Tetrahedron Letters No.48, pp. 5041-5043, 1968. Pergamon Press. Printed in Great Britain.

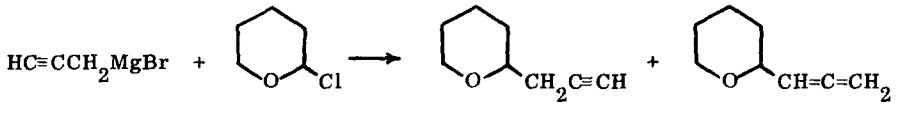
POSITION-SPECIFIC ALKYLATION OF LITHIO-1-TRIMETHYLSILYLPROPYNE, A USEFUL NEW ROUTE TO ACETYLENES AND 1,5-DIENES

E. J. Corey and H. A. Kirst

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

(Received in USA 12 August 1968; received in UK for publication 2 September 1968)

This investigation originated in an attempt to develop an efficient new synthetic method for the stereospecific elaboration of carbon chains containing the 1,5-diene system characteristic of acyclic isoprenoids. Although there are numerous allylic coupling reactions which generate 1,5-dienes, they all suffer from three serious limitations: (a) lack of coupling specificity in reactions involving two unlike allylic groups, (b) lack of control over 1,3-allylic transposition, and (c) lack of control of stereochemistry (1). Another obvious approach, synthesis via a 1-en-5-yne structure, $-C{\equiv}C-\overset{|}{C}-\overset{|}{C}-C=C-$, has been impeded because of difficulties in generating this system efficiently. The ethynylation of homoallylic halides by metallo acetylides is rendered inoperable (2) or inefficient (3,4) by the intervention of an elimination process. An alternative route to the 1-en-5-yne system, the alkylation of a propargylic anion by an allylic halide, is complicated by the tendency of propargylic alkylation reactions to afford allenic as well as acetylenic products, for example, I → II + III (5,6).



I II, 77% III, 23%

An extremely promising reagent has been devised for the synthesis of 1-en-5-yne derivatives and, indeed, for a wide variety of acetylenes, specifically lithio-1-trimethylsilylpropyne (V) (7). The trimethylsilyl group was selected for the reagent for two reasons: first, it functions as an easily removable protecting group replacing the acidic acetylenic proton at C_1 in propyne to allow metallation at C_3, and secondly, it acts as a sterically large group which screens C_1 in V against attack, thereby favoring reaction at C_3. The required 1-trimethylsilylpropyne (IV), b.p. 98-99° (8), was readily obtained from the reaction of trimethylchlorosilane with a 20% excess of propynyllithium (Foote Mineral Co.) in ether at reflux for 30 hr. Treatment of IV in ether at -5° with tetramethylethylenediamine (9) and an equivalent amount of n-butyllithium (Foote Mineral Co. in hexane) under argon led to complete metallation in 15 min. to form V. In practice the reaction of V with primary halides in ether at 0° for 12 hr. was found to give almost exclusively the

desired acetylene (VI) and only small amounts of the isomeric allene (VII), the ratios of VI to VII falling in

$$CH_3C{\equiv}CSi(CH_3)_3 \longrightarrow [CH_2C{\equiv}CSi(CH_3)_3]Li \xrightarrow{RX} RCH_2C{\equiv}CSi(CH_3)_3$$

IV V VI

$$CH_2{=}C{=}C(R){-}Si(CH_3)_3$$

VII

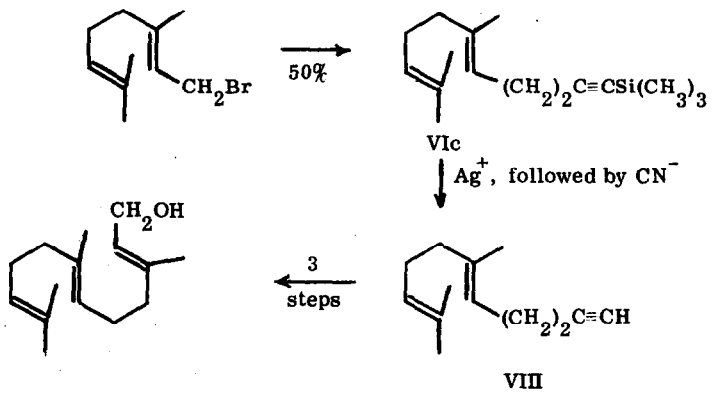
the range 10-20. The following halides were used in the alkylation of V to give acetylenes VI (10), isolated by distillation in the yields indicated (20 mmole scale):

$$CH_3(CH_2)_5I \xrightarrow[55\%]{} CH_3(CH_2)_6C{\equiv}CSi(CH_3)_3$$

VIa

$$C_6H_5CH_2I \xrightarrow[50\%]{} C_6H_5(CH_2)_2C{\equiv}CSi(CH_3)_3$$

VIb



VIII

The yields cited are probably not optimal since critical reaction parameters have not been investigated as yet; in addition, analytical yields by gc analysis were 10-15% higher than the isolated yields given. Further improvements might result from the use of the copper (11) or triethylsilyl analogs of the reagent V.

In contrast to the behavior of V, the lithio derivative of 2-butyne (9) undergoes alkylation by n-alkyl iodides to form acetylene and allene products in ratios between 1 : 1 and 2 : 1 (depending on reaction conditions).

Of special significance is the propynylation of geranyl bromide to form VIc stereospecifically. Treatment of VIc with ethanolic silver nitrate (12) at 25° followed by sodium cyanide afforded the acetylene VIII, first prepared in ca. 10% yield (but not fully purified) by the reaction of geranyl bromide with propargyl

magnesium bromide (13) and more recently prepared in two steps from geranyl acetone (14). The propynylation synthesis via VIc is by far the best of these routes to VIII. By the use of the method previously described (14), homogeranylacetylene VIII as obtained via VIc was converted stereospecifically to a synthetic farnesol, identical in all respects with naturally occurring trans,trans-farnesol.

Finally, the reagent lithio-1-trimethylsilylpropyne has been applied very effectively to the total synthesis of dl-C_{18} Cecropia juvenile hormone (4, 15).

REFERENCES

1. See E. J. Corey, M. F. Semmelhack, and L. S. Hegedus, J. Am. Chem. Soc. 90, 2416 (1968).
2. F. Sondheimer, J. Chem. Soc. 877 (1950).
3. W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, J. Am. Chem. Soc. 90, 2994 (1968) and personal communication from W. S. Johnson and K. Harding.
4. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. Roman, and B. Erickson, J. Am. Chem. Soc. in press (Stereospecific Total Synthesis of the dl-C_{18} Cecropia Juvenile Hormone).
5. L. Gouin, M.-C. Faroux, and O. Riobé, Bull. Soc. Chim. France 2320 (1966).
6. See also, for example, (a) G. Fontaine, C. André, J. Jolivet, and P. Maitte, ibid. 1447 (1963); (b) L. Brandsma, H. E. Wijers, and J. F. Arens, Rec. Trav. Chim. 82, 1040 (1963); (c) A. Schaap, L. Brandsma, and J. F. Arens, ibid. 86, 393 (1967); (d) J. H. Wotiz, J. Am. Chem. Soc. 72, 1639 (1950) and 73, 693 (1951); (e) T. L. Jacobs, R. Akawie, and R. G. Cooper, ibid. 73, 1273 (1951).
7. This designation is used for descriptive convenience and is not intended to imply structural assignment.
8. A. D. Petrov, L. L. Shchukovskaya, and Yu. P. Egorov, Dokl. Akad. Nauk. SSSR 93, 293 (1953).
9. G. G. Eberhardt and W. A. Butte, J. Org. Chem. 29, 2928 (1964). We have also applied this method to generate the lithio derivative of 2-butyne.
10. In each case purified products were characterized by infrared, nuclear magnetic resonance, and mass spectrometric analysis, the results of which were fully in accord with the assigned structures. Quantitative analyses were performed by gas chromatography (gc) using a 16-ft., 0.125-in. diam. column of 10% LAC-728 on Diatoport S (F and M Co.) which allowed separation of acetylenic (VI) and allenic (VII) isomers.
11. E. J. Corey and G. H. Posner, J. Am. Chem. Soc. 89, 3911 (1967).
12. For this elegant method for the removal of the trimethylsilyl group attached to C≡C, see H. M. Schmidt and J. F. Arens, Rec. Trav. Chim. 86, 1138 (1967). Other studies with this system have been reported by R. Eastmond and D. R. M. Walton, Chem. Commun. 204 (1968) and H. Gilman, A. G. Brook, and L. S. Miller, J. Am. Chem. Soc. 75, 4531 (1953).
13. P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, Helv. Chim. Acta 40, 1373 (1957).
14. E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, J. Am. Chem. Soc. 89, 4245 (1967).

15. This work was supported by the National Science Foundation and the National Institutes of Health.