

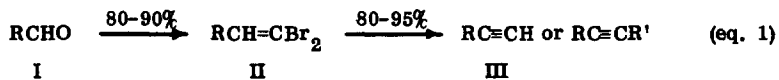
A SYNTHETIC METHOD FOR FORMYL-ETHYNYL CONVERSION ($\text{RCHO} \rightarrow \text{RC}\equiv\text{CH}$ or $\text{RC}\equiv\text{CR}'$)

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In connection with a number of synthetic problems now under study in these Laboratories, it became apparent that an efficient process in which an aldehyde RCHO can be transformed by chain extension to an acetylene $\text{RC}\equiv\text{CH}$ or $\text{RC}\equiv\text{CR}'$ would be of considerable value. This note reports a simple and expeditious method for effecting this change, which is based on the scheme outlined in equation 1.



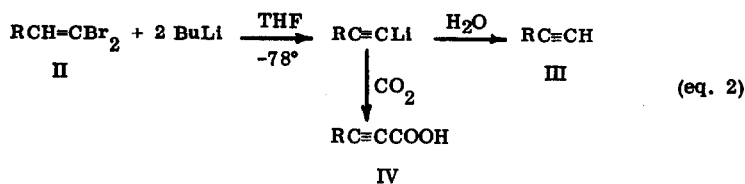
a: $\text{R} = \text{C}_6\text{H}_5$

b: $\text{R} = \underline{n}\text{-C}_7\text{H}_{15}$

c: $\text{R} =$ 

Three substrates, Ia-c, were chosen to document generality. The first step, chain extension of the aldehyde by one carbon to form dibromoolefins IIa-c, was accomplished conveniently by reaction of the aldehyde with the carbontetrabromide--triphenylphosphine reagent using either of two procedures: (A) addition of the aldehyde (1 equiv.) to a mixture of triphenylphosphine (4 equiv.) and carbontetrabromide (2 equiv.) in methylene chloride at 0° with a reaction time of 5 min. (1); or (B) addition of aldehyde (1 equiv.) to a reagent prepared from interaction of zinc dust (2 equiv.), triphenylphosphine (2 equiv.), and carbontetrabromide (2 equiv.) in methylene chloride at 23° for 24-30 hr. with a reaction time of 1-2 hr. at 23°. Procedure B is preferred, since less phosphine is required, the isolation procedure (2) is simpler, and the yields of dibromoolefins IIa-c are somewhat higher (range 80-90%).

The transformation of dibromoolefins IIa-c into the corresponding terminal acetylenes IIIa-c could be brought about in two ways. Reaction of the bromo compounds IIa-c with 2 equiv. of *n*-butyllithium in tetrahydrofuran at -78° for 1 hr. and 25° for 1 hr. resulted in rapid formation of the lithio derivatives (3, 4)

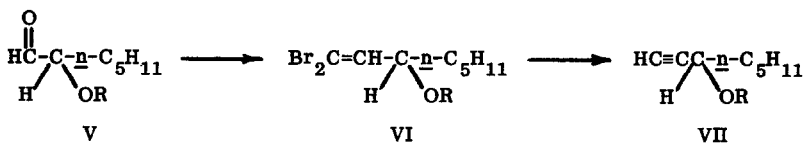


of IIIa-c (cf. eq. 2). Carbonation of the intermediate lithium acetylide produced propargylic acid (IVa-c) in 82-90% yield, and simple hydrolysis produced terminal acetylenes IIIa-c (80-95%). Clearly, the synthesis of a wide variety of acetylenic compounds is possible by treatment of the intermediate lithium acetylides with reagents such as carbon halides, aldehydes, ketones, and epoxides. Thus the methodology outlined herein can be regarded as an analog of the Wittig olefin synthesis (eq. 3) which allows the general conversion of aldehydes to acetylenes (eq. 4):



A number of other reagents were investigated for the transformation of dibromoolefins II to acetylenes in order to extend the scope of the process to substrates having groups which are reactive toward alkyl-lithium reagents. Magnesium metal was found to be ineffective, whereas lithium metal was shown to effect both dehalogenation to form acetylene and further reduction to terminal olefin. However, 1.5% lithium amalgam (5) was found to be an excellent reagent. For example, reaction of dibromide IIb with 7 atm. equiv. of 1.5% lithium amalgam (powdered) in tetrahydrofuran (ca. 10 ml./mmol. of IIb) at 25° for 19 hr. cleanly produced 1-nonyne (94% yield, less than 0.5% contamination by 1-nonene by vapor phase chromatographic analysis). Acetylenes IIIa and IIIc were likewise prepared in good yield and high purity using lithium amalgam. Thus two alternative procedures and reagents are available for the synthesis of acetylenes from dibromoolefins.

One example of the application of the method described above to a specific problem will be presented. Reaction of the (\pm)- α -hydroxyaldehyde derivative V (R = THP) with 4 equiv. of carbontetrabromide



in the presence of zinc dust and triphenylphosphine (4 equiv. each) in methylene chloride at 25° for 1 hr. afforded the bromoolefin VI (R = THP) which after extractive isolation (2) was directly treated with 2.1 equiv. of *n*-butyllithium in tetrahydrofuran at -78° for 1 hr. and at 25° for 1 hr. to produce after hydrolysis and extraction the (±)-acetylenic tetrahydropyranyl ether VII (R = THP) in 62% overall yield from V (6). The (S)-antipode of VII represents a valuable intermediate for the synthesis of prostaglandins. Since various protected derivatives of the (S)-aldehyde V can be prepared in fully optically active form from either D-mannitol or (S)-(-)-malic acid without resolution (7), a direct route to ethers of (S)-VII becomes available.

Other examples illustrating the utility of this route to acetylenes via aldehydes will be described in due course. Although there are other methods for effecting the overall transformation I - III (3, 8), the route detailed here can be recommended as convenient, efficient, and practical.

The following experimental procedure is presented to provide operational detail for the key step II -> III or IV.

1-Nonyne. A solution of 0.875 g. of 1,1-dibromonon-1-ene (IIb) in 17 ml. of tetrahydrofuran at -78° under nitrogen was treated with 5.6 ml. of 1.16 M solution of *n*-butyllithium in pentane (Foote Mineral Co.). After being stirred for 1 hr. at -78°, the reaction mixture was warmed to 25° and maintained for 1 hr. at that temperature. Addition of water, extraction with pentane, and distillation afforded 0.35 g. (95%) of 1-nonyne, identified by comparison with an authentic sample (Farchan Chemical Co.).

2-Decynoic Acid. Repetition of the above procedure with 0.98 g. of IIb, except that the reaction mixture was not hydrolyzed but cooled to -60° and treated with solid carbon dioxide (ca. 5 g.), gave a mixture which was allowed to warm gradually to 25°, poured into water, washed with pentane, acidified to pH 1 with hydrochloric acid, and extracted three times with ether. Drying and evaporation of the extract afforded spectrally (6) pure 2-decynoic acid, 0.506 g. (87%) (9).

References

1. (a) C. Raulet and E. Levas, *Compt. Rend. Acad. Sci. Paris, C*, 1467 (1970); and (b) F. Ramirez, N. B. Desai, and N. McKelvie, *J. Amer. Chem. Soc.*, **84**, 1745 (1962).
2. Isolation of dibromoolefin was accomplished by addition of pentane (4 vol.) to the reaction mixture, filtration to remove insoluble material and evaporation of pentane--methylene chloride. The insoluble fraction was reworked by additional cycles of methylene chloride extraction and pentane precipitation to remove all of the olefinic product. The dibromoolefins II were thus obtained in essentially pure form and could be distilled with very little loss in yield.
3. The reaction of vinylic monohalides with 2 equiv. of alkyllithium also is known to produce lithium acetylides. See (s) D. Y. Curtin and E. E. Harris, *J. Amer. Chem. Soc.*, **73**, 4519 (1951); (b) H. Gilman, W. Langham, and F. W. Moore, *Ibid.*, **62**, 2327 (1940); and (c) G. Köbrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.*, **99**, 689 (1966).

4. The reaction of the dibromoolefins II with 1 equiv. of alkyllithium leads to formation of a mixture of $RCH=CHBr$ and $RC\equiv CLi$.
5. See (a) R. Criegee and G. Louis, Chem. Ber., 90, 423 (1957); (b) J. Alexander and G. S. Krishna Rao, J. Chem. Educ., 47, 277 (1970), and references cited therein.
6. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained for all reaction products.
7. Unpublished work in these Laboratories by Drs. H. Shirahama, A. Venkateswarlu, and P. A. Grieco; see also E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, J. Amer. Chem. Soc., 93, 1490 (1971).
8. E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 91, 4318 (1969). See also A. A. Bothner-By, ibid., 77, 3293 (1955).
9. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.