4,4-dimethyl-2-oxazoline–β-ionone adduct, 51869-21-7; ethyl β-ionylideneacetate, 5452-61-9; ethyl *retro*-β-ionylideneacetate, 51869-22-8; 2-(2-ketopropyl)-4,4-dimethyloxazolidine, 32385-89-0.

References and Notes

(1) Postdoctoral Fellow, Louisiana State University, 1969–1970.
(2) Postdoctoral Fellow, Wayne State University, 1970–1972.
(3) P. L. Creger, *J. Amer. Chem. Soc.*, **89,** 2500 (1967); **92,** 1396 (1970); *J. Org. Chem.*, **37,** 1907 (1972).
(4) H. C. Brown and M. M. Rogic, *J. Amer. Chem. Soc.*, **91,** 2146 (1969); J. Hooz and D. M. Gunn, *ibid.*, **91,** 6195 (1969); H. C. Brown, M. M. Midland, and A. B. Levy, *ibid.*, **94,** 3662 (1972).
(5) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93,** 2318 (1971).
(6) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35,** 262 (1970); *Tetrahedron Lett.*, 699 (1970).
(7) I. Kuwajima and Y. Doi, *Tetrahedron Lett.*, 1163 (1972).
(8) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).
(9) (a) A. I. Meyers and D. L. Temple, *J. Amer. Chem. Soc.*, **92,** 6644, 6646 (1970); (b) A. I. Meyers, E. D. Mihelich, and R. L. Nolen, *J. Org. Chem.*, **39,** 2783 (1974).
(10) P. Allen and J. Ginos, *J. Org. Chem.*, **28,** 2759 (1963).
(11) D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972); C. U. Pittman, S. P. McManus, and J. W. Larson, *Chem. Rev.*, **72,** 357 (1972).
(12) (a) For more recent methods of preparation *cf.* E. Ghera and S. Shoua, *J. Chem. Soc., Chem. Commun.*, 639 (1972); R. A. Wohl and J. Cannie, *J. Org. Chem.*, **37,** 1787 (1972); (b) A. I. Meyers, D. L. Temple, D. Haidukewych and E. D. Mihelich, *J. Org. Chem.*, **39,** 2787 (1974).
(13) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38,** 36 (1973); (b) A. I. Meyers, M. S. Ao, and E. M. Smith, *ibid.*, **38,** 2129 (1973); C. Lion and J. E. Dubois, *Tetrahedron*, **29,** 3417 (1973).
(14) An alternative mechanism leading to **16** may be invoked which allows **12** to add to the C=N link of trace amounts of unmetalated 2-methyloxazoline. This route has been observed in the dimerization of lithiomethyl thiazoles: G. Knaus and A. I. Meyers, *J. Org. Chem.*, **39** 1189 (1974).
(15) For other recent syntheses of β-hydroxy esters and acids see E. Negishi and T. Hoshida, *J. Amer. Chem. Soc.*, **95,** 6837 (1973); S. Watanabe, *Chem. Ind. (London)*, 1811 (1969); G. Read, *et al.*, *J. Chem. Soc. C*, 2799 (1969); P. E. Pfeffer, E. Kinsel, and L. S. Silbert, *J. Org. Chem.*, **37,** 1256 (1972); G. W. Moersch and A. R. Burkett, *ibid.*, **36,** 1149 (1971); M. W. Rathke, *J. Amer. Chem. Soc.*, **92,** 3222 (1970).
(16) W. Adam, J. Baeza, and J.-C. Liu, *J. Amer. Chem. Soc.*, **94,** 2000 (1972), and previous references cited therein.
(17) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, **41,** 1662 (1963).
(18) Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn.
(19) S. M. McElvain and L. R. Morris, *J. Amer. Chem. Soc.*, **74,** 2657 (1952).
(20) Prepared by treating the bromoacetal [H. Brederèck, *et al.*, *Chem. Ber.*, **97,** 827 (1964)] with 5.0 equiv of sodium iodide in acetone and heating for 48 hr, bp 32° (0.25 mm), 66% yield.
(21) R. E. Marker, H. M. Crooks, R. B. Wagner, A. C. Shabica, E. M. Jones, and E. L. Wittbecken, *J. Amer. Chem. Soc.*, **64,** 822 (1942).
(22) See Table II, footnote *e*.

Oxazolines. X. Synthesis of γ-Butyrolactones

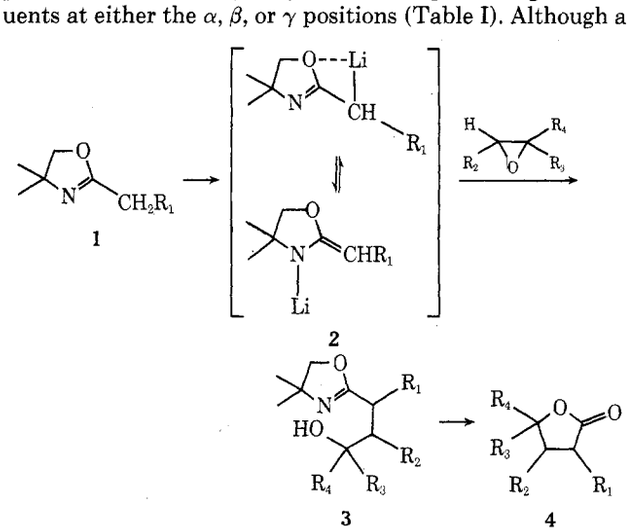
A. I. Meyers,* Edward D. Mihelich, and Robert L. Nolen

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

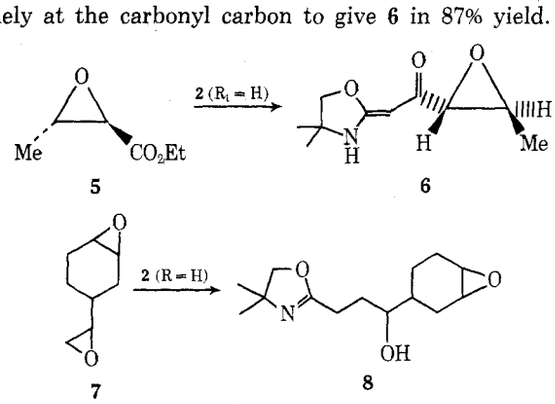
Received April 16, 1974

A variety of butyrolactones (4), substituted in the α, β, and/or γ positions with alkyl groups, is described. The approach originates from the lithio salt of 2,4,4-trimethyl-2-oxazoline (1, R = H) and higher 2-alkyl homologs (1, R = alkyl) which readily reacts with epoxides at low temperature to produce the 2-(β-hydroxyalkyl)oxazolines 3. Hydrolysis of the latter leads to the butyrolactones 4 in good overall yields. Several examples in which the epoxide is part of a polyfunctional molecule are given to indicate the selectivity of the lithio oxazoline.

In the previous article[1] a series of homologated acetic acids were prepared by treating the lithio salt of 2-substituted 4,4-dimethyl-2-oxazolines **2** with a variety of alkyl halides and carbonyl compounds. Further work on this useful heterocyclic system (**1**) has revealed that its lithio salt **2** may also react with epoxides at low temperature, resulting in the hydroxypropyloxazolines **3**. Hydrolysis of the latter produces a variety of γ-butyrolactones **4** possessing substituents at either the α, β, or γ positions (Table I). Although a

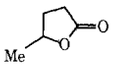
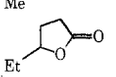
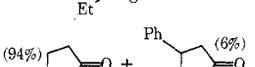
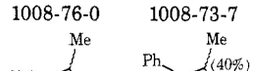
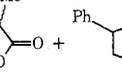
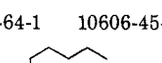
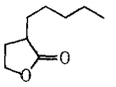
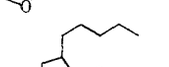
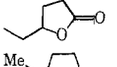
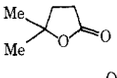
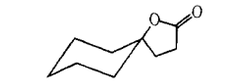
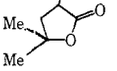
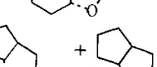
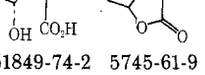


number of epoxides gave good yields of lactones, others proved to be resistant to alkylation. For example, 1,2-disubstituted epoxides (entries 13, 14, and 15) gave little or no ring-opened products except for cyclohexene and cyclopentene oxides. For the latter case, the lactone (entry 12) was poorly formed, since this would necessitate a trans-fused product which involves considerable strain. However, the trans hydroxy acid was the major product formed. The extent to which 1,2 disubstitution prevents epoxide ring opening was clearly seen when the epoxy ester **5** was treated at −78° with the lithio oxazoline. Reaction occurred solely at the carbonyl carbon to give **6** in 87% yield. Al-



though tautomers were expected, the product was found to be entirely **6**, which appeared as a crystalline material. Other organometallics were reported to react with **5** to give ring-opened products[2] with varying degrees of selectivity. On the other hand, α-cyano epoxides were found to react with organolithium reagents exclusively at the cyano group.[3,4] When the bis epoxide **7** was subjected to the lithio oxazoline at −60°, the adduct **8** was isolated in 70% yield.

Table I
γ-Butyrolactones from Epoxides and Lithio Oxazolines

Entry	1, R_1	Registry no.	Epoxide[a]	Registry no.	% 3[b]	Registry no.	Lactone 4	Registry no.	Overall yield, %[c]
1	H	1772-43-6		75-21-8	~100	51849-54-8		96-48-0	75[d]
2	H			75-56-9	80	51849-55-9		108-29-2	72[d]
3	H			106-88-7	85	51849-56-0		695-06-7	85[d]
4	H			96-09-3	~100	51849-57-1 51849-58-2	 1008-76-0 1008-73-7		89
5	Me	5146-88-3			80	51849-59-3 51849-60-6	 10606-64-1 10606-45-8		65
6	*n*-Amyl	51849-53-7			~100	51849-61-7		51849-71-9	72
7	*n*-Amyl				95	51849-62-8		51849-72-0	76
8	H			1558-30-5	99	51849-63-9		3123-97-5	72[d]
9	H			185-70-6	80	51849-64-0		699-61-6	56[e]
10	$PhCH_2$	13608-28-1			~100	51849-65-1		51849-73-1	70
11	H			286-20-4	83	51849-66-2		27345-71-7	65
12	H			285-67-6	95[h]	51849-67-3	 51849-74-2 (80–85%) 5745-61-9 (15–20%)		30[e]
13	H			286-62-4	~0				
14	H		 (cis or trans)	1758-33-4 (cis) 21490-63-1 (trans)	10–30	51849-68-4	 (50 : 50 mixture)	10150-95-5 (cis) 10150-96-6 (trans)	16[d]
15	H			23024-54-6	~0[f]				
16	Me				14	51849-69-5		2205-25-6	9[e]
17	H			6924-86-3	82	51849-70-8		7011-83-8	70

[a] 1.1 equiv of epoxide added at −78° and slowly allowed to rise to room temperature. For entries 9, 11, 12, and 17, the epoxide was added at −45°, stirred for 4–5 hr, and then allowed to warm slowly to room temperature. [b] Crude yield, used in subsequent step without purification. [c] Based on starting oxazoline; products were checked for purity by vpc after bulb-to-bulb distillation. Purity in all cases was >95%. [d] Hydrolysis of **3** performed in acidic ethanol. Yields were ~30% lower when hydrolysis was done in aqueous acid. [e] Hydrolysis in wet benzene–toluenesulfonic acid. [f] Epoxide was recovered in >80% yield. [g] The lithio salt **2** (R_1 = H) was complexed with 1.0 equiv of *N,N,N′,N′*-tetramethylethylenediamine prior to addition of styrene oxide. [h] 2.0 equiv of **1** (R_1 = H) employed.

Thus, the low-temperature alkylation of the lithio oxazolines proceeds with considerable selectivity, the predominant factor being the steric environment of the epoxide carbons. However, steric bulk on the lithio oxazoline was

also seen to affect the efficiency of the reaction (entries 11 *vs.* 16). The presence of a methyl group in **2** (R_1 = Me) coupled with the disubstitution in cyclohexene oxide caused a drop in yield from 83 to 14%. In those cases where reaction went poorly or failed completely (entries 13–16) a number of conditions were evaluated to improve the process. Changing solvents (from THF to ether), changing temperatures (−78 to 20°), and addition of complexing agents (TMEDA, HMPA) failed to provide any significant improvements. Only in the case of styrene oxide (entry 4) was the yield of alkylation increased (from 60 to 100%) when **2** was complexed with TMEDA.

Of further interest was the fact that the substitution pattern in the lactones could be introduced sequentially in a single operation. For example, the lactone in entry 10 was prepared by initially treating the parent lithio oxazoline **2** (R_1 = H) with 1.0 equiv of benzyl chloride at −78° and allowed to warm to 25° to ensure complete reaction. The solution was then recooled to −78° and 1.1 equiv of *n*-butyllithium and the epoxide were added. Upon work-up, the α-benzyl lactone was obtained in 70% overall yield. The anticipated mixture of products from sequential alkylation was held to less than 10% and the desired lactone could readily be purified by distillation. When the sequential alkylation was attempted with methyl iodide (entry 5) followed by styrene oxide, a 60:40 isomeric mixture was formed. This is believed to be the result of the initially formed lithium iodide acting as a Lewis acid which lowers the regioselectivity of the ring opening in styrene oxide. Note the high degree of regioselectivity when the parent lithio oxazoline is treated with styrene oxide (entry 4), a system which is devoid of any soluble Lewis acid. It would be expected, therefore, that a higher yield of the γ-phenyl lactone would result if the reaction began with the 2-ethyloxazoline **1** (R_1 = Me), although this has not been performed. Currently, this study is being directed toward a convenient synthesis of α-methylene lactones and further work on the consecutive alkylations is a necessary prerequisite to this goal. In summary, this method should find considerable use in the preparation of a variety of substituted γ-lactones and compares favorably with other recent techniques.[5-8]

Experimental Section

n-Butyllithium was purchased from Ventron (Alfa Division), Beverly, Mass. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Spectra were taken on a Perkin-Elmer 257 grating infrared, Varian T-60, and JEOL MH-100 nmr instrument. Gas chromatography was performed on a Hewlett-Packard 5750 instrument using two different columns (FFAP and UC-W98) to check homogeneity. The epoxides utilized were commercially available except as indicated; *exo*-methylenecyclohexane oxide (entry 9) and 2-methyl-1-octene oxide (entry 17) were prepared from the corresponding ketones according to Corey;[9] *cis*-1-methyl-2-(*n*-amyl)oxirane (entry 15) was prepared by epoxidation of *cis*-2-octene.[10]

2-Oxazolines. 2,4,4-Trimethyl-2-oxazoline (**1**, R_1 = H) was prepared as previously described.[1] 2-(*n*-Hexyl)-4,4-dimethyl-2-oxazoline (**1**, R_1 = *n*-amyl) was prepared in the same manner using *n*-heptanoic acid: 40%; bp 96–98° (15 mm); ir (film) 1660 cm^{-1}; nmr (CCl_4) δ 3.80 (s, 2), 2.15 (m, 2), 1.8–1.3 (m, 8), 1.2 (s, 6), 0.9 (t, 3).

Alkylation of Epoxides with Lithio Oxazolines. General Procedure. A solution containing 2.50 g (22 mmol) of 2,4,4-trimethyl-2-oxazoline (1.7 *M*) in 13 ml of anhydrous THF was cooled to −78° under a nitrogen atmosphere. A solution of *n*-butyllithium (2.25 *M* in hexane, 23.1 ml, 1.05 equiv) was added dropwise and the lithio oxazoline precipitated from solution as a colorless light powder. The suspension was stirred for 30 min at −78° and 1.1 equiv of the epoxide (neat or diluted equally with THF) was added dropwise and stirred for 30 min. The cooling bath was removed and the solution was allowed to reach room temperature (4–5 hr). If the reaction temperature was to be maintained at −45° (see Table I), the Dry Ice–acetone bath was replaced with a −45° cryostat (Dry Ice–chlorobenzene) and stirred for 3–5 hr.

The reaction contents were poured into water (150 ml) and work-up proceeded in either of the following manners. (a) For low molecular weight (volatile) or water-soluble epoxides, the aqueous solution was merely poured into 100 ml of ether, and the organic layer was separated and washed with saturated brine. Drying of the ethereal solution ($MgSO_4$) and concentration left the hydroxypropyloxazoline **3**. (b) For higher molecular weight or water-insoluble epoxides, the quenched reaction mixture was cooled to 0° and acidified to pH 2 (9 *N* HCl). The solution was extracted with pentane or pentane–ether (1:1) to remove unreacted epoxide and then neutralized, while still cold, with 40% sodium hydroxide (pH 8–10). The oxazoline was removed by extraction with ether, and the extracts were dried ($MgSO_4$) and concentrated to give **3**. The purity of this material was usually quite high (vpc) and further purification was necessary only for analytical samples. Physical data for **3** are presented in Table II.

Hydrolysis of Oxazolines 3 to γ-Butyrolactones. General Procedure. A. Acidic Aqueous Method. The oxazoline (22 mmol) was stirred in 50 ml of 3 *N* HCl to effect solution and then heated at reflux for 15–20 min. After cooling, the acidic solution was extracted with ether (3 × 75 ml), dried ($MgSO_4$), and concentrated to give lactones of high purity (>90%, vpc). The pure lactones were obtained by bulb-to-bulb distillation. Physical properties are given in Table II.

B. Acidic Ethanol Method. This method was used primarily in those cases where the lactone was water soluble (Table I). A solution of the oxazoline (22 mmol) in 150 ml of 95% ethanol containing 6.0 ml of concentrated sulfuric acid was heated to reflux for 16–18 hr, cooled, and concentrated to 15 ml by fractional distillation. Addition of 100 ml of ether to the concentrate was followed by extraction with 15 ml of saturated brine. The ethereal solution was dried ($MgSO_4$) and concentrated (by fractional distillation for low-boiling lactones) to produce the γ-butyrolactone.

C. Toluenesulfonic Acid–Benzene Method. For lactones that formed slowly from their hydroxy acids (entry 16), the oxazoline **3** (5 mmol) was dissolved in benzene (20 ml), and water (2.5 ml) and toluenesulfonic acid (1.92 g) were then added. The solution was heated to reflux (18 hr) and the water was collected in an azeotrope (Dean-Stark) trap. Heating was continued until all the water had been collected. The solution was cooled, water was added so that two layers appeared, and the benzene layer was removed, dried, and concentrated to produce the lactone.

Reaction of Lithio Oxazoline (1, R_1 = H) with Ethyl *trans*-2,3-Epoxybutyrate (5). To 1.25 g (11 mmol) of **1** (R_1 = H) in 6 ml of THF at −78° was added 5 ml (11 mmol) of *n*-butyllithium and stirring was performed for 30 min. To the resulting suspension was added 1.35 ml (11 mmol) of epoxide **5** in a single portion at −78°, which caused the precipitate to disappear immediately. After 30 min, the solution was quenched (−78°) with saturated ammonium chloride and poured into 100 ml of ether. The ether layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give a pale yellow solid. Recrystallization from ether–hexane gave 1.8 g (87%) of a colorless solid: mp 96.5–97.5°; ir (KBr) 3270, 3110, 1635, 1560 cm^{-1}; nmr (CCl_4) δ 9.7 (br s, 1), 4.9 (s, 1), 2.9 (m, 2), 1.5 (s, 6), 1.35 (m, 3). The structure was consistent with **6** and the trans stereochemistry based upon comparison with the nmr spectrum of **5**.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.70; H, 7.81; N, 7.02.

Reaction of 1 (R_1 = H) with Bis Epoxide 7. The lithio oxazoline **1** (R_1 = H) was prepared as described in the General Procedure. The solution was then warmed to −64°, and 3.08 g of the bis epoxide **7**[11] in 2 ml of THF was added, and the solution was stirred for 3.5 hr as the temperature rose slowly to −40°. The reaction solution was poured at this temperature into ice–water (50 ml), acidified with 9 *N* HCl (pH 2), and extracted with hexane (2 × 30 ml), and the hexane solution was discarded. The cold aqueous layer was neutralized with 40% alkali and extracted with ether, dried ($MgSO_4$), and concentrated to give 4.1 g (70–75%) of a clear, viscous oil. Distillation (bulb-to-bulb) at 0.02 mm gave pure **8**: ir (film) 3300, 1668 cm^{-1}; nmr (CCl_4) δ 4.4 (br s, OH), 3.85 (s, 2), 3.5–2.8 (m, 3), 2.3 (t, 2), 1.25 (s, 6), 2.2–0.9 (m, 9).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.54; H, 9.02.

Consecutive Alkylation. α-Benzyl-γ,γ-dimethyl-γ-butyrolactone (Entry 10). The lithio oxazoline **1** (R_1 = H) was formed as described in the General Procedure. At −78°, benzyl chloride (2.53 ml, 1.0 equiv) was added neat in a dropwise manner. After stirring

Table II
Physical Data for Oxazolines and Lactones

Entry	Oxazolines 3		Lactones 4	
	Ir (film), cm^{-1}	Nmr (CCl_4), δ	Ir (film), cm^{-1}	Nmr (CCl_4), δ
1	1660, 3320	5.1 (1, OH), 3.9 (s, 2), 3.6 (t, 2), 2.4 (m, 2), 1.9 (m, 2), 1.3 (s, 6)	1770[a]	
2	1665, 3360	4.0–3.7 (m, 4), 2.4 (m, 2), 1.8 (m, 2), 1.2–1.1 (s, 6; d, 3)	1770[b]	
3	1670, 3380	4.35 (s, OH), 3.85 (s, 2), 3.45 (m, 1), 2.35 (t, 2), 1.9–1.3 (m, 4), 1.25 (s, 6), 0.9 (br t, 3)	1778	4.4 (m, 1), 2.7–1.3 (m, 6), 1.0 (t, 3)[c]
4	1665, 3380	7.3 (m, 5), 4.7 (t, 1), 4.5 (br s, 1), 3.9 (s, 2), 2.1 (m, 4), 1.2 (s, 6)	1780	7.4 (s, 5), 5.4 (m, 1) 2.4 (m, 4)[d]
5	1658, 3250, 3320	7.3 (m, 5), 4.6 (m, 2), 4.0–1.6 (m, 5), 1.4–0.8 (m, 9)	1770	7.26 (m, 5), 5.3 (m, 0.6), 4.2 (m, 0.4) 3.6–2.0 (m, 3), 2.0–0.6 (m, 3)[e]
6	1660, 3300	3.85 (s, 2), 3.55 (m, 3), 2.45 (m, 1), 2.0–0.8 (m, 19)	1780	4.2 (m, 2), 2.7–0.7 (m, 14)[f]
7	1660, 3360	3.85 (s, 2), 3.6 (m, 2), 2.5 (m, 1), 1.8–0.7 (m, 24)	1770	4.35 (m, 1), 2.4 (m, 1), 2.2–0.7 (m, 18)[g]
8	1665, 3370	3.83 (s, 2), 3.55 (s, OH), 2.3 (m, 2), 1.75 (m, 2), 1.22 (s, 6), 1.15 (s, 6)	1770	2.53 (AA'BB', 2), 2.0 (AA'BB', 2), 1.43 (s, 6)[h]
9	1660, 3250 (KBr)	3.9 (s, 2), 3.55 (s, OH), 2.3 (m, 2), 2.0–0.8 (m, 18)	1775	2.55 (AA'BB', 2), 2.0 (AA'BB', 2), 1.6 (br s, 10)[i]
10	1665, 3400	7.2 (s, 5), 3.8 (s, 2) 3.7–1.1 (m, 18)	1770	7.25 (s, 5), 2.9 (m, 3), 1.85 (m, 2), 1.3 (2 s, 6)[j]
11	1660, 3300	3.83 (s, 2), 3.8–1.1 (m, 19)	1775	3.7 (m, 1), 2.6–0.8 (m, 11)[k]
12	1665, 3320	4.8 (s, OH), 3.9 (s, 2), 3.8 (m, 1), 2.5–0.8 (m, 15)[o]		*p*
14	1665, 3340	3.9–3.2 (m, 4), 2.4–1.4 (m, 3), 1.3–0.6 (m, 12)	1780	4.6 (m, ~0.5), 4.1 (m, ~0.5), 2.7–1.8 (m, 3), 1.5–0.9 (m, 6)[l]
16	1660, 3300	3.9 (s, 2), 3.7–3.1 (m, 2), 2.5–0.9 (m, 19)[m]	1785	3.8 (m, 1), 2.8–1.1 (m, 13)
17	1670, 3360	3.85 (s, 2), 3.45 (br s, OH), 2.3 (m, 2), 1.75 (m, 2), 1.35 (br s, 10), 1.25 (s, 6), 1.1 (s, 3), 0.90 (br t, 3)	1778	2.5 (AA'BB', 2) 1.75–2.1 (AA'BB', 2), 1.2–1.65 (m, 10), 1.35(s, 3), 0.90(br t, 3)[n]

[a] Sadtler Prism ir no. 5330. [b] Sadtler Prism ir no. 3407. [c] O. Riobe, *C. R. Acad. Sci.*, **247,** 1016 (1958). [d] C. H. Depuy, F. H. Breitbeil, and K. L. Eilers, *J. Org. Chem.*, **29,** 2810 (1964). [e] C. H. Depuy, F. W. Breitbeil, and K. R. DeBruin, *J. Amer. Chem. Soc.*, **88,** 3347 (1966). *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 6.74. [f] G. N. Nikishin, Yu. N. Ogibin, and A. D. Petrov, *Dokl. Akad. Nauk SSSR*, **38,** 498 (1961). [g] *Anal.* Calcd for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95. Found: C, 71.93; H, 10.99. [h] T. Tsuji and S. Hosaka, *J. Amer. Chem. Soc.*, **87,** 4075 (1965). [i] B. M. Trost and M. J. Bogdanowicz, *ibid.*, **95,** 5321 (1973). [j] *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.42; H, 7.90. Found: C, 76.18; H, 7.67. [k] W. Herz and L. A. Glick, *J. Org. Chem.*, **28,** 2970 (1963). *Anal.* Calcd for $C_9H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.48; H, 8.57. [l] J. F. Laporte and R. Rambaud, *C. R. Acad. Sci., Ser. C*, **262,** 1095 (1966). [m] *Anal.* Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.17; H, 10.58. [n] Reference *i* above; P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37,** 1947 (1972). [o] *Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.68; H, 9.65; N, 7.19. [p] Hydrolysis of the oxazoline adduct gave a mixture predominated by the hydroxy acid (ν_{max} 3400, 1720 cm^{-1}) (lactone, ν_{max} 1780 cm^{-1}) in low yield owing to the water solubility of the acid.

(30 min) the solution was allowed to warm to room temperature and again cooled to −78°. Addition of 11 ml (1.1 equiv) of 2.25 *M* *n*-butyllithium produced a red solution and after 30 min of stirring, 2.1 ml (24.2 mmol, 1.1 equiv) of isobutylene oxide was added neat in a dropwise manner. The red solution was immediately discolored and the reaction vessel was allowed to warm to ambient, with stirring overnight. Work-up followed the General Procedure given for water-insoluble epoxides and gave 6.78 g (~100%) of a clear oil. Vpc showed a major component (80–85%) along with some minor less volatile material (15–20%). The oily mixture (2.7 g) was heated in 50 ml of 3 *N* HCl for 15 min, cooled, saturated with salt, extracted with ether, dried (K_2CO_3), and concentrated. A clear oil, 1.6 g (80%), was obtained which was 88% pure (vpc). Distillation, bulb-to-bulb, gave pure (>95%) lactone. An analytical sample was collected from the vpc instrument. Physical and analytical data are given in Table II.

Acknowledgment. This work was supported by the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No—5, 36099-48-6; **6,** 51898-93-2; **7,** 106-87-6; **8,** 51849-75-3; heptanoic acid, 111-14-8.

References and Notes

(1) A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich, *J. Org. Chem.*, **39,** 2778 (1974).

(2) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973); R. B. Rickborn, T. Livinghouse, and B. C. Hartman, *ibid.*, **38**, 4346 (1973).
(3) J. M. Normant, *Tetrahedron Lett.*, 4253 (1973).
(4) Reaction of **5** and other glycidic esters with the lithium salt of methyl acetate and *N*-methylacetanilide at −78° also gave exclusive addition to the carbonyl group without effecting the epoxide function: A. I. Meyers and D. Horne, unpublished results.
(5) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972).
(6) B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 5321 (1973).
(7) A. Eschenmoser, T. K. Dasgupta, D. Felix, and U. M. Kempe, *Helv. Chim. Acta*, **55**, 2187 (1972).
(8) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972).
(9) E. J. Corey and M. Chaykowsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).
(10) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
(11) Aldrich Chemical Co., Milwaukee, Wis.

Oxazolines. XI. Synthesis of Functionalized Aromatic and Aliphatic Acids. A Useful Protecting Group for Carboxylic Acids against Grignard and Hydride Reagents

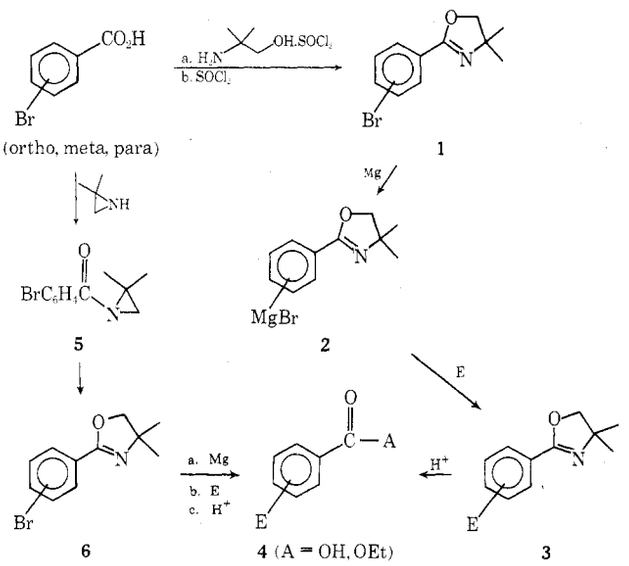
A. I. Meyers,* Davis L. Temple,[1] Dan Haidukewych,[2] and Edward D. Mihelich

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

Received April 16, 1974

The use of an oxazoline to mask a carboxyl group is described. Since the oxazoline moiety is inert to Grignard reagents and lithium aluminum hydride, this technique serves as a novel means to elaborate or functionalize carboxylic acid derivatives. The carboxyl function may be masked either as its acid or ester derivative under generally mild conditions. A series of substituted benzoic acids, using the Grignard reagent of the *o*-, *m*-, or *p*-bromo derivatives was prepared while the carboxyl group was protected as the oxazoline. Furthermore, a series of keto-containing carboxylic acids was treated with Grignard or hydride reagents, producing hydroxy acids.

The synthetic utility of simple 2-oxazolines toward homologated acetic acids[3] and γ-butyrolactones[4] has been described in previous articles. Application of this heterocyclic system to the synthesis of functionalized aromatic and aliphatic acids is now reported. The technique is based on masking of the carboxylic group as its oxazoline derivative, which is inert to either the Grignard or lithium aluminum hydride reagent. Thus, bromo-substituted benzoic acids may be transformed into the corresponding bromophenyloxazoline **1** in high yield and then converted to its Grignard reagent **2**, with the carboxyl group safely masked as the oxazoline.[5] Addition of a wide variety of electrophiles (E) results in the substituted phenyloxazoline **3** which,



upon acidic hydrolysis or ethanolysis, releases the carboxyl group and provides the substituted benzoic acid or ester **4** (Table I). Alternatively, the isomeric oxazoline **6** may be readily prepared by treating the bromobenzoic acid with 1,1-dimethylaziridine, which furnishes the *N*-acylaziridine **5**. Rearrangement of the latter under very mild acidic conditions produces the requisite bromophenyloxazine **6**. Similar treatment of **6** with magnesium to form the Grignard followed by addition of an electrophile leads to the substituted benzoic acids or esters **4**. Since the bromobenzoic acids are very stable systems, the 4,4-dimethyloxazolines **1** were found to be more conveniently prepared and utilized. However, masking of more sensitive carboxylic acids (as described below) was performed using the dimethylaziridine method. As seen from Table I, yields and a variety of substitutions are quite satisfactory. In the case of *N*-methylpiperidone, reaction with **2** was poor (31%) under the usual conditions (15 hr, 25°, THF). This was rectified by introduction of 2.0 equiv of anhydrous magnesium bromide to the oxazoline Grignard prior to addition of the piperidone. The yield in this case rose to 82%, presumably by complexing the lone pair on the piperidone nitrogen, thus allowing the Grignard reaction to proceed normally. Of further interest is the accessibility of specifically deuterated benzoic acids *via* this technique. Simple quenching of the oxazoline Grignard in deuterium oxide leads, after hydrolysis, to benzoic acids of high deuterium content (>98%). This method should compare favorably with the recently reported technique[6] requiring sodium borodeuteride–palladium chloride reduction of bromobenzoic acids.

The purity of the magnesium employed was found to be rather critical. When "reagent" grade magnesium was used to prepare the Grignard reagent, the reactions were found to be slow and the yields were erratic. By using triply sublimed magnesium, the yields were consistently good and reproducible. Hydrolysis of the elaborated phenyloxazolines **3** was accomplished in a manner designed to produce the ethyl esters **4** (A = OEt) or the free acids **4** (A = H). By refluxing an ethanol solution of **3** containing 1.5 *N* sulfuric acid, the ethyl esters were smoothly formed, undoubtedly *via* transesterification of the initially formed open-chain amino esters. Presumably, other esters could be directly formed by utilizing the appropriate alcohol as a solvent.[3] The hydrolysis of **3** to the free carboxylic acids could be readily accomplished in either of two ways (Table I, method B or C). The choice of method usually was determined by the nature of the aryl substituent. Since it was difficult