Tetrahedron Letters No.55, pp. 5787-5788, 1968. Pergamon Press. Printed in Great Britain.

A SYNTHETIC METHOD FOR THE HOMOLOGATION OF PRIMARY HALIDES

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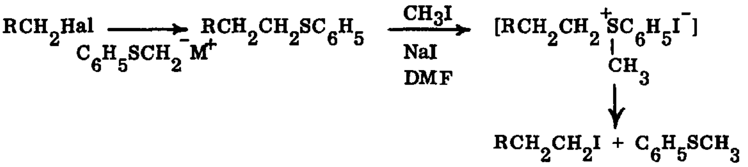
(Received in USA 12 August 1968; received in UK for publication 15 October 1968)

This note describes a new synthetic method which permits the conversion of a primary alkyl bromide or iodide (RCH_2Hal) to the homologous iodide (RCH_2CH_2I) in two steps. The conventional process for accomplishing this transformation consists of four steps, $RCH_2Hal \rightarrow RCH_2CN \rightarrow RCH_2COOH \rightarrow RCH_2CH_2OH \rightarrow RCH_2CH_2Hal$, and requires a considerably longer time for execution. The sequence for the two-step conversion is as follows:



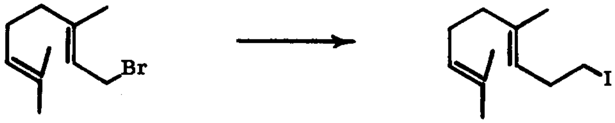
$$RCH_2Hal \xrightarrow[C_6H_5SCH_2^-M^+]{} RCH_2CH_2SC_6H_5 \xrightarrow[NaI\ DMF]{CH_3I} [RCH_2CH_2\underset{CH_3}{\overset{+}{S}}C_6H_5I^-] \downarrow RCH_2CH_2I + C_6H_5SCH_3$$

Two reagents have been applied to effect the first step, phenylthiomethyllithium (1) and the organocopper derivative formed from phenylthiomethyllithium and cuprous iodide. The use of the lithium reagent is advantageous except in certain cases, e.g., allylic halides, for which somewhat higher yields are obtained by the copper coupling method (2). The second step, the replacement of the phenylthio group by iodo, is accomplished by heating the sulfide with a large excess of methyl iodide in ca. 1 N-sodium iodide in dimethylformamide under anhydrous conditions. The following experimental procedures illustrate the method.

A. Conversion of 1-Iododecane to 1-Iodoundecane. 1-Iododecane (2.27 g., 8.2 mmoles) was added to a solution of phenylthiomethyllithium (10 mmoles) (1) in dry tetrahydrofuran under nitrogen at -70° with stirring. The reaction mixture which became quite thick after 30 min. at -70° was maintained at that temperature for 3 hr. and then allowed to warm slowly to room temperature. Addition of water, extraction with pentane, and evaporation of the pentane afforded phenyl n-undecyl sulfide (2.54 g.) as a liquid. This product was dissolved in a solution of 5 ml. of methyl iodide and 10 ml. of dimethylformamide containing 1.5 g. of sodium iodide, and the reaction mixture was heated under nitrogen for 18 hr. at reflux temperature (bath temperature, 75°). Addition of water, extraction with pentane, and distillation afforded thioanisol as a lower boiling component (0.83 g., 6.7 mmoles, b.p. 34° at 0.2 mm.) followed by 1-iodoundecane (2.14 g., 7.6 mmoles, 93%), b.p. 84° at 0.2 mm., identified by comparison of the infrared and nmr spectra with those of a reference sample.

B. Conversion of Allyl Bromide to 4-Iodo-1-butene. Cuprous iodide (dry, 2.1 g., 11 mmoles) was added to a vigorously stirred solution of phenylthiomethyllithium (10 mmoles) (1) in 30 ml. of tetrahydrofuran at -50°. After 60 min. at -45 to -50° a fine gray suspension resulted which responded negatively in the test for free alkyllithium using Michler's ketone (3). Allyl bromide (1.21 g., 10 mmoles) was added, and the mixture was stirred for 2 hr. during which the mixture was warmed slowly to 25°. Addition of water, extraction with pentane, and concentration afforded 1.63 g. of phenyl butenyl sulfide. This product was heated with 5 ml. of methyl iodide and 0.30 g. of sodium iodide in 10 ml. of dimethylformamide at 75° bath temperature in a reflux apparatus under nitrogen for 18 hr. The mixture was poured into water and extracted with pentane to give after distillation 0.962 g. (5.2 mmoles, 52%) of 4-iodo-1-butene, b.p. 84-88° at 120mm., identified by infrared, nmr, and mass spectra.

An especially crucial and significant application of the new homologation process is the conversion of geranyl bromide (I) to homogeranyl iodide (II) which is both time consuming and very inefficient using the cyanide homologation scheme. Treatment of geranyl bromide, prepared from geraniol and phosphorus tribromide (4), with phenylthiomethylcopper (1.1 equiv.) at -20° for 12 hr. afforded phenyl homogeranyl sulfide in 76% yield, b.p. 140-142° (0.2 mm.). The sulfide (6 g.) was transformed into II (b.p. ca. 80° at 0.04 mm.) in 58% yield by heating (67°, 20 hr.) with NaI (9.4 g.) and methyl iodide (44 g.) in dimethylformamide (39 ml.) under nitrogen in the presence of a small amount of calcium carbonate (150 mg.) and mercury (2 drops) (to prevent formation of HI or I_2). The reaction conditions specified for the generation of II are critical, since higher reaction temperatures or times lead to further reactions of this product, including isomerization of the Δ^3-olefinic linkage to give homoneryl iodide. Under the conditions specified above such isomerization amounts to only ca. 4% (by gas chromatographic analysis).



I II

A synthetic process analogous to this transformation of I → II has been applied to the total synthesis of C_{18} Cecropia juvenile hormone (5, 6).

REFERENCES

1. E. J. Corey and D. Seebach, J. Org. Chem. 31, 4097 (1966).
2. See E. J. Corey and G. H. Posner, J. Am. Chem. Soc. 89, 3911 (1967).
3. H. Gilman and F. Schulze, ibid. 47, 2002 (1925).
4. J. M. Osbond, J. Chem. Soc. 5270 (1961).
5. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. Roman, and B. W. Erickson, J. Am. Chem. Soc., in press.
6. We are indebted to the National Science Foundation and the National Institutes of Health for financial support of this work. We also wish to acknowledge the help of Mr. J. A. Katzenellenbogen in establishing the conditions for the preparation of II.