in 73% yield.[22] Methylation of **4** was accomplished using dimethyl sulfate and potassium carbonate; subsequent hydrolysis of the ethyl ester with potassium hydroxide in dimethyl sulfoxide[23] gave naphthoic acid (**5**), mp 149–50 °C.

The ortho disposed carboxyl and methyl functionalities used in the conversion of benzoate system **2** to naphthoate system **5** are retained and permit the annelation sequence to be repeated. Naphthoic acid (**5**), upon treatment with lithium diisopropylamide, was converted to a deep purple dilithium anion which was carboxylated and hydrolyzed to give naphthaleneacetic acid (**6**).[24] The reaction sequence described earlier for conversion of homophthalic acid (**2**) to isocoumarin (**3**) was employed again for the preparation of naphtho[2,3-*c*]pyran (**7**), mp 168–70 °C, in 56% overall yield from naphthoic acid (**5**). Reformatsky reaction on naphtho[2,3-*c*]pyran (**7**), gave 9,10-dimethoxy-1-hydroxy-3-methylanthracenecarboxylic acid (**8**), mp 159–161 °C, which bears a hydroxylation pattern found in naturally occurring linear polynuclear aromatic systems.

Studies to broaden the scope of this approach for synthesis of hydroxylated polynuclear aromatic compounds and to synthesize selected natural products are in progress.

Acknowledgment. The authors wish to thank the National Cancer Institute of DHEW, Grant No. CA 18141, for support of this work.

References and Notes

(1) The use of repetitive reaction sequences as a synthetic strategy to construct complex molecules is not totally new, as it has been employed extensively, even automated, in polypetide synthesis (G. R. Marshall and R. B. Merrifield, "Biochemical Aspects of Reactions on Solid Supports", G. Stark, Ed., Academic press, New York, N.Y., 1971, Chapter 3). Another application of this strategy is the synthesis of naturally occurring 1,5,10,*n*-polyene containing systems by repetitive Claisen–Cope rearrangement (S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975)). Recently an elegant synthesis of Semicorrin E was reported which employed repetitive addition of a nitrile oxide to an acetylene (R. V. Stevens and E. B. Reid, *Tetrahedron Lett.*, 4193 (1975)).
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(19) Satisfactory elemental analyses were obtained for previously unreported compounds. Mass and ^{1}H NMR spectra were, In each Instance, in accord with the assigned structures.
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(22) This is a modification of a reaction previously reported by M. Pailer and O. Vostrowsky, *Monatsh. Chem.*, **102**, 951 (1971).
(23) The ortho-disubstituted ester was virtually resistent to hydrolysis in ethanolic sodium or potassium hydroxide.
(24) Compound **6** could not be purified; however, comparison of the relative intensity of the ^{1}H NMR for the aromatic methyl group for the starting material (δ 2.42 ppm) with that for the methylene group of the phenyl acetic acid product (singlet at δ 3.81 ppm) indicated that the conversion of **5** to **6** had occurred in 85–90% yield.

Frank M. Hauser,* Richard Rhee
Department of Chemistry, Oregon Graduate Center
Beaverton, Oregon 97005
Received March 21, 1977

A Secondary Isotope Effect in the Cysteine-Promoted Dehalogenation of 5-Bromo-2′-deoxyuridine. Evidence for Transient 5,6-Dihydropyrimidine Intermediates

Sir:

There has been long-standing interest in 5-halogenated pyrimidines because of their use as biochemical tools and chemotherapeutic agents.[1,2] The metabolism of 5-bromo- and 5-iodouracils involves their dehalogenation, and numerous model systems have been investigated in attempts to understand the mechanism of these reactions.[3-12] Most studies have centered about the bisulfite mediated halide release and its replacement by proton; the same reaction is prompted by thiols, which is more relevant to enzymic conversions, but less well understood. The proposed mechanism for the thiol mediated dehalogenation of 1-substituted 5-bromouracils is depicted in Scheme I; a similar pathway is believed to exist for dehalogenation of corresponding 5-iodouracils.[10] The initial, and perhaps rate-determining,[9,10] step is believed to involve attack of thiolate at the 6 position of the heterocycle **1** and protonation of C-5 to produce the 5-bromo-6-thiol-5,6-dihydrouracil **2**. Two general pathways have been proposed[9,10,12] to account for subsequent steps leading to the dehalogenated product. The first, E2 Hal, involves abstraction of bromonium (Br^+) ion from **2** to provide intermediate **3** and a sulfenyl halide. The latter would react with a thiol to provide the halide ion and

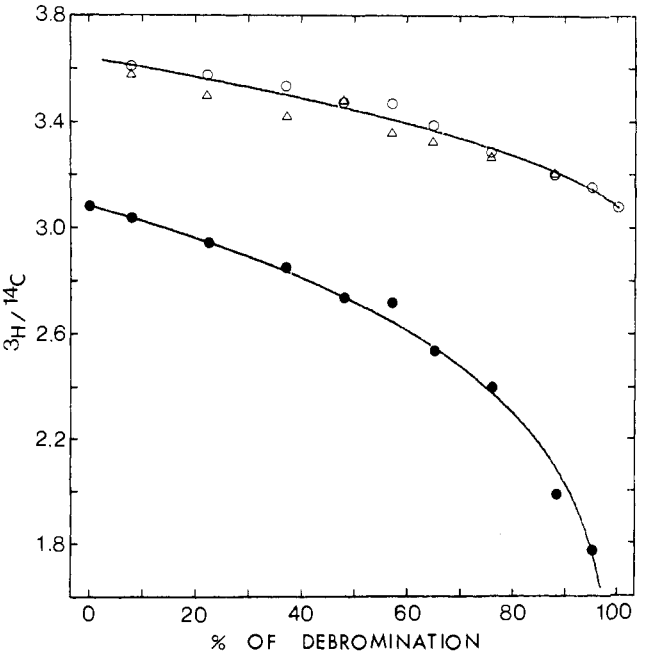
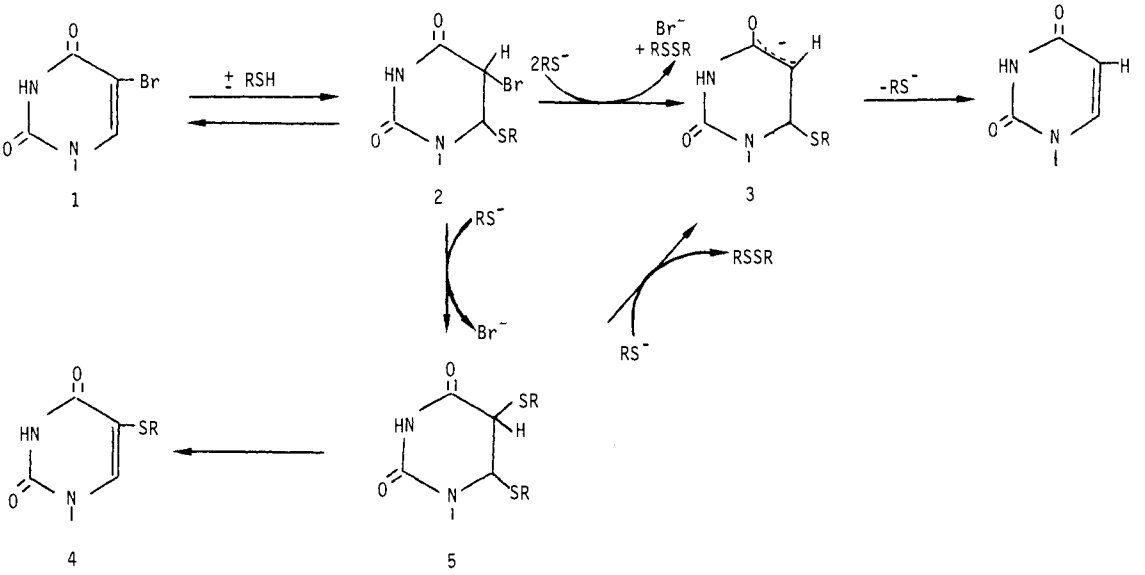


Figure 1. Secondary isotope effect on the cysteine-promoted dehalogenation of BrdUrd. Experimental points refer to the $^3H/^{14}C$ ratio of BrdUrd (●), dUrd (○), and (△) 5-CysdUrd. The lines are theoretical[15] for a secondary isotope effect of $k_T/k_H = 1.18$.

Scheme I



oxidized thiol; a β-elimination of **3** would yield products. The second mechanism (S_N2) involves nucleophilic displacement of Br^- from **2** by thiolate to give the intermediate **5**. Further reaction with RS^- would yield the oxidized thiol (R-SS-R) and intermediate **3** which is common with the E2 Hal mechanism and would yield the dehalogenated pyrimidine upon β-elimination. The cysteine induced dehalogenation of 5-bromo-2′-deoxyuridine (BrdUrd) is also accompanied by formation of *S*-[5-(2′-deoxyuridyl)]cysteine (5-CysdUrd),[9] the mechanism of which has been proposed to involve conversion of **5** to **4**.

The proposed mechanism of the reactions of thiols with 5-halogenated pyrimidines is in accord with kinetic data,[9,10] but rests almost completely upon analogy with the bisulfite mediated dehalogenation where direct evidence of 5,6-dihydropyrimidine intermediates has been established.[5-7] While the mechanisms depicted in Scheme I are reasonable, the supposed 5,6-dihydropyrimidine intermediates are unstable and have not been directly demonstrated. We report here a method for detection of such transient intermediates which could be applicable to many reactions of pyrimidines believed to proceed via 5,6-dihydro intermediates. The method involves the use of kinetic secondary α-hydrogen isotope effects which are expected to accompany sp^2 to sp^3 rehybridization of C-6 of the heterocycle if they occur prior to or at the rate-determining step. Thus, using 6-tritiated pyrimidines, and measurement of the isotopic ratio of reactant and products, k_T/k_H values of 1.15 (k_D/k_H = 1.1) or greater would be indicative of rehybridization.[13]

A solution (330 μL) containing 10 mM [2-^{14}C,6-^{3}H] BrdUrd (^{14}C, 0.614 μCi; ^{3}H, 1.89 μCi) and 0.25 M L-cysteine at pH 7.3 was incubated at 37 °C. Aliquots (10 μL) were removed at specified intervals, and the extent of debromination was monitored spectrophotometrically;[9] the pseudo-first-order rate constant was 2.2×10^{-2} min^{-1}. The reactant, BrdUrd, and products, dUrd and 5-CysdUrd were separated as the reaction progressed and the $^3H/^{14}C$ ratio of each was determined;[14] upon completion, dUrd accounted for 92% of the product, the remaining 8% being 5-CysdUrd. As shown in Figure 1, the tritium content of both products is enriched at initial stages of the reaction, and approaches that of the initial reactant as dehalogenation progresses. Conversely, the $^3H/^{14}C$ ratio of the reactant decreases as the reaction proceeds. From these data, calculated[15] k_T/k_H values for formation of dUrd and 5-CysdUrd are 1.19 ± 0.02 and 1.16 ± 0.02, respectively; k_T/k_H for dehalogenation of BrdUrd is 1.17 ± 0.02.

The magnitude of the secondary isotope effect provides strong evidence for sp^2 to sp^3 rehybridization of C-6 of the heterocycle in the cysteine mediated conversion of BrdUrd to both dUrd and 5-CysdUrd; in addition, since the isotope effects observed in formation of both products are identical, they likely emanate from a common intermediate in which C-6 is tetrahedral (i.e., **2**). Thus the isotope effects are best interpreted to be a manifestation of the conversion of **1** to **2** in the pre-rate-determining or rate-determining step of the reaction. Most important, the use of secondary isotope effects as described here provides a tool for detection of transient dihydropyrimidine intermediates which have been indirectly implicated in a number of chemical and enzymic conversions of pyrimidine heterocycles.

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(14) At the time of spectral analyses, 12-μL aliquots were added to 6 μL of a mixture of BrdUrd (0.14 μmol), dUrd (0.14 μmol), 5-CysdUrd (0.10 μmol), and AcOH (14 μmol) and chromatographed in two dimensions on 20 × 20 cm cellulose TLC (Merck, 0.10 mm): (1) 1-butanol–water (86:14) and (2) 1-butanol–AcOH–water (2:1:1). Compounds were detected by visualization under UV, eluted with 1.5 mL water, and dissolved in 10 mL of xylene containing 0.4% Omnifluor and 25% Triton X-114. Isotopes were counted

to an accuracy of ±0.5% on an Isocap 300 liquid scintillation spectrometer using the ESR method for dpm calculations.
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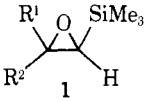
Yusuke Wataya, Daniel V. Santi*
Department of Biochemistry and Biophysics and Department of Pharmaceutical Chemistry University of California, San Francisco, California 94143
Received December 6, 1976

α-Chloro-α-trimethylsilyl Carbanion, a Reagent for Homologation of Ketones and Aldehydes via α,β-Epoxysilanes

Sir:

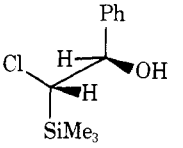
α,β-Epoxysilanes **1** have recently enjoyed conspicuous use in synthetic procedures that require a masked carbonyl group or vinyl cation equivalent.[1] Unfortunately, without exception all the methods used to prepare this functional group proceed via the epoxidation of vinylsilanes, and, since vinylsilanes are not readily available, the chemistry of α,β-epoxysilanes, while useful, remains a specialist area. Here we describe a general solution that enables aldehydes and ketones, the most ubiquitous functional groups, to be converted directly into α,β-epoxysilanes **1**.

α-Chloromethyltrimethylsilane (**2**) was deprotonated by treatment with *sec*-butyllithium in THF containing TMEDA (1 equiv) at −78 °C to give a species whose reactions indicate it to be α-chloro-α-trimethylsilyl carbanion (**3**, CTC).[2] Surprisingly **3** was comparatively stable to −40 °C and then only decomposed slowly (~1 h).[3] Table I lists a number of ketones and an aldehyde that have been treated with **2** to establish its scope in this particular type of reaction. If the reaction of CTC (**3**) with benzaldehyde is quenched at −55 °C, then a mixture


1

Me_3SiCH_2Cl **2**

$Me_3SiCH(Li)Cl$ **3**


erythro-**4a**

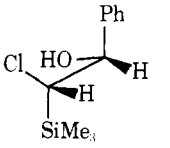
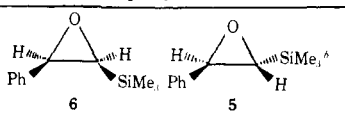
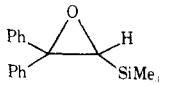
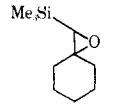
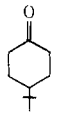
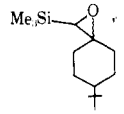
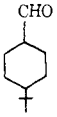
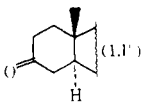
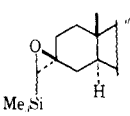
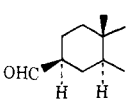
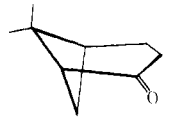
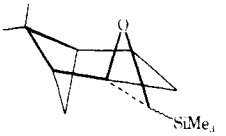
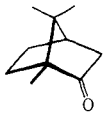
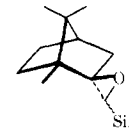
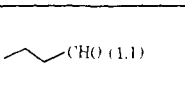
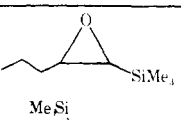
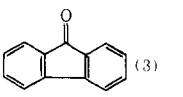
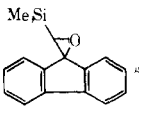
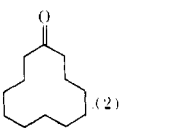
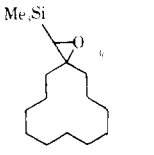
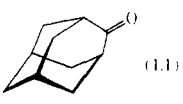
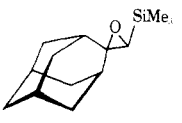
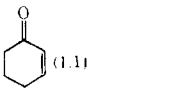
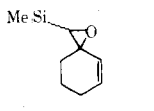
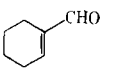
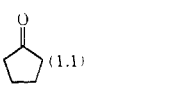
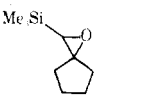

threo-**4b**

Table I[a]

Substrate (equiv of CTC)	Epoxysilane	% Yield	Aldehyde
PhCHO (1)	 **6** **5**	≥95	$PhCH_2CHO$
PhCOPh (3)		≥95	
 (1.1)	 **7**	≥95	
		≥95	 (1:1)
 (1.1)		≥95	
cholestanone	+ 3 α epimer		+ 3 α epimer
		~40	
		≥20	

Substrate (equiv of CTC)	Epoxysilane	% Yield	Aldehyde
 (1.1)		≥75	
 (3)		≥60	
 (2)		≥70	
 (1.1)		≥90	
 (1.1)		≥80	
 (1.1)		≥90	

[a] All compounds were identified by IR, NMR, and accurate mass spectral measurements. Known compounds (aldehydes) were derivatized (2,4-DNP). Yields refer to isolated material at least 90% pure (NMR, TLC). A representative experiment follows. Chloromethyltrimethylsilane (0.75 g, 6.14 mmol) in dry THF (8 mL) at −78 °C under N_2 was treated with *sec*-butyllithium in cyclohexane (4.50 mL, 6.75 mmol, 1.5 M solution) followed by TMEDA (0.97 mL, 6.45 mmol). After this mixture was stirred at −78 °C for 40 min the solution was warmed to −55 °C and cyclohexanone (0.59 mL, 5.68 mmol) added. The mixture was kept at −40 °C for 0.5 h, then allowed to warm to 20°. Work-up by pouring the mixture into sat. ammonium chloride, extraction, and drying gave the epoxysilane 7 (95%), bp 32–35 °C (0.35 mm). Anal. C, H. [b] J. J. Eisch and J. E. Galle, *J. Org. Chem.*, 41, 2615 (1976). [c] No assignment of stereochemistry could be made from the available data. [d] A 1:1 mixture of epimers was formed. [e] Attempts to increase the yield were unsuccessful. It should be noted that isopropyllithium adds to the extent of only 2–5%. [f] A mixture of cis and trans epoxides. [g] For complete formation of the epoxide the reaction mixture (chlorohydrin) is left at room temperature for 15 h. [h] Incomplete reaction owing to ~30% enolization. [i] 2-Adamantanecarboxaldehyde is unstable: D. Farcasin, *Synthesis*, 615 (1972).