Tetrahedron Letters No.26, pp. 2247-2250, 1970. Pergamon Press. Printed in Great Britain.

THE UTILITY OF THE COUPLING REACTION BETWEEN PROPARGYL GRIGNARD REAGENT AND ALLYLIC HALIDES FOR THE SYNTHESIS OF ACETYLENES

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(Received in USA 3 April 1970; received in UK for publication 7 May 1970)

The intrinsic value of the coupling reaction between the propargyl Grignard reagent and substituted allylic halides for the synthesis of intermediate acetylenic olefins which are of use in the preparation of acyclic isoprenoid polyenes is apparent from the work of Corey and his collaborators (1). These workers have developed an extremely efficient and general procedure for the stereospecific conversion of the acetylenic system to the required trisubstituted double bond (2) and have demonstrated the usefulness of the synthon in their synthesis of *dl*-C_{18}-Cecropia juvenile hormone (1). In connection with this and other syntheses, the Harvard group also found it advisable to circumvent the more obvious propargyl Grignard coupling reaction for the synthesis of the desired acetylenic substrates due to the formation of *both* acetylenic and allenic coupling products and the yield-lowering separation problems associated with this result (4). Their solution to this problem was the replacement of the propargyl Grignard reagent with lithio-1-trimethylsilylpropyne (3) which allowed the isolation of the acetylenic product as its trimethylsilyl derivatives. Application of the Arens detrimethylsilylation sequence (5) provided a satisfactory alternative to the older (4) preparation of the required enynes.

Recently, we have had occasion to be concerned with similar transformations in order to prepare the endiyne 3, a useful intermediate for a proposed triterpenoid synthesis (6). Application of the lithio-1-trimethylsilylpropyne coupling procedure to the *trans*-dibromide 1 (7) afforded less than 5% (vpc) of the expected disilyl derivative 2. The dibromide 1 that was not recovered appeared to have suffered dehydrobromination and/or polymerization. Since

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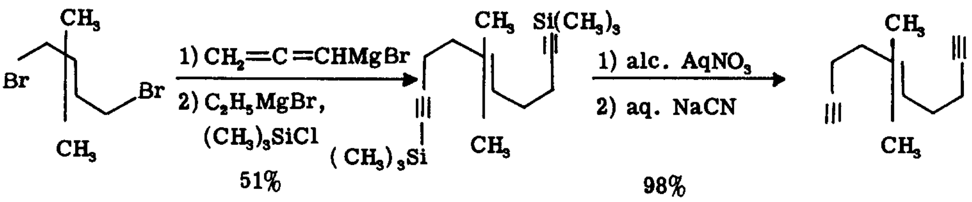
*Contribution No. 4033

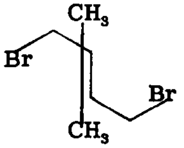
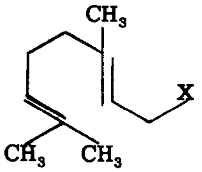
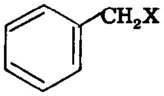
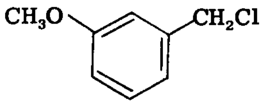


1 2 3

the dibromide 1 coupled very efficiently with various allylic Grignard reagents (6), the similar coupling reaction with propargyl Grignard reagent was investigated with the expectation that subsequent trimethylsilyation of the crude product would provide an effective, hitherto unexplored method for the separation of acetylenic and allenic material. Indeed this approach proved quite successful and the crystalline bistrimethylsilylendiyne 2 (8) (mp 65-67°) became available in 51% overall yield (9). Removal of the trimethylsilyl groups proceeded as efficiently as reported (8) (liquid, evap. dist. at 110-120°/25 mm) and the desired endiyne 3 was obtained in 50% overall yield.

The striking contrast between these results led us to investigate the propargyl Grignard coupling sequence more broadly. As shown in Table I, both procedures afforded virtually the same yields of propynylation product with simple allylic halides (geranyl halide) and benzylic halides. While a representative saturated alkyl halide (1-iodohexane) is reported to be effectively propynylated by the lithio-1-trimethylsilylpropyne reagent, this halide is almost inert to coupling with the propargyl Grignard reagent. These latter results suggest that the two propynylation procedures are complementary and that the Grignard coupling process may be particularly suited to reactive, base sensitive allylic halides, such as the dibromide 1, and the lithio-1-trimethylsilylpropyne reagent may be the method of choice for the less reactive, saturated alkyl halides, such as 1-iodohexane. Either process appears equally effective for the intermediate cases regardless of the character of the halogen used. In fact, the known or expected ease of solvolytic displacement (10) of the halide substrate would appear to be a good indication of the more applicable propynylation procedure. This suggests that carbon-halogen bond breaking is an important factor in the transition state for the Grignard coupling reaction, while the greater nucleophilicity of the lithio propyne reagent accounts for the success of this procedure with the less readily ionized halides.

TABLE I: Isolated Yields of Trimethylsilyl Acetylenes

	1) $HC \equiv CCH_2Br$, Mg 2) C_2H_5MgBr, $(CH_3)_3SiCl$	$LiCH_2C{\equiv}C{-}Si(CH_3)_3$
	51%	$<5\%$[b]
	60%(X—Cl)	50%(X—Br)[a]
	53%(X—Br)	50%(X—I)[a]
	38%	-----
$CH_3(CH_2)_4CH_2I$	$<20\%$[b]	55%[a]

[a] From the report by E. J. Corey and H. A. Kirst (3). [b] By gas-liquid chromatographic analysis on 6 ft. 4% SE30 on chromosorb P column at 60 °.

Acknowledgment: This work was supported in part by a National Institutes of Health Fellowship (GM 39806) to C.A. Lipinski from the National Institute of General Medical Sciences and a grant (GP 7810) from the National Science Foundation.

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(4) See, for example, F. Sondheimer, R. Wolovsky, and D.A. Ben-Efraim, *J. Amer. Chem. Soc.*, **83**, 1686 (1961); and P.A. Stadler, A. Nechvatal, A.J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957).

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(6) R.E. Ireland, M.I. Dawson, J. Bordner, and R.E. Dickerson, *J. Amer. Chem. Soc.*, in press.

(7) O.J. Sweeting and J.R. Johnson, *J. Amer. Chem. Soc.*, **68**, 1057 (1946).

(8) In each case, purified products were characterized by infrared and nuclear magnetic resonance spectrometric analysis and the results were in accord with the assigned structures. Satisfactory combustion analyses were obtained on all new compounds reported.

(9) While the infrared spectrum of the crude coupling product prior to silyation had bands attributable to the presence of both acetylenic and allenic groups, absorption due to the allenic system was not present in the spectrum of the bistrimethylsilyl derivative **2**.

(10) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill Book Co., Inc., New York, N.Y., 1962.