taining 10 residue per cent lauroyl groups). For each nitrophenyl ester the rate is substantially greater with lauroylpolyethylenimine than with polymer containing no acyl group. Furthermore the trend in k is now markedly *upward* as the acyl group is increased from 2 to 12 carbons (see Table I). Compared to k for propylamine with nitrophenyl laurate, the corresponding k for lauroylpolyethylenimine is 10^4 times greater. Such a comparison may not be fully appropriate if the low rate with reference amine is due primarily to the micellar state of the lauroyl nitrophenyl ester. If one assumes that in the absence of micelle formation the long-chain ester would show a rate comparable to that of acetyl nitrophenyl ester, then the enhancement factor in the presence of lauroylpolyethylenimine still is of the order of 10^3. In any event it is clear that the introduction of strong binding sites on the polymer leads to marked rate enhancements. This polymer with binding sites thus should provide a suitable framework for the further introduction of catalytic functional groups to produce a macromolecule with capacity for enhanced rates combined with true turnover of substrate.

(6) Postdoctoral Fellow, National Institute of General Medical Sciences, U. S. Public Health Service, 1968–1970.
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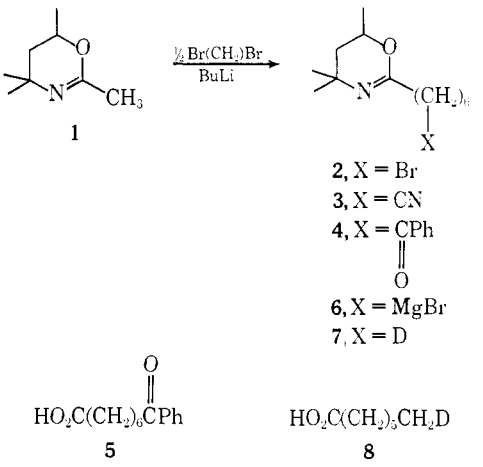
Syntheses *via* Dihydro-1,3-oxazines. VI. A Carboxyl Protecting Group Stable to the Grignard Reagent. A New Synthesis of Carboxylic Acids

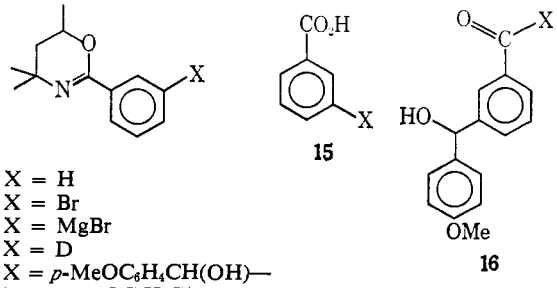
Sir:

It was found early in our studies that the 2-methyl-5,6-dihydro-1,3-oxazine (**1**),[1] though converted to its anion by alkyllithium reagents, is totally inert to various Grignard reagents. We now report that this behavior has indeed proved useful in obtaining alkyl and aryl carboxylic acids,[2] from appropriately substituted dihydro-1,3-oxazines by use of usual Grignard techniques. The value of this approach is obvious in light of the rarity of carboxyl protecting groups toward RMgX.[3] Thus, the methods now known[1] to alkylate **1** coupled with the facile regeneration of carboxylic acids from dihydro-1,3-oxazines[4] provides substituted acids hitherto obtained only with difficulty.

The readily available[5] 2-methyl-5,6-dihydro-1,3-oxazine (**1**) was alkylated with 1,5-dibromopentane producing the 6-bromohexyl derivative **2** in 90% yield (oil; 1658 cm^{-1}; τ 6.68, t, 2, CH_2Br) which was transformed into the corresponding nitrile **3** in 95% yield with sodium cyanide in DMSO[6] (bp 108° (0.25 mm); 2240, 1658 cm^{-1}). The reaction of **3** with phenylmagnesium bromide in ether followed by hydrolysis gave the keto oxazine derivative **4** (90%; oil, 1675 and 1658 cm^{-1}) which was hydrolyzed with aqueous hydrobromic acid saturated with sodium bromide (reflux, 12 hr) to 7-benzoyl heptanoic acid **5** (90% mp 85°).[7] The 6-bromohexyl oxazine was also converted to the corresponding Grignard reagent **6** in THF (reflux, 3 hr) and hydrolyzed in deuterium oxide to the 6-deuteriohexyl derivative **7** in 80% yield (bp 64° (1.2 mm); 1659 cm^{-1}; *m/e* calcd 212, found 212). Acidic cleavage of **7** in aqueous hydrobromic acid resulted in the formation of 7-deuterioheptanoic acid **8**.



Aromatic acids **15** were likewise formed by this sequence, employing as starting material the 2-phenyldihydro-1,3-oxazine **9**.[8] Bromination[9] of the latter gave, in 95% yield, exclusively *m*-bromo isomer, **10** (bp 120° (0.075 mm), 1640 cm^{-1}) which was transformed into the Grignard reagent **11** in THF (reflux, 5 hr). Both the bromophenyl derivative **10** and the Grignard reagent **11**, after hydrolysis in deuterium oxide, were cleaved to the *meta*-substituted benzoic acids **15** (X = Br) and **15** (X = D) in 99 and 98% yields, respectively. The Grignard reagent **11** was also found to react normally with *p*-anisaldehyde affording **13** in quantitative yield (glass, purified *via* tlc; 1640 and 3400 cm^{-1}). Attempts to hydrolyze **13** to the acid **16** (X = OH) gave tarry products due to polymerization of the benzhydryl cation. However, borohydride reduction of **13** and



9, X = H
10, X = Br
11, X = MgBr
12, X = D
13, X = *p*-$MeOC_6H_4CH(OH)$—
14, X = *p*-$MeOC_6H_4C(=O)$—

(1) (a) H. W. Adickes, I. R. Politzer, and A. I. Meyers, *J. Amer. Chem. Soc.*, 91, 2155 (1969); (b) A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 1783 (1969); (c) *Org. Proc. Prep.*, 1, 193, 213 (1969).
(2) Similarly substituted aldehydes may also be prepared by reduction of the dihydro-1,3-oxazines **2** and **9** followed by ring cleavage. This will be the subject of a future report.
(3) Ortho esters, the only known protection group for carboxylic acids against Grignard reagents, frequently cleave to acetals and ketals; J. F. W. McOmie, *Advan. Org. Chem.*, 3, 248 (1963).
(4) Z. Eckstein and T. Urbanski, *Advan. Heterocyclic Chem.*, 2, 336 (1963).
(5) Columbia Organic Chemicals, Columbia, S. C.
(6) L. Friedman and H. Shechter, *J. Org. Chem.*, 25, 877 (1960).
(7) T. Weil and D. Ginsburg, *J. Chem. Soc.*, 1291 (1951), reported mp 85°.
(8) Prepared in 200-g quantities using benzonitrile, 2,4-dimethyl-2,4-pentanediol and 96% sulfuric acid according to J. J. Ritter and E. J. Tillmans, *J. Org. Chem.*, 22, 839 (1957).
(9) M. A. Khan, B. M. Lynch, and Y. Hung, *Can. J. Chem.*, 41, 1540 (1963).

mild acidic cleavage produced the aldehyde **16** (X = H) in 75% yield (3450, 1690 cm^{-1}; τ 9.8 CHO). The difficulty encountered in the hydrolysis of **13** was circumvented by chromic acid oxidation of **13** to the ketone oxazine **14** (80%; mp 99–101; 1640 and 1660 cm^{-1}) which proceeded without damage to the oxazine ring. Hydrolysis of **14** in aqueous acid afforded *m*-(*p*-anisoyl)-benzoic acid **15** (X = COC_6H_4OMe) in good yield (80%, mp 189–190°; ir (KBr) 3200–3500, 1680, 1650, and 1590 cm^{-1}; nmr (TFA) τ 5.98 (s, 3, CH_3O), 1.2–3.0 (m, 8,ArH)). The formation of this product now allows a route to compounds inaccessible by Friedel–Crafts acylations. Studies to realize the full potential of this synthesis are under active investigation.[10]

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(10) All new compounds gave satisfactory combustion analyses.

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Syntheses *via* Dihydro-1,3-oxazines. VII. A Simple Synthesis of Unsymmetrical Ketones

Sir:

The versatility of 5,6-dihydro-1,3-oxazines (**1**) as useful precursors to aldehydes containing two[1] or three[2] additional carbon atoms has recently been demonstrated. We wish to report that the readily accessible[3] 2-isopropenyl oxazine **2** has now been shown to react with Grignard or organolithium reagents in tetrahydrofuran to produce the 2,2-dialkyl tetrahydro-1,3-oxazines (**3**) which are precursors to unsymmetrical α-methyl ketones **4**. The major feature of this new reaction centers around the fact that the organometallic (RM) reagents are added in a single sequence[4] to produce **3**. If R = R′, then the dialkylated derivative, **3**, may be formed by merely introducing 2.0–2.5 equiv of the Grignard or organolithium reagent into a solution of **2** in THF. If R and R′ are different, then the initial alkyl or aryl metallic is added followed by addition of the second alkyl or aryl metallic after approximately 1 hr. The isolation of **3** is simply a matter of dilution of the reactants with water, extraction of the product with ether, and cleavage of the crude product to **4** using aqueous oxalic acid (reflux, 2 hr). The ketones thus obtained were formed in good yields (Table I) on a preparative scale (4–10 g).[5] The nature of the *initially introduced* organometallic appears to be independent of the reaction requirements; however, the second step is limited to primary alkyl or phenyl metallics. Thus **3** will only form if R′M is not isopropyl, *sec*-butyl, cyclohexyl, or *t*-butyl. In these cases only monoalkylation occurs, as was observed when 2.5 equiv of cyclohexylmagnesium bromide was treated with **2**. The oxazine **5** was formed in 98% yield, which upon reduction and acid cleavage[1]

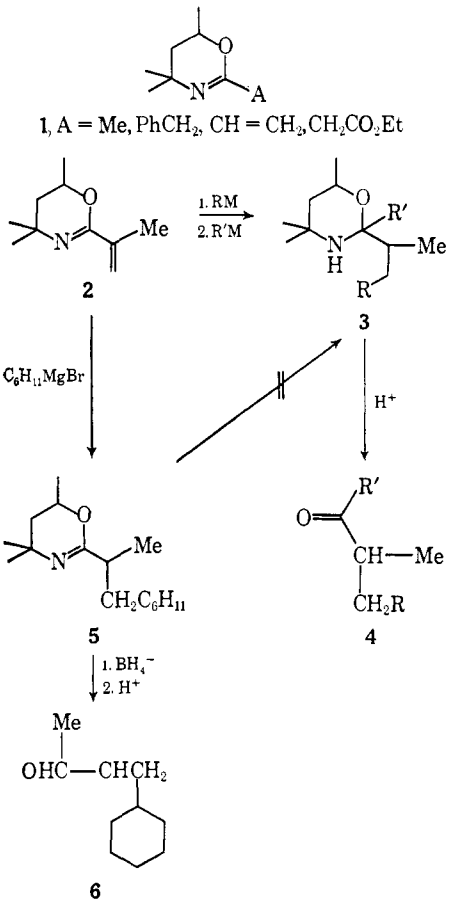

Table I. Formation of α-Methyl Ketones (**4**)

Entry	RM	R′M	% **4**, overall[a]
1	*n*-BuMgBr	*n*-BuMgBr	79
2	*t*-BuLi	MeLi	73[b]
3	*t*-BuLi	EtMgBr	67
4	*t*-BuLi	*n*-BuMgBr	77
5	PhMgBr	PhMgBr	47[c]
6	EtMgBr	EtMgBr	67
7	*n*-PrMgI	*n*-PrMgI	80
8	$C_6H_{11}MgBr$	MeLi	82
9	$C_6H_{11}MgBr$	$NaBH_4$	80[d]

[a] All products were obtained in pure state and gave satisfactory elemental analysis, mass spectra, and derivatives (2,4-DNP or semicarbazone). [b] M. F. Ansell, W. J. Hickenbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955), report 2,4-DNP, mp 65°; found mp 64–65°. [c] L. I. Smith and J. R. Holum, *J. Amer. Chem. Soc.*, **78**, 3417 (1956), report 2,4-DNP, mp 134°; found mp 133°. [d] Overall yield of aldehyde **6**; 2,4-DNP, 146–148°.

(1) H. W. Adickes, I. R. Politzer, and A. I. Meyers, *J. Amer. Chem. Soc.*, **91**, 2155 (1969), and other references cited therein; preparative procedures have appeared, *Org. Proc. Prep.*, **1**, 193 (1969); **1**, 213 (1969).

(2) A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 1783 (1969).

(3) Prepared from methacrylonitrile and 2,4-dimethyl-2,4-pentanediol according to J. J. Ritter and E. J. Tillmans, *J. Org. Chem.*, **22**, 839 (1957). Commercially available from Columbia Organic Chemicals, Columbia, S. C.

(4) Addition to the isopropenyl oxazine may be performed at temperatures between 25 and −78° with essentially the same results. This aspect of the process provides unusual latitude with respect to the type of organometallic employed.

(5) It is interesting to note that the vinyl derivative **1** does not display the ability to doubly alkylate in the manner shown by **2**. Similar reaction conditions result in complete polymerization of **1**. This is probably due to the instability of the corresponding ketenimine **8** (Me = H).