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ADDITION OF A METHYLCOPPER COMPLEX TO ACETYLENES. SYNTHESIS OF TRISUBSTITUTED OLEFINS

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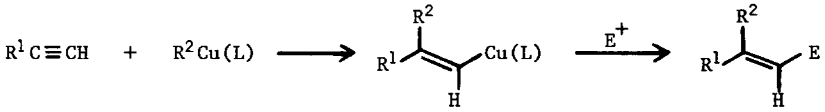
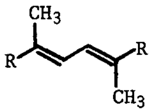
Because of the widespread occurrence of the trisubstituted olefin unit in many classes of naturally occurring compounds, the synthesis of these olefins has received considerable attention.[1,2] Among the more promising approaches have been methods based upon the addition of organocopper compounds to acetylenes (equation 1, E^+ = an electrophilic species, L = various ligands and/or associated metal salts), as first reported by Normant[4] and subsequently studied extensively by the group at Utrecht.[5] Most of the naturally occurring trisubstituted olefins bear a methyl group as at least one of the olefinic substituents. Therefore, the above approach would be most generally useful if the addition of methylcopper complexes to acetylenes were possible. However, attempts to perform this addition with simple, unactivated acetylenes[6] have had limited success. For example, Normant reported that methylcopper, which is a very insoluble, polymeric solid and less reactive than many other alkylcopper complexes,[7] adds to acetylenes only under conditions that lead to rapid thermal decomposition of the resulting vinylcopper complexes to give 1,3-dienes (1),[4a] More recently the Utrecht group reported that the addition of a soluble and much more reactive dimethylcuprate complex to a simple aliphatic acetylene proceeds with high "conversion", but a very large excess



(1)



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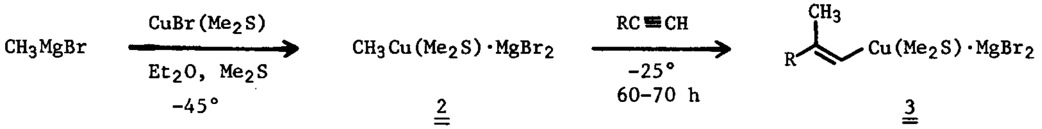
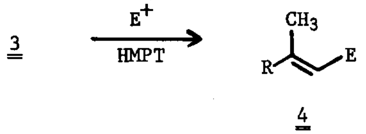
(5 mole equivalents) of the copper reagent is used.[8]

Because of the shortcomings of these methods, we have begun an investigation of other conditions for effecting the desired addition reaction. Earlier we[3] and others[9] had reported an improved procedure for the addition of *n*-alkylcopper complexes to acetylenes through use of the dimethyl sulfide complex of cuprous bromide.[10] We are now pleased to report that this procedure is also applicable to the addition of a methylcopper complex (**2**) [11] to simple aliphatic acetylenes (equation 2). Although the addition is rather slow (**2** has poor solubility in the reaction medium), the reaction proceeds very efficiently with a *stoichiometric amount or only a small excess* (10-15%) of the copper reagent. The efficiency is indicated by the 90% yield of olefin (**4**,E=H) obtained upon hydrolysis of the reaction mixture with aqueous ammonium chloride. The reactions of **3** with various electrophilic organic reagents, usually in the presence of hexamethylphosphoric triamide (HMPT), produce trisubstituted olefins (**4**, equation 3); typical results are shown in Table I.[12] Careful control of temperature and maintenance of an inert atmosphere throughout the reaction sequence are necessary to avoid formation of substantial amounts of the dienes (**1**).[13] As in our earlier work,[3] the assignment of stereochemistry of the trisubstituted olefins (**4**) is based upon Normant's observation that alkylcopper complexes undergo *cis*-addition to acetylenes.[14,15]



(2)

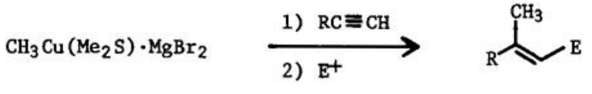


(3)

A typical procedure is given below.

(4E)-5-Methyl-1,4-undecadiene (4, E-allyl). A solution of the cuprous bromide/dimethyl sulfide complex (0.82 g, 4.0 mmol),[10] ether (5 ml), and dimethyl sulfide (4 ml) under nitrogen was cooled to -45°C, and a 2.90 M solution of methylmagnesium bromide (1.38 ml, 4.0 mmol) was added dropwise. After the resulting suspension of yellow solid was stirred at -45°C for 2 hr, 1-octyne (0.52 ml, 3.5 mmol) was added over a 1-min period, and the mixture was stirred at -25°C for 65 hr. After the resulting dark green solution was cooled to -78°C, HMPT (1.4 ml, 8.0 mmol) and allyl bromide (0.40 ml, 4.6 mmol) were added separately. The mixture was then stirred at -30°C for 12 hr, warmed to 0°C, quenched with saturated aq. ammonium chloride solution (adjusted to pH 8 with ammonia), and partitioned between additional ether and water. The product was isolated in crude form from the ether solution, and analysis by glpc (180-cm x 3-mm 5% SE-30, 110°-240°C @ 16°/min) with *n*-pentadecane as the internal standard indicated the presence of 0.47 g (81%) of **4** (E=allyl). Bulb-to-bulb distillation

Table I. Synthesis of Olefins



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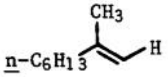
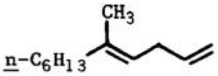
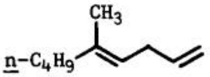
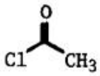
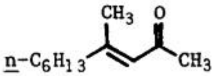
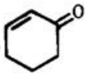
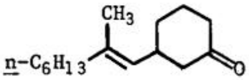
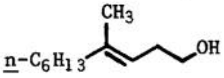
R	Electrophile (E^+)	Product [a]	Yield (%) [b]
n-C_6H_{13}	NH_4Cl		90
n-C_6H_{13}			81
n-C_4H_9			84
n-C_6H_{13}			65
n-C_6H_{13}	 c		63
n-C_6H_{13}	 d		75 [e]

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[a] All reactions were quenched by the addition of aq. ammonium chloride. [b] Unless otherwise indicated, the yields were determined by glpc with an internal standard. [c] HMPT was not employed. [d] The alkylation was done in the presence of 1-lithio-1-hexyne (see ref. 3). [e] Isolated yield.

and preparative glpc provided a pure sample: ^{1}H-nmr ($CDCl_3$) 5.48-6.05 (m, 1 H), 4.87-5.30 (m, 3 H), 2.74 (t, J = 6.5 Hz, 2 H), and 0.65-2.12 (several overlapping multiplets and a sharp singlet at 1.59, C=C-CH_3,[16] total area 16 H); ir (neat film) 3076, 2910, 1666, 1638, 992, 920, and 846 cm^{-1}; ms (high resolution, 70 eV) m/e 166.1750 (M^+, calculated for $C_{12}H_{22}$, 166.1722.

The addition of methylcopper complexes to acetylenes should prove to be quite useful in natural products synthesis. Further work is in progress to study the scope and applications of this reaction.

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FOOTNOTES AND REFERENCES

1. For reviews of olefin synthesis see (a) J. Reucroft and P. G. Sammes, Q. Rev. Chem. Soc., **25**, 135 (1971); (b) D. J. Faulkner, Synthesis, 175 (1971); (c) A. S. Arora and I. K. Ugi in "Methoden der Organischen Chemie (Houben-Weyl)", Vol. V/1b, 4th ed., E. Muller, Ed., G. Thieme Verlag, Stuttgart, 1972, pp. 728-945.

2. For a summary of more recent methods for the synthesis of trisubstituted olefins see ref. 3.

3. A. Marfat, P. R. McGuirk, R. Kramer, and P. Helquist, J. Am. Chem. Soc., **99**, 253 (1977).

4. (a) J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villieras, Bull. Soc. Chim. France, 1656 (1974); (b) A. Alexakis, J. Normant, and J. Villieras, Tetrahedron Lett., 3461 (1976).

5. H. Westmijze, H. Kleijn, and P. Vermeer, ibid., 2023 (1977).

6. The addition of methylcopper complexes occurs with acetylenes bearing various activating substituents. For an example see: A. Alexakis, A. Commercon, J. Villieras, and J. F. Normant, ibid., 2313 (1976).

7. H.Gilman, R. G. Jones, and L. A. Woods, J. Org. Chem., **17**, 1630 (1952).

8. H. Westmijze, J. Meijer, H. J. T. Bos, and P. Vermeer, Rec. Trav. Chim., **95**, 304 (1976).

9. A. B. Levy, P. Talley, and J. A. Dunford, Tetrahedron Lett., 3545 (1977).

10. H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, J. Org. Chem., **40**, 1460 (1975).

11. We do not intend to imply specific structures for any of the organometallic intermediates involved in this work.

12. All new compounds exhibit appropriate spectroscopic data.

13. Normally, the dienes (**1**) are produced in only very small yields (<3%).

14. J. F. Normant, G. Cahiez, and J. Villieras, Tetrahedron Lett., 2407 (1973); J. F. Normant and M. Bourgain, ibid., 2583 (1971).

15. Furthermore, the stereochemistry that we have assigned to the olefins (**4**) is consistent with preliminary nmr studies, the details of which will be reported in a later paper.

16. This peak position is consistent with the assigned *E*-stereochemistry of the olefin. For leading references see: L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, 1969, p. 225.