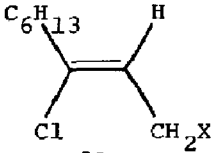
Methyl 8-hydroxy-5,6-octadienoate (2c), an anti-fungal agent isolated from *Sapium japonicum*,[10] was synthesized from methyl 6-heptynoate (1c).[11] Treatment of 1c with trioxane and Me_2AlCl gives no reaction, apparently due to interference by the ester group. Fortunately, use of a slightly stronger Lewis acid, methylaluminum sesquichloride (2 eq $AlCl_3$, 2 eq $AlMe_3$, 4 eq CH_2O) gives a 40% yield of a 5:2:1 mixture of 2c, 3c, and 4c and a 40% yield of recovered 1c. Reverse phase chromatography[3] gives a 15% yield of 2c identical to natural material (except for optical activity) by spectroscopic comparison.[10]

Both allenic alcohol 2 and chloroalcohol 3 are probably formed from the vinyl cation 7[13] (see scheme 1). An intramolecular chlorine transfer will give 8 with complete control of stereochemistry. A 1,5-hydride shift will give the ene adduct $\cdot Me_2AlCl$ complex which rapidly loses CH_4 to give aluminum alkoxide 9, thus preventing proton catalyzed rearrangements or solvolysis of 2. Alkoxide 9 may be formed by direct loss of CH_4 from 7. Since the $CH_2O \cdot Me_2AlCl$ complex is a reactive enophile,[2] allenic alcohol 2 may be formed by a concerted Lewis acid catalyzed ene reaction. To the best of our knowledge, the only previous example of an alkyne acting as an "ene" in an intermolecular ene reaction used perfluorocyclobutanone as the enophile.[14] Friedel-Crafts additions of acyl and alkyl halides to alkynes are well known.[15] Anti addition predominates, although mixtures of products are usually formed. Stereospecific syn addition to an alkyne in a Friedel-Crafts reaction, resulting from intramolecular delivery of a nucleophile, is unprecedented.



Scheme 1

The zinc chloride catalyzed addition of chloromethyl methyl ether to alkynes has been reported.[16] In our hands, reaction with 1-octyne gives a complex mixtur from which we isolated 6% of 10a,[17] 3% of 11a, 7% of 10b, 10% of 11b, 4% of 12 and 4% of 13. This reaction is not only non-stereospecific, but the primary products, 10a and 11a, react further to give 10b and 11b. In contrast, reaction of $CH_2O{\cdot}Me_2AlCl$ with 1-octyne is stereospecific and gives products stable to the reaction conditions.



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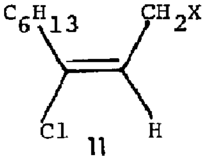

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a, X = OCH_3
b, X = Cl

$C_6H_{13}C\equiv CCH_2OCH_3$

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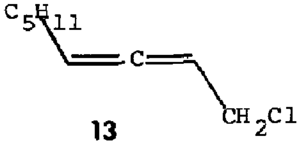

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Further studies of the reactions of electrophilic carbon species with alkyne are underway.[18]

REFERENCES AND NOTES

1. Fellow of the Alfred P. Sloan Foundation, 1979-81.
2. B. B. Snider and D. J. Rodini, *Tetrahedron Lett.* 21, 1815 (1980).
3. Evaporative distillation of the crude reaction mixture gave a 90% pure mixture of 2 and 3 in the indicated yield which were separated by a reverse phase medium pressure LC on an EM LOBAR LiChroprep RP-8 column with 5:1 methanol-water as eluent to give an 80% recovery of 2[4] and 3[4] in the expected ratio.
4. All new compounds were characterized by NMR, IR and mass spectroscopy and elemental analysis. Stereochemistry of 3 was assigned by NMR spectral comparison to closely related compounds.[5]
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11. Reaction of 5-chloropentanoic acid with lithium acetylide ethylenediamine complex in DMSO[12] gave 6-heptynoic acid in 86% yield. Esterification with sulfuric acid in methanol gave 1c in 77% yield. See F. Bohlmann, E. Inhoffen and P. Herbst, *Chem. Ber.* 90, 1661 (1957).
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13. Other mechanisms for the formation of 2 and 3 can be considered. Limited mechanistic information is available. Both 2a and 3a are stable to the reaction conditions. At -80°C, 2a and 3a are formed in the same ratio but in low yield, since ethanol formation competes more effectively at low temperatures. Use of nitromethane or pentane as solvent gives a 10 and 35% yield respectively, of similar mixtures of products except that small amounts of 4a are also formed. Use of Et$_2$AlCl (6 eq) and CH$_2$O (6 eq) gives a 15% yield of a 2:1 mixture of 2a and 3a. Use of Et$_2$AlCl instead of Me$_2$AlCl results in a significant change in the ratio of products but much lower yields are obtained since the ethyl group is more nucleophilic and reacts to give propanol. Alkynes do not react with Me$_2$AlCl.
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17. Methylation of 3a with NaH and MeI gave 10a in quantitative yield.
18. We thank the National Institutes of Health (GM23159) for generous financial support. A Halcon fellowship to D. J. R. is gratefully acknowledged.

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