Supplementary Material Available: Experimental Section of this paper (5 pages). Ordering information is given on any current masthead page.

References and Notes

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(3) (a) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965); (b) W. Oppolzer, *ibid.*, **93**, 3833, 3834 (1971); W. Oppolzer and K. Keller, *ibid.*, **93**, 3836 (1971); (c) B. J. Arnold and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1034 (1972); (d) M. E. Jung, *ibid.*, 956 (1974). (e) R. K. Hill and R. G. Carlson, *J. Org. Chem.*, **30**, 2414 (1965).

(4) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).

(5) The reactants were irradiated in anhydrous ether at room temperature with a medium-pressure lamp (Hanovia 450 W) through a corex sleeve. Typical irradiation times were 8–24 h. The enol acetate was purified by distillation to remove traces of acid, and all apparatus was washed with methanolic KOH, rinsed with methanol (anhydrous), and dried thoroughly.

(6) Cantrell (cf. ref 4) reports only the formation of *trans*-**2** in ~45% yield. This substance was isolated from the crude product mixture by preparative VPC. This procedure undoubtedly led to loss of any cis adduct **2** via loss of acetic acid to **3**, opening to **4**, and decomposition. At no time did we isolate or characterize the cis adduct, although we cannot exclude its presence in the crude mixture and transformation to **3** during workup.

(7) Alumina is known to catalyze the epimerization of trans-fused bicyclo[4.2.0]octan-2-one systems to the thermodynamically more stable cis system (cf ref 1a). In this case elimination of acetic acid occurred simultaneously.

(8) All new substances described have satisfactory spectral data [NMR, UV, and mass spectra (low resolution)] and analytical data or high resolution data. All yields refer to isolated and purified materials.

(9) Spectral data. **5**: NMR δ 2–2.7 (m, 6 H), 3.18 (s, 6H), 3.28 [s (br), 2 H], 3.83 (s, 6 H). **7**: NMR δ 2.30 (m, 2 H), 2.90 (t, 2 H), 3.30 (t, 2 H), 3.98 (s, 3 H), 8.18 (s, 1 H). **8a**: NMR δ 2.16 (dt, 2 H), 2.65 (t, 2 H), 3.03 (t, 2 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 7.70 (dd, J_{ortho} = 8.0 Hz, 2 H). **9**: NMR δ 2.23 (dt, 2 H), 2.78 (t, 2 H), 3.18 (t, 2 H), 4.0 (s, 3 H), 7.71 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2 H), 8.22 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2 H). **16**: NMR δ 2.26 (pentuplet, 2 H), 2.83 (t, 2 H), 3.23 (t, 2 H), 8.30 (s, 1 H), 9.03 (s, 1 H). **7** was characterized by conversion to diester **6**.

(10) The production of these photoadducts is particularly facile. An unusually low stoichiometric ratio of olefin to enone can be maintained, and high yields are still obtained. No evidence of significant amounts of oxetane formation by reaction with the solvent is seen; however, the yields are reduced markedly if corex-filtered UV is utilized as in the production of adducts **2**. Spectral data for **10b** [bp 113–120 °C (0.3 mm)]:NMR δ 1.25 (m, 6 H), 2.00, 2.05 (s, 3 H), 3.60 (m, 4 H). **11b** NMR: δ 1.20 (m, 6 H), 2.70 (d, 1 H), 4.0 (d, 1 H).

(11) H. Hikino and P. DeMayo, *J. Am. Chem. Soc.*, **86**, 3582 (1964).

(12) S. Arthur, Ph. D. Dissertation, University of California, Berkeley, Calif., 1976; cf. also ref 4 and T. Cantrell, *Tetrahedron*, **27**, 1227 (1970).

(13) The structure of the photoproduct ($h\nu$/corex/ether) is supported by IR, NMR, and mass spectra (low resolution). Apparently, elimination is not unidirectional (both methanol and acetic acid are lost), and under the usual reaction conditions no Diels–Alder adducts are obtained.

(14) (a) I. Fleming, F. L. Gianni, and T. Mah, *Tetrahedron Lett.*, 881 (1976); (b) K. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).

(15) For example, daunomycin, adriamycin, the rhodomycins; cf. I.A. Scott and T. Devon, "Handbook of Naturally Occurring Compounds", Vol. 1, Academic Press, New York, N.Y., 1975.

(16) If excess base is utilized, the yields are lowered. A variety of amine bases were investigated and all proved unsatisfactory due to incompatibility with the haloquinone at elevated temperatures.

(17) This result may be due to the stereochemical orientation of the leaving groups and hydrogens in the intermediate Diels–Alder adduct. If the structure of the photoadducts have the alkoxyl groups cis, the diene must be cis,trans and the resulting adduct has only 1 mol of HCl trans deposed and readily eliminated. This result could also arise by sequential loss of Cl_2 and methanol.

(18) The structure of **22** is inferred from the quantitative production of the hydroquinone. Presently, we are attempting to trap the *o*-quinodimethane derived from **22**, which undoubtedly results from thermal opening of **22** under the reaction conditions.

(19) G. A. Reynolds and J. A. VanAllen, *J. Org. Chem.*, **29**, 3591 (1964).

(20) S. W. Baldwin, R. E. Gawley, R. J. Doll, and K. H. Leung, *J. Org. Chem.*, **40**, 1865 (1975).

(21) Fellow of the Alfred P. Sloan Foundation (1976–1978).

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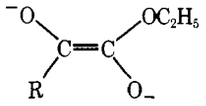
Received January 12, 1977

Alkoxy Enediolates

Summary: Multiple deprotonations of α-hydroxy esters by lithium diisopropylamide lead directly to alkoxy enediolates, which are useful as synthetic intermediates in electrophilic substitution reactions with primary and secondary alkyl halides and sulfonates to form disubstituted α-hydroxy esters, and with carbonyl compounds and ethylene oxide to form substituted glyceric acids and a substituted α-hydroxy-δ-butyrolactone, respectively.

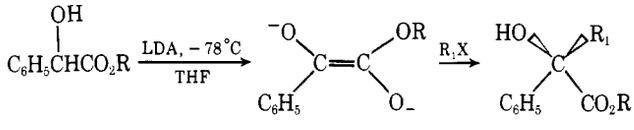
Sir: In this communication we describe procedures for the preparation, characterization, and use of dianions derived from α-hydroxy esters by reaction with lithium diisopropylamide (LDA) in THF. The alkoxy enediolates (**1**)[2] prepared in this fashion can be used in reactions with a variety of alkylation reagents to form more complex α-hydroxy esters. Preliminary results indicate that carbonyl compounds and epoxides also react as electrophiles with the alkoxy enediolates. Oxidative decarboxylation of the product α-hydroxy acids derived from these esters by hydrolysis leads to carbonyl compounds and makes intermediates like 1 acyl anion



1a, R = Ph
b, R = CH_3

equivalents.[3–6] While geminal enediolates from carboxylic acids[7] and vicinal enediolates from α-hydroxy ketones[8] have previously been prepared by deprotonation with LDA, alkoxy enediolates have not been prepared before. Enediolates are also postulated to be intermediates in the acyloin condensation.[9]

Alkoxy enediolates are synthetically useful in alkylation reactions such as eq 1, leading to disubstituted α-hydroxy



(1)

esters. These reactions are characterized by high isolated yields of products and can be utilized in a variety of systems as is shown by representative data in Table I. We find that primary alkyl iodides, bromides, tosylates, and mesylates work about equally well as alkylating agents in these reactions, but a less reactive primary alkyl chloride is unsatisfactory. Extension of these reactions to secondary systems shows that even cyclohexyl iodide, which is prone to elimination reactions, reacts with enediolate **1a** to give a 66% yield of ethyl cyclohexylhydroxyphenylacetate. Preliminary work indicates that these reactions are tolerant of some functional groups in the alkylating agent. For example, we have successfully used both allyl bromide and ethyl bromoacetate as reagents in reactions with **1a**. Halides known to be unreactive in S_N2 reactions (*e.g.*, tertiary and aryl halides) do not react with alkoxy enediolates.

Although most of our initial work has concerned reactions of enediolate **1a**, we have also examined enediolates in which the phenyl group of **1a** has been replaced by either a methyl or a hydrogen. While enediolates derived from ethyl lactate (**1b**) can be successfully alkylated with primary alkyl bromides and iodides, similar reactions with ethyl glycolate (**1**, R = H) fail. In both of these cases, elimination of HX from the alkyl halide to form alkene or possibly decomposition of the alkoxy enediolate is a limitation of these reactions. Addition of

Table I. Alkylation of Alkoxy Enediolates

α-Hydroxy acid ester precursor	Method used for preparation of enediolate[a]	Alkylation reagent	Product	Isolated yield, %[b]
Ethyl mandelate	A	n-C_4H_9Br	$C_6H_5C(OH)(n\text{-}C_4H_9)CO_2C_2H_5$	79 (92)[c]
	B	CH_3I	$C_6H_5C(OH)(CH_3)CO_2C_2H_5$	79 (96)[c]
	B	$C_6H_5CH_2Br$	$C_6H_5C(OH)(C_6H_5CH_2)CO_2C_2H_5$	85
	A	$(CH_3)_2CHI$	$C_6H_5C(OH)(CH(CH_3)_2)CO_2C_2H_5$	57[d] (75)[c]
	B	c-$C_6H_{11}I$	$C_6H_5C(OH)(c\text{-}C_6H_{11})CO_2C_2H_5$	66
	B	$BrCH_2CO_2C_2H_5$	$C_6H_5C(OH)(CH_2CO_2C_2H_5)CO_2C_2H_5$	69
	B	$CH_2{=}CHCH_2Br$	$C_6H_5C(OH)(CH_2CH{=}CH_2)CO_2C_2H_5$	82 (85)[c]
Ethyl lactate	B	n-$C_{10}H_{21}I$	$CH_3C(OH)(n\text{-}C_{10}H_{21})CO_2C_2H_5$	(69)[c]
	B	n-$C_{10}H_{21}Br$		(60)[c]
	B	n-C_4H_9I	$CH_3C(OH)(n\text{-}C_4H_9)CO_2C_2H_5$	(53)[c]
	B	$(CH_3)_2CHI$	*e*	0[e]
Ethyl glycolate	A or B	n-$C_{10}H_{21}I$	*e*	0[e,f]

[a] Details of these methods are provided in the text. [b] These yields are based on the starting ester and are spectroscopically pure products obtained by either chromatography or distillation. [c] Yield determined by gas chromatography. [d] This distilled product also contained 16% ethyl mandelate. [e] No alkylated products were found by gas chromatography. [f] In these cases, the starting halide mainly eliminated to form 1-decene.

HMPA as a cosolvent failed to circumvent this problem. The secondary halide, 2-iodopropane, does not alkylate enediolate **1b**.

We have employed two different experimental procedures in the alkylation reactions. In the first (method A), the halide is added to the α-hydroxy ester and LDA at −78 °C, and the reaction mixture is allowed to warm to room temperature. In the second procedure (method B), the enediolate is first generated by addition of the α-hydroxy ester to LDA in THF at −78 °C followed by warming at 0 °C for 0.5 h. Recooling to −78 °C and addition of an alkylation agent followed by warming to room temperature results in high isolated yields of alkylated mandelic acid esters, even when highly reactive alkylating reagents such as methyl iodide, benzyl bromide, allyl bromide, and ethyl bromoacetate are used. The latter procedure is preferable for synthetic purposes.

In a representative reaction, a solution of 788 mg (4.38 mmol) of ethyl mandelate in 4 mL of THF was added to 14 mL of a THF solution of 9.9 mmol of LDA (prepared from n-butyllithium and diisopropylamine in THF) at −78 °C.[10] After warming this solution to 0 °C and stirring for 90 min, the orange solution of the alkoxy enediolate was cooled to −78 °C. Addition of excess benzyl bromide (10 mmol) in 4 mL of THF at −78 °C gave a yellow solution which was stirred for 30 min at −78 °C and finally for several hours at room temperature. The reaction mixture was then quenched with 10% aqueous HCl and diluted with ether. The ethereal phase was washed successively with 10% aqueous HCl and saturated aqueous sodium chloride, and dried ($MgSO_4$). Distillation of the solvent in vacuo gave a residue which was purified by silica gel chromatography (1:1 hexane/benzene (v/v) elution) to give 1.0 g (3.7 mmol, 85%) of ethyl 2-hydroxy-2,3-diphenylpropionate, which was pure by both GC and NMR. Earlier chromatographic fractions contained unreacted benzyl bromide and stilbenes (from the reaction of benzyl bromide with excess base).

The presence of alkoxy enediolate **1a** has been confirmed by deuteration experiments in which the alkoxy enediolate prepared by method B from ethyl mandelate was quenched with deuterium oxide. NMR analysis of the products of this reaction showed only ethyl mandelate, which was >87% d_1. We have also briefly studied the stability of the enediolates by simply protonating the reaction mixtures after varying amounts of time and measuring the amount of starting α-hydroxy ester recovered. These studies show that the enediolate **1a** decomposes in THF at room temperature with a half-life of about 10 h. Other alkoxy enediolates like **1b** are qualitatively less stable, but can be kept for periods of up to 1 h at room temperature without significant decomposition. The products of these decomposition reactions are not known.

The procedures described above provide a useful alternative to existing routes to α-hydroxy-disubstituted carboxylic acid esters. Although the basicity of alkoxy enediolates is a problem in some cases, the use of readily available starting materials in these carbon–carbon bond forming reactions is advantageous. In other reactions such as cyanohydrin formation and hydrolysis, oxidation of ester enolates,[11] and Grignard additions to α-keto esters,[12] more synthetic steps are usually necessary and the final synthetic yields are consequently lower.

We have made a cursory study of reactions of alkoxy enediolates with other electrophiles. Propionaldehyde and ethylene oxide react with **1a** to give ethyl 2-phenyl-2,3-dihydroxypentanoate[13] (65% of a mixture of diastereomers) and α-phenyl-α-hydroxy-δ-butyrolactone[13] (60%), respectively. Similarly, enediolate **1b** and cyclohexanone give ethyl 2-hydroxy-2-(1-hydroxycyclohexyl)propanoate[13] (54%). In these reactions we used experimental method B described above. The fair to good yields obtained in these preliminary studies using enolizable carbonyl compounds and an epoxide suggest that alkoxy enediolates may have many synthetic applications, and further studies are in progress.

Acknowledgment is made to the Robert A. Welch Foundation and to Texas A&M Organized Research funds for the support of this work. We would also like to acknowledge the experimental assistance of Mr. Robert Burke in the early stages of this work.

References and Notes

(1) Welch Undergraduate Scholar.
(2) While our drawings of **1a** and **1b** show only the *E* configuration for these alkoxy enediolates, we have not excluded the possibility that significant amounts of the *Z* isomer are also present. However, consideration of the effect of the vicinal negatively charged centers on each other in the alkoxy enediolates suggests that the *E* configuration should be favored for both kinetic and thermodynamic reasons.
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(4) For example, oxidation of α-benzylmandelic acid with potassium dichromate in acetic acid was reported to give phenyl benzyl ketone in "excellent" yield: O. Widman, *Ber.*, **49**, 477 (1916).
(5) P. A. Grieco and C.-L. J. Wang, *J. Chem. Soc., Chem. Commun.*, 714 (1975), have described acyl anion equivalents derived from phenylthioacetic acid dianions. Acyl anion equivalents from α-amino acid esters have also been described recently; cf. G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976). Oxidation of carbanions derived from nitriles and acids has also been used as a method for introduction of an acyl anion equivalent; cf. S. J. Selikson and D. S. Watt, *ibid.*, **40**, 267 (1975); H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4611 (1976).

(6) Multi-charged anionic derivatives of amino esters have also been reported by A. P. Krapcho and E. A. Dundulis, *Tetrahedron Lett.*, 2205 (1976).
(7) P. L. Creger, *J. Am. Chem. Soc.*, **92**, 1396 (1970); A. J. Birch, *J. Chem. Soc.*, 1551 (1950); P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, *J. Org. Chem.*, **37**, 451 (1972).
(8) Thermodynamic formation of vicinal enediolates from α-hydroxy ketones has been described; cf. S. R. Wilson, M. E. Walters, and B. Orbaugh, *J. Org. Chem.*, **41**, 378 (1976).
(9) J. J. Bloomfield, D. C. Omsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).
(10) These procedures employ unexceptional organometallic experimental techniques similar to those described by H. C. Brown in "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(11) H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 1731 (1975); E. Vedejs, *J. Am. Chem. Soc.*, **96**, 5944 (1974).
(12) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, N.Y., 1954.
(13) The yields of these compounds were determined by gas chromatography. The compounds were characterized by NMR and mass spectra and elemental analyses.

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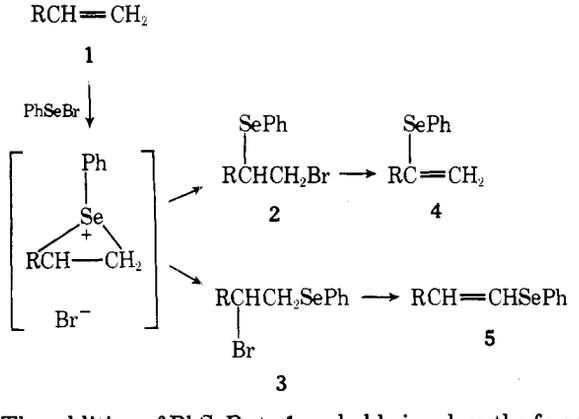
Received April 11, 1977

Regioselective Synthesis of Vinyl Phenylselenides[1]

Summary: Reaction of monosubstituted alkenes with phenylselenenyl bromide under either kinetically or thermodynamically controlled conditions followed by dehydrohalogenation of the resulting adducts provides a method for the regioselective synthesis of either 2-phenylselenoalkenes or 1-phenylselenoalkenes, respectively.

Sir: The utility and versatility of organoselenium compounds has become apparent.[2] Recently we undertook the preparation of both 2-phenylselenoalkenes **4** and 1-phenylselenoalkenes **5**, since these compounds are potentially useful for a number of synthetic transformations.[3] An obvious approach to the synthesis of **4** and **5** involves dehydrohalogenation of the appropriate β-bromoalkyl phenylselenides **2** and **3**, respectively. We therefore initiated a study to determine the feasibility of converting alkenes **1** to the desired vinyl phenylselenides **4** or **5** regioselectively via addition of PhSeBr and subsequent dehydrohalogenation.



The addition of PhSeBr to **1** probably involves the formation of a seleniranium ion, which may then be attacked by bromide ion, either at the less hindered but less electropositive primary carbon to give the anti-Markownikoff adduct **2**, or at the more electropositive but more hindered secondary carbon to give the Markownikoff adduct **3**.[4] Preliminary regioselectivity studies indicated that 1-hexene and PhSeBr react under kinetically controlled conditions (CCl_4, −20 °C) to give predominantly the anti-Markownikoff adduct **2b** [^{1}H NMR (CCl_4): δ 3.8–3.2 (m, 3 H)], which isomerizes[5] slowly in CCl_4 (48 h, 25 °C) or very rapidly in CH_3CN (<5 min, 25 °C) to give predominantly the Markownikoff adduct **3b** [^{1}H NMR (CCl_4): $-CH_2SePh$, δ 3.30 (dd, J = 12, 10 Hz) and 3.65 (dd, J = 12, 7 Hz), total 2 H; $-CHBr$, δ 4.3–3.8 (m, 1 H)]; however, due to the proximity and complexity of the ^{1}H NMR signals[6] and the thermal lability of the β-bromoalkyl phenylselenides, the exact determination of regioselectivity was deferred until both the addition and dehydrohalogenation were affected.

Table I. Percentage of 4/5 Formed Under Kinetic and Thermodynamic Conditions[a]

Entry	Alkene	Kinetic conditions[b] 4/5	Thermodynamic conditions[c] 4/5
a	Propene	85:15	9:91
b	1-Hexene	90:10	8:92
c	1-Octene	90:10	9:91
d	1-Hexadecene	90:10	7:93
e	4-Methyl-1-pentene	90:10	8:92
f	3-Phenyl-1-propene	98:2	2:98
g	3-Methyl-1-butene	98:2	3:97
h	3,3-Dimethyl-1-butene	100:0	0:100
i	3,3-Dimethyl-1-heptene	100:0	0:100

[a] Percentages determined by VPC (see ref 8). [b] PhSeBr (THF, −78 °C); *t*-BuOK (THF, −78 to 25 °C). [c] PhSeBr (CH_3CN, 25 °C); *t*-BuOK (THF, 25 °C).

For the kinetically controlled conditions the reaction of **1** with PhSeBr and subsequent dehydrohalogenation with *t*-BuOK was carried out in THF at −78 °C without isolation[7] of the intermediate β-bromoalkyl phenylselenide to give **4** regioselectively in high overall yield (Table I).[8] The regioselectivity of this process increases with increasing steric bulk at C-3 in **1**.

A typical procedure for the kinetically controlled conditions follows: a solution of 1-hexene (2.0 mmol) in dry THF (5 mL) was added dropwise (2 min) to a cooled (−78 °C) stirring solution of PhSeBr (2.0 mmol) in dry THF (20 mL). Stirring was continued until the dark brown color dissappeared (1 min) and *t*-BuOK (4.0 mmol) was added immediately.[9] The mixture was stirred at −78 °C for 5 min, allowed to warm to 25 °C, and stirred for 30 min. The THF was removed in vacuo, and the residue was extracted with ether, washed with brine, dried ($MgSO_4$), and purified by evaporative distillation (85 °C, 0.01 mm) to give a colorless liquid (430 mg, 90%): [^{1}H NMR (CCl_4) δ 2.4–2.1 (m, 2 H), 5.06 (s, 1 H), 5.45 (t, J = 0.5 Hz, 1 H)]. VPC analysis showed a 90:10 ratio of **4b/5b**.[8]

For the thermodynamically controlled conditions the reaction of **1** with PhSeBr was carried out in CH_3CN at 25 °C, the CH_3CN was removed in vacuo, and the resulting β-bromoalkyl phenylselenide was dehydrohalogenated with *t*-BuOK in THF at 25 °C to give **5** regioselectively in high overall yield (Table I). The ^{1}H NMR of **5h** [(CCl_4) δ 0.90 (s, 9H), 6.03 (d, J = 15 Hz, 1 H), 6.40 (d, J = 15 Hz, 1 H)] and **5i** [(CCl_4) δ 6.00 (d, J = 15 Hz, 1 H), 6.38 (d, J = 15 Hz, 1 H)] indicates that only the *E* isomer is formed; however, compounds **5a–g** are mixtures of *E* and *Z* isomers.

A typical procedure for the thermodynamically controlled conditions follows: a solution of 1-hexene (2.0 mmol) in CH_2Cl_2 (2 mL) was added to a solution of PhSeBr (2.0 mmol) in dry CH_3CN (10 mL) at 25 °C. The dark brown color disappeared immediately, and stirring was continued for 30 min. The solvents were removed in vacuo (25 °C), the residue was dissolved in THF (10 mL), and *t*-BuOK (4.0 mmol) was added. The mixture was stirred at 25 °C for 30 min, the THF removed in vacuo, the residue extracted with ether, washed with brine, dried ($MgSO_4$), and purified by evaporative distillation (85 °C, 0.01 mm) to give a colorless liquid (439 mg,