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.

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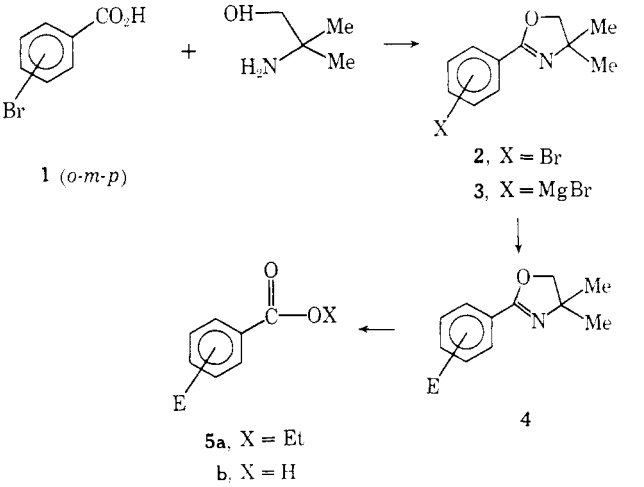
Syntheses *via* 2-Oxazolines. III. The Formation of Substituted Benzoic Acids or Esters Utilizing the Grignard Reagent of 2-(Bromophenyl)-2-oxazolines

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).



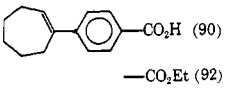
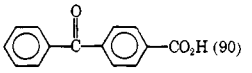
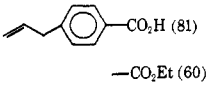
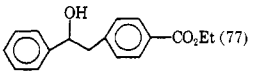
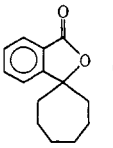
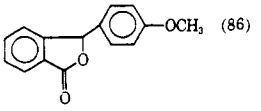
The electrophiles utilized in the reaction of the oxazolinylmagnesium bromide **3** represent a diversity of functional groups and the products obtained were those expected from a "normal" Grignard reagent. The formation of the latter was surprisingly rapid and required external cooling. The presence 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).

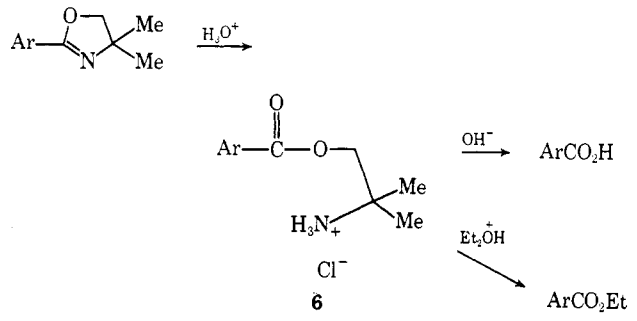
(2) Prepared by adding a solution of 49 g of *o*-bromobenzoyl chloride in 100 ml of dichloromethane to a solution of 39 g of 2-amino-2-methylpropanol in 100 ml of dichloromethane at 0°. The hydroxyamide so obtained (62 g, 100%, mp 135–136°) was cyclized to the 2-(*o*-bromophenyl)-2-oxazoline (2) by the 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.

Table I. Formation of Substituted Ethyl Benzoates (**5a**) or Benzoic Acids (**5b**)

Grignard[a] reagent (**3**)	Electrophile (E)	% **4**[b]	Acid (**5b**) or ester (**5a**) (%)	Mp,[f] °C
p-Bromophenyl	Cycloheptanone	86		175–178 Oil
p-Bromophenyl	Benzonitrile	90		196–198[d]
p-Bromophenyl	Allyl bromide	88[c]		215–217[e] Oil
p-Bromophenyl	Styrene oxide	93		53–55
o-Bromophenyl	Cycloheptanone	92	 (85)	85–87
o-Bromophenyl	*p*-Methoxybenzaldehyde	90		110–112

[a] Triply sublimed magnesium (Dow) was utilized for all Grignard reagents. We express our gratitude to Dr. Jack Little for providing us with generous quantities of magnesium. [b] Yields are of crude isolated products which were used directly in the hydrolysis to acids or esters. [c] Performed in the presence of 1.0 equiv of magnesium bromide. [d] E. Bengtsson, *Acta Chem. Scand.*, **9**, 177 (1955). [e] R. Quelet, *Bull. Soc. Chim. Fr.*, [4] **45**, 255 (1929). [f] All new compounds gave satisfactory elemental, mass, nmr, and ir analyses.

which was collected and heated for 30 min in methanolic alkali to give the substituted benzoic acid.[3] Regarding



the conversion of the aryl oxazolines to their ethyl esters, **6** most probably undergoes transesterification in the ethanolic medium.

Elaboration of benzoic acids *via* the oxazoline should provide facile entry into many systems where the bromo (or chloro[4]) derivative is available. This method should not be limited to simple benzene derivatives and we are investigating this behavior in other aromatic systems.

The sequence may be illustrated by the preparation of *p*-(cycloheptylidine)benzoic acid and its ethyl ester. The Grignard reagent was formed using 0.02 mol of **2** (X = *p*-Br) and 0.02 g-atom of triply sublimed magnesium in 60 ml of THF. The formation was rapid and required external cooling. After 2 hr the reagent was utilized by the addition of 0.021 mol of cycloheptanone and allowed to stir for 15 hr at room temperature. Decomposition was effected by pouring into ice–water and acidifying with 5% HCl. The cold aqueous solution was extracted with pentane (discarded) and neutralized with 5% sodium hydroxide, extracted with ether, dried, and concentrated producing the carbinol (98%), mp 106–108° (petroleum ether). The latter was converted to the benzoic *acid* by heating a solution containing 2.0 g in 50 ml of 3 *N* HCl for 10 min and then removing the crystalline amino ester hydrochloride (mp 188–190°) and heating in 50 ml of methanol–water (1:1) containing 20% sodium hydroxide for 30 min. Concentration to half the volume of solution was followed by acidification (9 *N* HCl) which resulted in the solid product (1.45 g, 95%, mp 175–178°). To obtain the *ethyl ester*, the above carbinol (5 mmol) was dissolved in 40 ml of 7% ethanolic sulfuric acid and heated to reflux for 15 hr. The mixture was diluted with 200 ml of ether, washed thoroughly (bicarbonate, water), dried, and concentrated to give ethyl *p*-cycloheptylidinebenzoate (oil, 90%, purified by elution with ether though neutral alumina). *Anal.* Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.68; H, 8.29.

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 Hoffmann-La Roche Foundation for financial assistance.

(3) Amino esters have been considered as intermediates in the acidic hydrolysis of 2-oxazolines [G. R. Porter, H. N. Rydon, and J. A. Schofield, *J. Chem. Soc.*, 2686 (1960)].

(4) We have shown that the chlorophenyl derivatives of 2-oxazolines are also useful precursors to elaborated benzoic acids and esters.

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