The Synthesis of Ketones from Dihydro-1,3-oxazines *via* Stepwise Alkyl or Aryl Introduction

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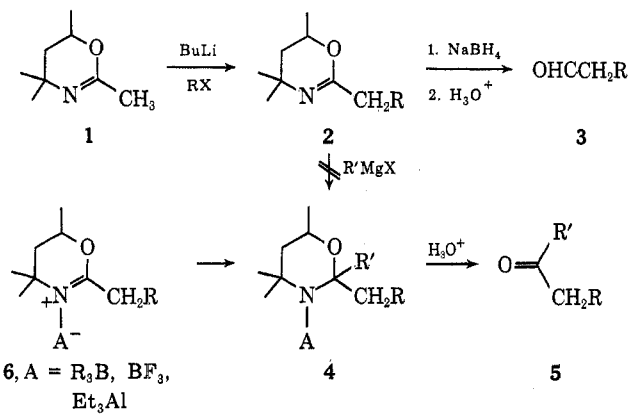
Although the dihydro-1,3-oxazine system is inert to Grignard reagents, the *in situ* formation of their corresponding *N*-methyl quaternary salts allows introduction of alkyl or aryl groups. Hydrolysis of the Grignard addition products leads to a variety of ketonic products. The scope and limitations of this process are described.

The synthetic utility of dihydro-1,3-oxazines as precursors to homologated acetaldehyde derivatives has been described in detail[3] (Scheme I, 1 → 2 → 3). The

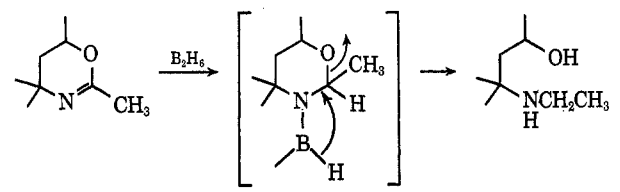
SCHEME I



ease of introduction of a variety of substituents in **1** by virtue of its lithio salt suggested that an equally versatile ketone synthesis was possible provided that a nucleophilic carbon species could be induced to add to the C=N moiety. This would afford the 2,2-disubstituted oxazine **4** which, after hydrolysis, would produce the ketone derivatives **5**. All attempts to add Grignard reagents to **2** were without success, resulting in complete recovery of starting material. This property of dihydro-1,3-oxazines has been capitalized upon by demonstrating that the ring system is an excellent protecting group against the Grignard reagent.[3-5] The inertness of the C=N link in **2** is undoubtedly due to the delocalization present in the OC=N group, rendering it poorly electrophilic.

It soon became apparent that some type of complex was required (*e.g.*, **6**) in order to increase the electrophilic nature of carbon 2 in the oxazine ring. Since it is well known that iminium bonds (>C=N<$^+$) are highly reactive toward nucleophiles (RMgX, $^-$OR, etc.), an effort in this direction was undertaken.

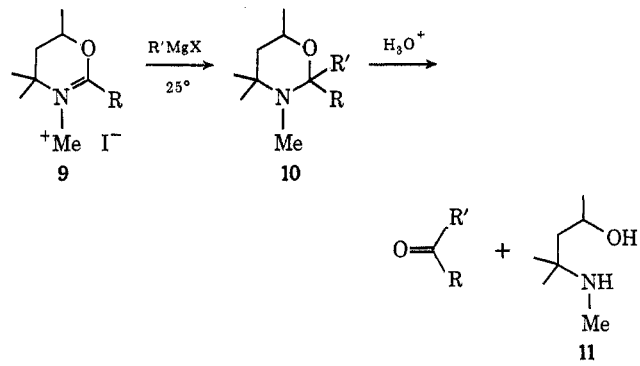
Treatment of **1** with 1 equiv of boron trifluoride etherate gave a solid complex **6** (A = BF_3) which failed to yield any appreciable quantity of **4** (R′ = Ph; R = H) when added to phenylmagnesium bromide in ether or tetrahydrofuran. A variety of experiments involving trioctylborane, triethylaluminum, and triphenylborane as complexing agents likewise produced unsatisfactory results. Although small yields of the desired products were obtained in most of these experiments, the complexity of handling and preparing these reagents detracted from the potential of this ketone synthesis and further study was terminated. Only the reaction of **1** with diborane, which was also evaluated as a complexing agent, is worthy of note. When equimolar amounts of **1** and diborane were allowed to react for 30 min in tetrahydrofuran, a good yield of the amino alcohol **7** was isolated. Thus the oxazine is reduced, initially to the tetrahydro derivative **8** and



1 **8** **7**

then on to the open-chain amino alcohol. This result is reminiscent of the susceptibility of dihydro-1,3-oxazine to reductively cleave to amino alcohols with other reducing agents.[3]

The failure of the above complexing agents to enhance the reactivity of the C=N link in dihydro-1,3-oxazines prompted an investigation on the behavior of the *N*-methyl quaternary salts **9** toward Grignard addition.[6] The oxazines **1** and **2** all formed stable *N*-methyl quaternary iodides in good yield merely by stirring in excess methyl iodide at room temperature or at the boiling point of methyl iodide. The portionwise addition of the solid methiodides to a solution of Grignard reagent (2–2.5 equiv) and stirring at room temperature



9 **10**

11

produced variable yields of the adduct **10** which upon treatment with aqueous oxalic acid led to the ketone (Table I). The amino alcohol **11** could be isolated in

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(3) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. Portnoy, *J. Org. Chem.*, in press.

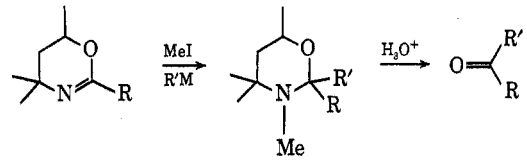
(4) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5887 (1969).

(5) A. I. Meyers and D. L. Temple, *ibid.*, **92**, 6644, 6646 (1970).

(6) A preliminary report has appeared: A. I. Meyers and E. M. Smith, *ibid.*, **92**, 1084 (1970).

TABLE I

FORMATION OF KETONES FROM 2-SUBSTITUTED 4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3-OXAZINES AND ORGANOMETALLICS



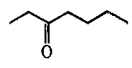
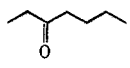
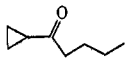
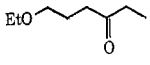
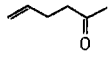
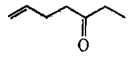
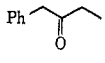
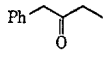
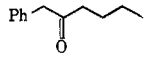
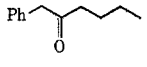
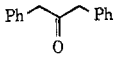
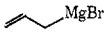
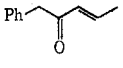
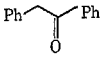
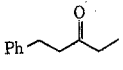
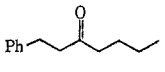
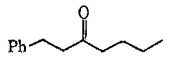
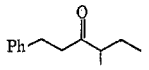
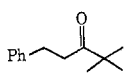
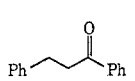
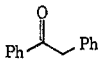
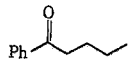
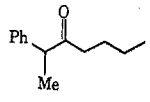
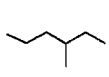
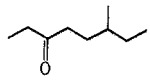
Entry	R	R'M	Ketone	Registry no.	Yield, %	Derivative mp,[a] °C
1	Me	*n*-BuMgBr		106-35-4	22	121–123 Sm[e]
2	Et	*n*-BuMgBr			58	97–98 Sm[f]
3		MeMgBr		765-43-5	30[d]	145–148 Dn[f]
4		*n*-BuMgBr		14113-86-1	35[d]	110–111 Dn[g]
5	$EtO(CH_2)_3$	EtMgBr		36808-92-1	53	88–90 Sm[h]
6		MeMgBr		109-49-9	70	98–100 Sm[f]
7		EtMgBr		2565-39-1	63	83–84[f]
8	$PhCH_2$	EtMgBr		1007-32-5	55	119–120 Dn[f,i]
9	Et	$PhCH_2MgBr$			20	
10	$PhCH_2$	MeMgI		103-79-7	58	148–150 Dn[e,i]
11	$PhCH_2$	*n*-BuMgBr		25870-62-6	52	113–114 Sm[i]
12	$PhCH_2$	*n*-BuLi			35	
13	$PhCH_2$	$PhCH_2MgBr$		102-04-5	25	108–110 Dn[f]
14	$PhCH_2$			36808-95-4	40	*b*, *o*
15	$PhCH_2$	PhLi		451-40-1	23	146–148 Sm[f]
16	$PhCH_2CH_2$	EtMgBr		20795-51-1	85	108–115 Sm[f]
17	$PhCH_2CH_2$[c]	*n*-BuMgBr		19969-04-1	70	118–120 Dn[k]
18	$PhCH_2CH_2$[c]	*n*-BuLi			50	
19	$PhCH_2CH_2$	*sec*-BuMgBr		36808-96-5	46	*b*
20	$PhCH_2CH_2$	*t*-BuLi		5195-24-4	28	175–176 Dn[l]
21	$PhCH_2CH_2$	PhLi		1083-30-3	75	140–142 Sm[m]
22		MeMgBr		26965-15-1	57	121–123 Dn[n]

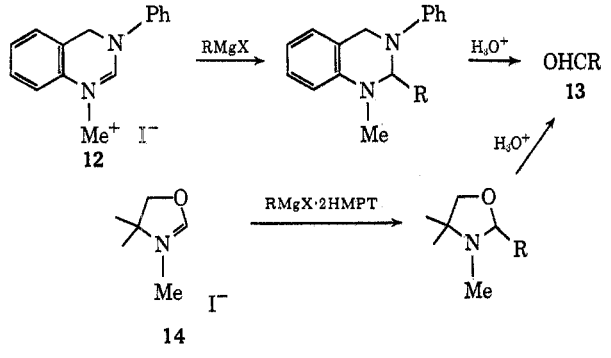
TABLE I (*Continued*)

Entry	R	R'M	Ketone	Registry no.	Yield, %	Derivative mp,[a] C°
23	Ph	EtMgBr		93-55-0	70	191–192 Dn[e]
24	Ph	MeMgBr		98-86-2	55	252–254 Dn[e]
25	Ph	$PhCH_2MgBr$		451-40-1	12	144–146 Sm[f]
26	Ph[c]	*n*-BuLi		1009-14-9	53	164–166 Sm[e]
27		*n*-BuMgBr		7661-44-1	54	*b*
28		EtMgBr		36808-98-7	74	90–95° (30 mm)[b]

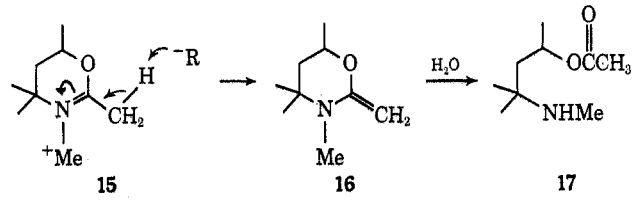
[a] Sm = semicarbazone, Dn = 2,4-dinitrophenylhydrazone. [b] Compound gave correct mass and combustion analysis. [c] Methiodide and methanesulfonate salts gave comparable yield results. [d] Azeotropes with ether thus making isolation difficult; *cf. Org. Syn.*, **31**, 74 (1951). [e] A. I. Vogel, "Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1957. [f] I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1956. [g] M. Julia, S. Julia, and T. S. Yu, *Bull. Soc. Chim. Fr.*, 1849 (1961). [h] H. Normant, *C. R. Acad. Sci.*, **232**, 1942 (1951). [i] Infrared spectrum identical with that of an authentic sample (Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Pa.). [j] H. H. Schlubach and A. Braun, *Justus Liebigs Ann. Chem.*, **627**, 28 (1959). [k] I. N. Nazarov and L. I. Shmonina, *Zh. Obshch. Khim.*, **20**, 1114 (1950). [l] E. Berliner and F. Berliner, *J. Amer. Chem. Soc.*, **72**, 222 (1950). [m] N. Maxim, *C. R. Acad. Sci.*, **182**, 1393 (1926). [n] M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, 346 (1957). [o] Ir (neat) 1660–1695 (C=O), 1626 cm^{-1} (C=C); nmr (CCl_4) 7.15 (s, 5), 6.66 (q, 1, J = 17 Hz), 6.00 (d, 1, J = 1 Hz), 3.65 (s, 2), 1.76 ppm (d, 3).

comparable yields to the ketone by neutralization and extraction of the oxalic acid solution.

It was subsequently found that the *N*-methyl salts **9** need not be prepared in a separate operation, but may be obtained, ready for use, by formation in the same reaction vessel in which the Grignard addition is carried out (Experimental Section). Thus, the aim of the study was achieved not by a Lewis acid complex, but by a simple derivative, the *N*-methyl quaternary salt. A report by Fales[7] for converting Grignard reagents to their formyl derivatives **13** *via* *N*-methylquinazolinium salts (**12**), and the report[8] of Grignard addition to *N*-methyloxazolinium salts **14** and ultimately to aldehydes, demonstrate the enhanced electrophilicity of C=N in related systems.



An examination of Table I reveals that the yields of ketone from various 2-substituted dihydro-1,3-oxazines (*via* the *N*-methyl salts) range from poor (12–20%) to good (50–85%). These results are a function of either the nature of the 2 substituent on the oxazine or the organometallic employed. When the 2 substituent is methyl (**15**), the Grignard reagent is sufficiently basic to remove the α proton as well as addition to the C=N+-Me linkage. Proof of proton abstraction was obtained by isolation of the ketene *N*,*O*-acetal **16** using various bases. The synthetic utility of **16** is the subject of another investigation.[9] The first entry in Table I, showing a poor yield of the methyl ketone, is a reflection of the competing proton-abstraction process. The major product obtained was the amino ester **17**, which is



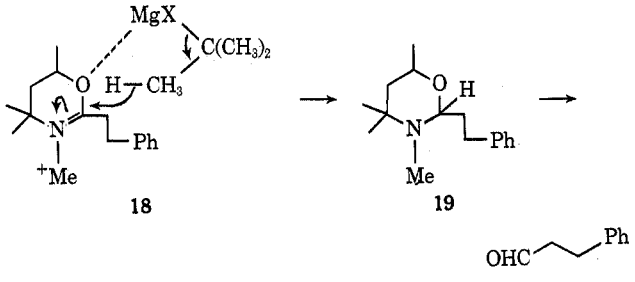
formed by reaction of the ketene *N*,*O*-acetal with water during the aqueous work-up. The second entry in Table I involves addition of a typical Grignard to the 2-ethyloxazine. The yield of ethyl ketone (58%) is considered close to optimum for this sequence, but more important is the fact that the acidity of the α proton in this oxazine is sufficiently reduced so as not to interfere with Grignard addition to the iminium linkage.

It was both fortunate and surprising to learn that the 2-benzyl substituent (entry 8) did not exhibit its usual acidity when the ethyl Grignard reagent was introduced. The 55% yield of benzyl ketone indicates that the Grignard's poor basicity decreases proton abstraction, thus allowing nucleophilic addition to proceed efficiently. When this reaction was repeated using *n*-butyllithium (entry 12) in place of the Grignard (entry 11) the yield of ketone was lower, reflecting the greater base strength of the lithium reagent. Of fur-

(7) H. M. Fales, *J. Amer. Chem. Soc.*,., **77**, 5118 (1955).
(8) A. I. Meyers and E. W. Collington, *ibid.*, **92**, 6676 (1970).
(9) A. I. Meyers and N. Nazerenko, *ibid.*, **94**, 3243 (1972).

ther interest is the reaction of the 2-phenethyloxazine (entry 17, 18) with butyl Grignard and lithium reagents. The removal of the activating phenyl group to a β position in the oxazine now allowed a 70% yield of the phenethyl ketone from the Grignard and 50% from the lithium reagent. Since the oxazine may be elaborated in high yield to a variety of 2 substituents (Scheme 1), the choice of oxazine and Grignard reagent for a desired ketone may be made to provide optimum results. This is seen from entries 8 and 9 in Table I. The use of ethylmagnesium bromide on the readily available 2-benzyloxazine[3] is favored over the addition of benzyl Grignard to the ethyloxazine. Coupling products (bibenzyl) were the reason for almost consistently low yields whenever the benzyl Grignard reagent was utilized (*cf.* entries 13 and 25). Furthermore, since the 2-methyloxazinium salt **15** failed to give good yields of Grignard addition products, the synthesis of methyl ketones could be made quite efficient by utilizing methyl Grignard reagents in place of 2-methyloxazinium salts. This is seen from entries 6, 10, 22, and 24 to lead to good yields of methyl ketones. The absence of phenyl Grignard reagents from Table I of ketones is due to their failure to add in a number of attempted experiments. However, this limitation may also be overcome by using the 2-phenyloxazinium methiodides and the appropriate organometallic (entries 23–26). The reason for the failure of phenyl Grignard reagents can only be ascribed to its bulk and hence its reluctance to add to the C=N$^+$–Me moiety. This is further avoided by use of the phenyllithium reagent, which added normally (entries 15 and 21).

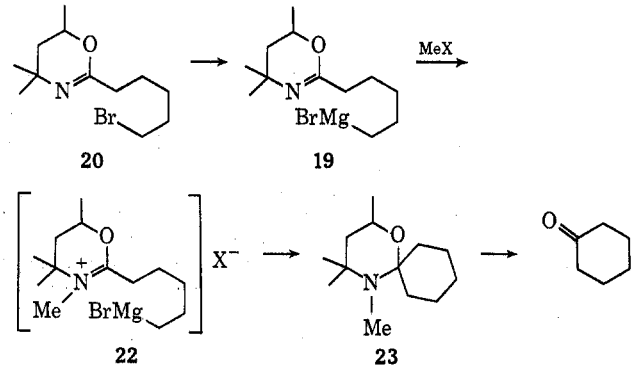
The use of organolithium reagents on the *N*-methyl quaternary salts must also be judiciously chosen, as seen by entries 12, 15, 18, 20, 21, and 26. The strongly basic nature of organolithium reagents precludes the presence of activated α protons in the oxazinium salts. However, in the case of the 2-phenethyloxazinium salts (entries 18–21), the expected reaction took place using *n*-butyl-, *sec*-butyl-, and *tert*-butyllithium reagents. As mentioned earlier, the yields were higher when the corresponding Grignard reagents were utilized owing to the weaker basic nature which minimized proton abstraction. In that instance, when *tert*-butylmagnesium chloride was utilized, no addition occurred owing to the competing reduction which is so typical of hindered Grignard reagents.[10] Thus, addition of *tert*-butylmagnesium chloride to the 2-phenethyloxazinium iodide (**18**) gave the tetrahydrooxazine **19**



which upon hydrolysis afforded 3-phenylpropionaldehyde.

In some instances, depending upon the complexity of the 2 substituent, the methiodide salts were not crystalline, but viscous oils. This could involve a cumbersome purification prior to Grignard addition and it would be desirable to avoid this problem. In this regard, the methanesulfonate or fluoroborate salts were found to be satisfactory crystalline products.[11]

Studies to extend this ketone synthesis to cyclic ketones utilizing the principle already discussed met only with disappointments. Although the 5-bromopentyloxazine **20** and its corresponding Grignard reagent **21** have been previously prepared and utilized,[3] all efforts to form the quaternary salt **22** (X = I, SO_4Me, BF_4), which would be expected to rapidly cyclize to the ketone precursor **23**, failed. The study was discontinued at this point.



Experimental Section

Infrared spectra were taken on a Perkin-Elmer 257 grating spectrophotometer, and nmr spectra were taken on a Varian T-60 instrument using tetramethylsilane as the internal standard. Melting points are uncorrected. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Mass spectra were taken on a AEI MS-9 instrument. The organolithium reagents were obtained from Lithium Corp., Bessemer City, N. C., and utilized as received.

Dihydro-1,3-oxazines 1 and 2 (R = Ph) were purchased from Columbia Organic Chemicals, Columbia, S. C., whereas the other oxazines in Table I were prepared by procedures already described.[3]

2-Phenyloxazine (entry 23, Table I) was prepared in 63% yield from benzonitrile and 2-methyl-2,4-pentanediol.[12]

2-Phenethyloxazine (entry 16, Table I) was prepared in 93% yield from the lithio salt of **1** and benzyl chloride, bp 151–153° (12 mm).

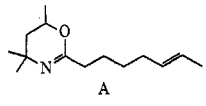
2-(3-Butenyl)oxazine (entry 6, Table I) was prepared in 91% yield from the lithio salt of **1** and allyl chloride, bp 90–93° (20 mm).

2-(3-Ethoxypropyl)oxazine (entry 5, Table I) was prepared in 89% yield from the lithio salt of **1** and 2-bromoethyl ether or ethylene oxide followed by addition of ethyl iodide, bp 100–102° (1.8 mm).

2-(1-Phenylethyl)oxazine (entry 27, Table I) was prepared in 99% yield from the lithio salt of **2** (R = Ph) and methyl iodide, bp 85–88° (0.2 mm).

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954.

(11) Although all the compounds in Table I gave crystalline methiodide salts, we have encountered during the course of another study the oxazine A, which gave an oily methiodide. However, addition of the oxazine to a



A

suspension of $Me_3O^+BF_4^-$ in dichloromethane resulted in formation of the soluble *N*-methyl fluoroborate salt. Filtration of any excess $Me_3O^+BF_4^-$, followed by concentration of the dichloromethane solution, gave crystalline oxazinium fluoroborate which was sufficiently pure for Grignard addition.

(12) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).

2-(1-Phenyl-3-butenyl)oxazine (entry 22, Table I) was prepared in 97% yield from the lithio salt of **2** (R = Ph) and allyl chloride, bp 104–106° (0.25 mm).

2-(3-Methyl-*n*-amyl)oxazine [R = $CH_2CH_2CH(CH_3)CH_2CH_3$] was prepared by addition of 1-iodo-2-methylbutane[13] to the lithio salt of 1 in 87% yield, bp 80–84° (0.3 mm).

Preparation of 2-Substituted 4,4,6-Trimethyl-5,6-dihydro-1,3-oxazine Methiodides (9). Method A.—A solution of the oxazine (20–60 mmol) in 5 equiv of methyl iodide was heated to reflux for 2 hr. Tetrahydrofuran (30–50 ml) was added and the suspension was stirred for 3–18 hr at room temperature after which the quaternary salt was removed by filtration, washed with ether, and dried *in vacuo*. No further purification was performed (Table II)

TABLE II

2-SUBSTITUTED OXAZINE METHIODIDES (9)

Registry no.	R	Method	Yield, %	Mp, °C	ν(C=N⁺-Me), cm⁻¹
36808-99-8	Et	A	74	175–180	1605
36809-00-4	Ph	A	33	143–144	1620
		B	83		
36809-01-5	$PhCH_2$	B	99[a]	135–138	1609
36809-02-6	$CH_2{=}CH(CH_2)_2$	A	70	165–167	1612
36809-03-7	$PhCH_2CH_2$	B	98	195–196	1612
36809-04-8	Cyclopropyl	A	90	184–185	1603

[a] Unstable in air and was stored under nitrogen.

and the methiodides (Table I) were used directly for the synthesis of ketones.

Method B.—The mixture of oxazine and methyl iodide was stirred at room temperature overnight (12–15 hr) followed by addition of anhydrous ether to precipitate the methiodides. Filtration, washing, and drying were performed as above.

Synthesis of Ketones from Previously Isolated *N*-Methyloxazinium Iodides. General Procedure.—A 100-ml three-necked round-bottomed flask equipped with a magnetic stirring bar, a three-way stopcock with a gas bubbler, a rubber septum, and a flask containing the oxazine methiodide salt attached by Gooch tubing was flushed with nitrogen. The Grignard reagent (2.5 equiv) was injected into the 100-ml flask. The oxazine methiodide salt (0.01 mol) was added in small portions to the Grignard reagent over 5 min. Gas evolution and heat were observed during this addition. The resulting pale yellow to orange-brown solution was stirred at room temperature for 48 hr, and then decomposed with 30 ml of ice water. The aqueous solution was extracted with five 40-ml portions of ether. These ether extracts were dried (K_2CO_3) and evaporated under vacuum on a rotary evaporator. A yellow to orange oil (crude tetrahydro-1,3-oxazine, **10**) was obtained.

Cleavage of Crude Tetrahydro-1,3-oxazine (10). A. *Via* Steam Distillation.—In a 250-ml flask equipped with a steam distillation head and steam inlet, the crude tetrahydro-1,3-oxazine was added to a solution of 5 g (0.04 mol) of hydrated oxalic acid in 100 ml of water. The steam distillation was continued until the distillate was free of organic material (*ca.* 400–700 ml). The distillate was extracted with three 40-ml portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate or potassium carbonate and evaporation of the ether under vacuum on a rotary evaporator gave the ketone, yield 45–60%.

B. *Via* Ether Extraction.—The tetrahydro-1,3-oxazine was placed in a flask together with 5 g of hydrated oxalic acid and 40 ml of water, and the mixture was heated under reflux for 1 hour. The aqueous solution was cooled and extracted with four 40-ml portions of ether. The ether extracts were washed with two 25-ml portions of 5.0% sodium bicarbonate. The dried (K_2CO_3) ether solution was evaporated *in vacuo* to yield the ketone.

Synthesis of Ketones by *in Situ* Preparation of Methiodide Salts of Dihydro-1,3-oxazines. General Procedure.—A three-necked reaction flask fitted with a magnetic stirring bar, a three-way stopcock containing an oil bubbler, and a rubber septum was flushed with nitrogen and thereafter maintained under a static pressure (0.1 atm) of nitrogen. The appropriate 2-substituted dihydro-1,3-oxazine was introduced (10 mmol) into the flask *via* syringe followed by a similar introduction of methyl iodide (5 ml). The solution was allowed to stir overnight and the suspension was treated with anhydrous ether, introduced and removed carefully *via* syringe. The salt was dried for 30–60 min *in vacuo* in the reaction flask by applying vacuum to the three-way stopcock. The Grignard (or lithium) reagent was added through the septum, using a syringe, and the suspension was stirred at room temperature for 4–18 hr. The syrupy mixture, which may in some instances contain a suspension of magnesium or lithium salts, was decomposed with 50 ml of ice water and the aqueous mixture was extracted with 5 × 40 ml of ether or ether–pentane (1:1). Drying (K_2CO_3) and concentration gave the 2,2-dialkyltetrahydro-1,3-oxazine (**10**). Hydrolysis to the ketone was performed using either the steam distillation technique or extraction directly from oxalic acid solution as described above.

Acknowledgment.—Financial assistance for this study was provided by the National Institutes of Health and the Petroleum Research Fund, administered by the American Chemical Society. The authors are also thankful to the Lithium Corporation for generous supplies of organolithium reagents.

(13) H. Schechter and H. Stone, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 323.