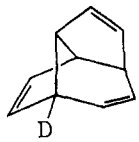


IV

tane as the eluent. The nmr spectrum of the purified material was determined in CCl_4 solution at $-12°$ and is shown in Figure 1a. When the nmr spectrum was redetermined after the sample had been allowed to remain at room temperature overnight, the spectrum changed to that shown in Figure 1b. The latter spectrum is that of II;[12] the former we attribute to I.

(2) When the purified material was hydrogenated at -5 to $-15°$ in methanol with 5% rhodium on carbon catalyst,[13] the gas chromatogram of the distilled product showed only two major peaks accounting for 86% of the area of the chromatogram. The components accounting for these peaks were collected by preparative glpc, and the major one, accounting for 61% of the original glpc trace, was identified as the saturated hexahydro derivative of I; it was identical (ir, nmr, glpc) with the hydrocarbon obtained upon Wolff–Kishner reduction of tricyclo[5.3.0.$0^{2,10}$]decan-9-one.[9] The minor product of the hydrogenation, accounting for 25% of the glpc trace, was identified as the hexahydro derivative of II by comparing it with the product obtained by hydrogenating (with rhodium on carbon) an authentic sample of II.

(3) When the product of the reaction of lithium cyclononatetraenide with methylene chloride plus *n*-butyllithium at low temperature[14] is allowed to react in liquid ammonia with a large amount of sodium and then methanol,[15] the major product isolable by distillation and preparative glpc is a *cis*-bicyclo[5.3.0]decadiene, identified by the parent peak in its mass spectrum (*m/e* 134, the base peak at 75 V) and the product of its hydrogenation in methanol over PtO_2, *cis*-bicyclo[5.3.0]-decane,[16] identical (ir, nmr) with the hydrogenation product (PtO_2 in HOAc) of azulene.[16a] The sodium–ammonia–methanol reduction of II under the conditions described gave none (nmr and glpc) of the bicyclo[5.3.0]-decadiene.

The simplest explanation for 1, 2, and 3 above, as well as for the previous observation[2] that lithium cyclononatetraenide reacts with CD_2Cl_2 plus *n*-butyllithium to give, after warming, IV is that the initial product is isobullvalene.

The conversion of isobullvalene (I) to II was monitored in CCl_4 solution by proton nmr spectroscopy.[17] From the rate constants for the reaction determined at 20, 25, and 35° the enthalpy of activation was determined to be 19.5 ± 0.8 kcal/mol and the entropy of activation to be -9.1 ± 3 eu. This means that the half-life for the conversion of isobullvalene to II is 35 min at 25° and 13 hr at 0°.

(12) (a) M. Jones, Jr., *J. Amer. Chem. Soc.*, **89**, 4236 (1967); (b) M. Jones, Jr., S. D. Reich, and L. T. Scott, *ibid.*, **92**, 3118 (1970).

(13) *Cf.* ref 7, footnote 4.

(14) For this experiment the product was purified by distillation at low temperature.

(15) *Cf.* the reduction of bullvalene: G. Schröder, *Chem. Ber.*, **97**, 3140 (1964).

(16) (a) F. Šorm and M. Romaňuk, *Collect. Czech. Chem. Commun.*, **22**, 779 (1957); (b) E. Korváts, A. Fürst, and Hs. H. Günthard, *Helv. Chim. Acta*, **37**, 534 (1954); (c) N. L. Allinger and V. B. Zalkow, *J. Amer. Chem. Soc.*, **83**, 1144 (1961).

(17) The intensity of the resonance of II at τ 3.45 was measured.

Acknowledgments. We are grateful to the National Institutes of Health (MH-08912) for its support, Badische Anilin und Sodafabrik, A. G., for gifts of cyclooctatetraene, and Professor S. Masamune for informing us of similar experiments performed in his laboratory.[18]

(18) K. Hojo, R. T. Seidner, and S. Masamune, *J. Amer. Chem. Soc.*, **92**, 6641 (1970).

* Address correspondence to this author.

Thomas J. Katz,* J. J. Cheung, Nancy Acton
Department of Chemistry, Columbia University
New York, New York 10027

Received July 6, 1970

Syntheses *via* 2-Oxazolines. II. A Versatile Synthesis of Aliphatic Carboxylic Acids and Esters. Mono- and Dialkylation of Acids Masked by a Simple Protecting Group

Sir:

The recent reports[1,2] concerning the elaboration of aliphatic carboxylic acids through their dianions prompts us to describe our preliminary results which offer a potentially useful synthesis of carboxylic esters and acids. During our studies involving dihydro-1,3-oxazines which have shown considerable utility as precursors to aldehydes[3] and ketones,[4] we routinely examined the analogous 2-oxazoline system (**1**) which has long been known[5] and readily prepared[6] from 2-aminoethanol derivatives and carboxylic acids. After investigation of a host of 2-oxazolines we chose the 2-substituted 4,4-dimethyl-2-oxazoline (**1**) as a potential precursor for elaborated carboxylic acids due to (a) ease of formation,[6] (b) ready availability of starting materials, and (c) stability toward a wide variety of temperatures and reagents. Although we found that the 2-methyl group can be smoothly metalated with butyllithium (THF, $-78°$) and the resulting lithio derivative alkylated with various electrophiles (alkyl halides, carbonyl compounds, epoxides) to **2**, no conditions could be found to effect an efficient reduction of the C=N link which would provide aldehyde precursors.[7] On the other hand we observed that the 2-oxazoline ring could be easily transformed into the corresponding ethyl esters (**3**) by heating in 5–7% ethanolic sulfuric acid. Thus a method to elaborate carboxylic acid derivatives and convert them directly to their ethyl esters was at hand. The simplest 2-oxazoline derivative **1** (R = H) can be made in quantity by the method previously described[6] and can be utilized as a $>CHCO_2Et$

(1) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); *ibid.*, **92**, 1396 (1970).

(2) P. E. Pfeffer and I. S. Silbert, *Tetrahedron Lett.*, 699 (1970).

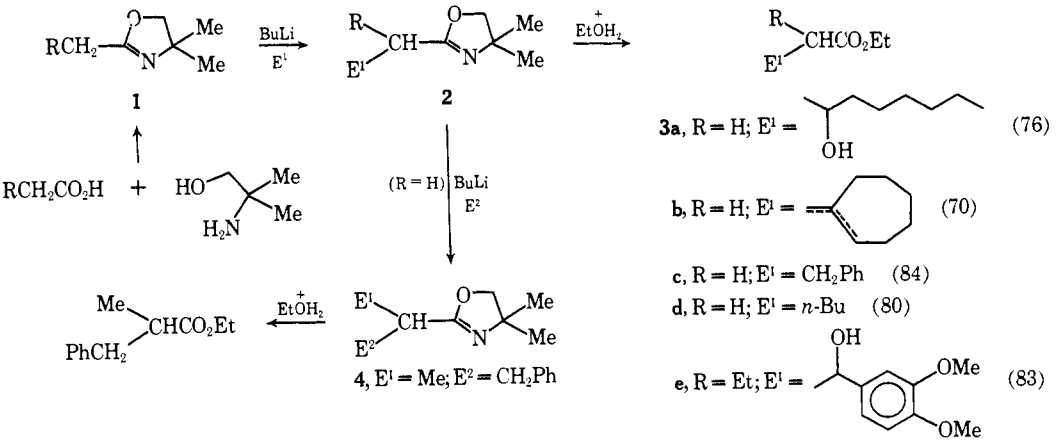
(3) H. W. Adickes, I. R. Politzer, and A. I. Meyers, *J. Amer. Chem. Soc.*, **91**, 2155 (1969), and earlier references cited.

(4) A. I. Meyers and A. C. Kovelesky, *ibid.*, **91**, 5857 (1969); A. I. Meyers and E. M. Smith, *ibid.*, **92**, 1084 (1970).

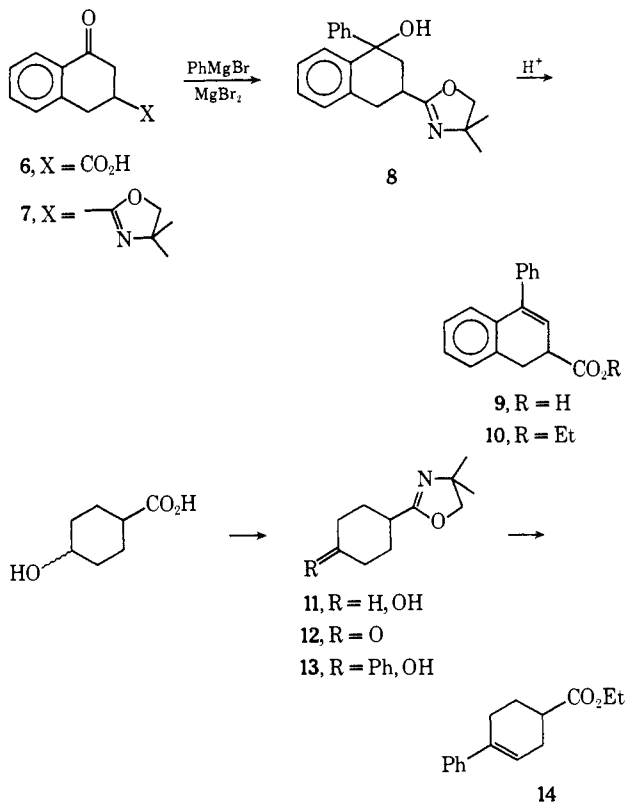
(5) J. W. Cornforth, *Heterocycl. Compounds*, **5**, 386 (1957).

(6) H. L. Wehrmeister, *J. Org. Chem.*, **27**, 4418 (1962); P. Allen and J. Ginos, *ibid.*, **28**, 2759 (1963); commercially available from Columbia Organic Chemicals, Columbia, S. C.

(7) Recent reports [R. M. Srivastara, K. Weissman, and L. B. Clapp, *J. Heterocycl. Chem.*, **4**, 114 (1967); J. V. Paukstelis and R. M. Hammaker, *Tetrahedron Lett.*, 3557 (1968)] have described the facile tautomerism of oxazolidines and imines as a function of temperature, solvents, and substituents. Since the imine form is more prevalent than that observed in the tetrahydro-1,3-oxazines, overreduction to the saturated amino alcohols cannot be circumvented [A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967)].



synthon[8] to form malonic ester products (mono- or dialkylated acetic esters) or Reformatsky products (β-hydroxy esters). In order to exemplify this technique, the lithio salt of the oxazoline[1] was treated with *n*-heptaldehyde and the resulting oxazoline **2** was converted by ethanolic sulfuric acid to the β-hydroxy ester **3a**.[9] Addition of cycloheptanone transformed the anion of the 2-methyloxazoline in quantitative yield to the adduct **2** which afforded the cycloheptylidine acetic ester **3b**.[10,11] Reaction of the lithio salt of **1** (R = H) with benzyl chloride or *n*-butyl bromide proceeded in high yield, producing, after ethanolysis, good yields of the phenylpropionic (**3c**) and hexanoic (**3d**) esters, respectively.[12] Successive alkylation leading to disubstituted acetic esters was demonstrated by treating the anion of **1** (R = H) with methyl iodide to give **2** (R = H; E^1 = Me) which was alkylated further[13] using benzyl chloride producing **4** in 95% yield. Cleavage in acidic ethanol resulted in the disubstituted ester, **5**. Alternatively, disubstituted acetic esters may be prepared by conversion of the appropriate carboxylic acid to the oxazoline derivative, generation of the lithio salt, addition of an electrophile, and cleavage to the alkylated ester.[14] In this manner, butyric acid was transformed (88%) into the 2-(*n*-propyl)-2-oxazoline **1** (R = Et) and upon treatment with butyllithium and veratraldehyde, the oxazoline **2** (R = Et; E^1 = $(MeO)_2C_6H_3CHOH$) was obtained in 94% yield. Ethanolysis in the usual manner produced the hydroxy ester **3e** in good yield.



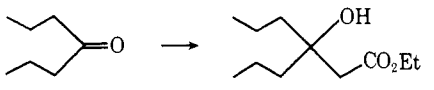
The ready formation of 2-oxazolines from carboxylic acids suggested a further and perhaps more significant application of this simple heterocycle in synthesis. The previous observation[15] that dihydro-1,3-oxazines were inert to the Grignard reagent prompted us to examine the related 2-oxazoline system in this respect. If functionally substituted carboxylic acids could be protected as the oxazoline and then be subjected to a Grignard step, followed by regeneration of the carboxyl function, a highly useful synthetic operation could be effected. To test this procedure, the tetralone carboxylic acid **6** was heated with 1.1 equiv of 2-amino-2-methylpropanol and gave the oxazoline **7** [bp 170° (0.10 Torr); mp 95–96°; ir 1655 (C=N) and 1680 cm^{-1} (C=O)]. Reaction with phenylmagnesium bromide (2.0 equiv) and magnesium bromide (1.0 equiv) in THF produced the tertiary alcohol **8** (96%; mp 148–149°; ir 1655 and 3200 cm^{-1}) which was treated with 3 *N* HCl (95°, 15 min) to regenerate the carboxylic acid **9** (91%;

(8) E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970).

(9) Yields of products (based on **1**) given in parentheses. Alternatively, refluxing the oxazolines **3** in 3 *N* HCl for 15–20 min yields the corresponding carboxylic acid (see ref 6).

(10) Isolated as a 78% (endo)–22% (exo) mixture which was separated by vpc and characterized completely.

(11) In those cases where the β carbon carried a monoaryl or dialkyl substituent, but not cycloalkyl as in **3b**, the products were >90% β-hydroxy ester. For example, 4-heptanone (i) was converted to the β-hydroxy ester (ii) in 75% yield using 7% concentrated sulfuric acid in 95% ethanol. The use of 15–20% ethanolic sulfuric acid gives only



i ii

the unsaturated esters (Dr. E. W. Collington, research in progress).

(12) Both crude products contained 3–10% dialkylated material (vpc) which was removed during the final distillation stage.

(13) Purified prior to second alkylation step to eliminate product mixtures (<10%).

(14) In some ways, this approach to dialkylated acetic esters is more convenient since 2-(*n*-alkyl)-2-oxazolines which form only the secondary carbanion after alkylation do not form a tertiary carbanion. Thus, successive alkylation cannot occur to give undesirable products.

(15) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5886 (1969).

mp 160–161°; ir 1690 cm^{-1}). Furthermore, the ester **10** (84%: oil; ir 1730 cm^{-1}; *Anal.* Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.85; H, 6.73) was formed by cleavage of the alcohol **8** using 7% ethanolic sulfuric acid (80°, 12 hr). Expectedly, in both cases, the hydroxyl group was lost during the removal of the oxazoline ring.

In a further example to demonstrate the utility of the oxazoline system, 4-hydroxycyclohexanecarboxylic acid was converted to the oxazoline derivative **11** (oil; ir 1655, and 3300 cm^{-1}). The alcohol was oxidized (CrO_3–pyridine) to the keto-derivative **12** (oil; ir 1710 and 1660 cm^{-1}) without destruction of the oxazoline ring. Treatment with phenylmagnesium bromide–magnesium bromide in THF produced **13** (77%; mp 146–149°; ir 3200 and 1650 cm^{-1}; tlc (ether) showed one spot, R_f = 0.40), which was transformed with 10% ethanolic sulfuric acid into the unsaturated ester **14** [79%: oil; *m/e* 230; ir 1730 cm^{-1}; nmr ($CDCl_3$) δ 7.30–7.50 (m, 5 H), 6.0–6.2 (m, 1 H), 4.18 (q, 2 H), 2.3–2.7 (m, 5 H), 1.9–2.2 (m, 2 H), 1.24 (t, 3 H); *Anal.* Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.09; H, 7.99].

Thus, in preliminary form we have demonstrated that the 2-oxazoline ring may serve as a useful precursor to aliphatic acids or ethyl esters as well as a suitable blocking group for reactions involving the Grignard reagent. Further studies to determine the potential of this method as a useful alternative to classical carboxylic acid syntheses (which are incompatible with Grignard reagents) are in progress.

Acknowledgment. The authors express their gratitude to the National Science Foundation (GP-22541), the Petroleum Research Fund (administered by the American Chemical Society), and the Hofmann-La Roche Foundation for financial assistance, and to the Lithium Corporation for generous supplies of organolithium reagents used in this study.

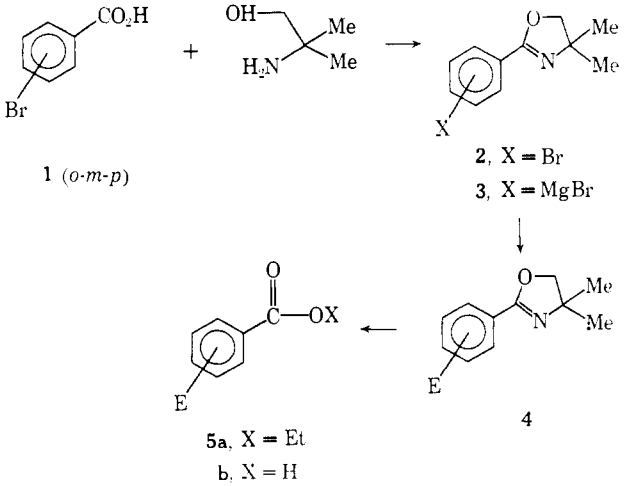
* Address correspondence to this author at the Department of Chemistry, Wayne State University, Detroit, Michigan 48202.

A. I. Meyers,* Davis L. Temple, Jr.
Department of Chemistry
Louisiana State University in New Orleans
New Orleans, Louisiana 70122
Received August 15, 1970

Syntheses *via* 2-Oxazolines. III. The Formation of Substituted Benzoic Acids or Esters Utilizing the Grignard Reagent of 2-(Bromophenyl)-2-oxazolines

Sir:

The introduction of carbon substituents into aromatic nuclei containing electron-withdrawing groups has long required an oblique approach primarily due to their low affinity for electrophilic reagents. Although the Grignard (or lithium) reagent of aryl halides has always been a favored mode of forming aryl–carbon bonds, this technique has been deterred by the presence of sensitive (electron-withdrawing) groups in the aromatic nucleus. In this report, we describe our preliminary, yet promising, results which overcome the difficulties stated above. In the previous paper,[1] we demonstrated that the 2-oxazoline ring represents an effective protecting group against the Grignard reagent thus allowing unusual latitude in the elaboration of aliphatic carboxylic acids and esters. This same concept can be extended to bromobenzoic acids **1** by converting them to their corresponding 2-oxazolines[2] **2** which were smoothly transformed (THF, Mg) into the Grignard reagent **3**. This latter species now represents a very useful reactive intermediate which is, in effect, an aryl Grignard reagent containing a disguised carboxyl function. Treatment of **3** with a variety of electrophiles (E) under usual Grignard conditions led to the elaborated derivative **4** in good yield (Table I). The hydrolysis of **4** in 5–7% ethanolic sulfuric acid produced the substituted benzoic esters **5a**, or, if hydrolysis was done in aqueous medium, the benzoic acids **5b** were formed (Table I).



The electrophiles utilized in the reaction of the oxazolinylmagnesium bromide **3** represent a diversity of functional groups and the products obtained were those expected from a "normal" Grignard reagent. The formation of the latter was surprisingly rapid and required external cooling. The presence of the unshared pairs of electrons on nitrogen and oxygen may be responsible for this facile reaction especially for the *o*-bromo derivative **3**. The degree of self-coupling was never a problem since triply sublimed magnesium and nitrogen atmospheres were used throughout this study. In cases where a lower purity of magnesium was utilized, self-coupling of **2** (or **3**) ranged as high as 25%. Those reactions which required extended periods of heating (benzonitrile, allyl bromide) led to the self-coupling products, but not when the pure magnesium was present.

Unlike the aliphatic oxazolizines, the aryl oxazolines could not be cleaved directly to the *acid* in aqueous medium. Heating in 3 *N* HCl for 10–15 min resulted in the precipation of the amino ester hydrochloride **6**,

(1) A. I. Meyers and D. L. Temple, Jr., *J. Amer. Chem. Soc.*, **92**, 6644 (1970).

(2) Prepared by adding a solution of 49 g of *o*-bromobenzoyl chloride in 100 ml of dichloromethane to a solution of 39 g of 2-amino-2-methylpropanol in 100 ml of dichloromethane at 0°. The hydroxyamide so obtained (62 g, 100%, mp 135–136°) was cyclized to the 2-(*o*-bromophenyl)-2-oxazoline (2) by the method of Leffler and Adams [*J. Amer. Chem. Soc.*, **59**, 2252 (1937)]. The hydrochloride, initially formed (100%, mp 108–110°), was neutralized with 20% sodium hydroxide and extracted with ether to give a pale yellow viscous oil [ir 1650 cm^{-1}, nmr δ (CCl_4) 7.66 (m, 2 H), 7.27 (m, 2 H), 4.05 (s, 2 H), 1.37 (s, 6 H)]. The 2-(*p*-bromophenyl)-2-oxazoline was similarly prepared [viscous oil; purified by eluting with ether through neutral alumina; ir 1650 cm^{-1}; nmr δ ($CDCl_3$) 7.60 (d, 2 H), 7.70 (d, 2 H), 4.01 (s, 2 H), 1.32 (s, 6 H)]. The *m*-bromophenyl derivative of **2** was not prepared for this study but its formation in the usual manner is anticipated.