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The Chemistry of 2-Chloromethyl-5,6-dihydro-1,3-oxazines. Grignard Coupling and Metalation Studies. A Synthesis of α-Chloro Aldehydes and Arylacetic Acids[1]

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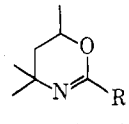
Treatment of the 2-chloromethyloxazine **2** with lithium hexamethylsilazane produces the α-chloromethyloxazine carbanion **12** which, upon alkylation, leads to the elaborated oxazine. The latter may be reduced and hydrolyzed to α-chloro aldehydes or directly hydrolyzed to α-chlorocarboxylic acids. Studies on **2** using aryl Grignard reagents gave satisfactory yields of coupling products which ultimately led to arylacetic acids. However, alkyl Grignard or lithium reagents led to an array of products, indicating that this process would not be synthetically useful.

The synthetic utility of the 2-substituted 5,6-dihydro-1,3-oxazine **1** has been well established in previous reports from these laboratories. A series of substituted acetaldehydes has been prepared from the 2-methyl-, 2-benzyl-, and 2-carboethoxyoxazines **1a**,[3] while α,β-disubstituted propionaldehydes have been obtained from the 2-vinyl system **1b**.[3] Use of the 2-isopropyl- or other 2-isoalkyloxazines **1c** served as precursors to α-(quaternary carbon) ketones,[4] whereas the 2-alkylidene derivatives **1d** led to additional α-branched ketones.[1] It, therefore, becomes evident that the nature of the R moiety in the oxazine **1** imparts considerable versatility to its synthetic usefulness and further studies were undertaken to introduce other substituents of varied structure. One such substituent chosen for its potential utility was the chloromethyl group, **2**. This derivative was readily prepared by condensing chloroacetonitrile and 2-methyl-2,4-pentanediol in cold sulfuric acid according to previously described procedures for obtaining these oxazines.[3]

DHOR ≡ 

1a, R = CH_3; CH_2Ph; CO_2Et
1b, R = $CH{=}CH_2$
1c, R = $CHMe_2$
1d, R = $MeCH{=}CH_2$, $PhCH{=}CH_2$
2, R = CH_2Cl

Results and Discussion

Reaction of 2-Chloromethyloxazine (2) with Grignard Reagents. A study to determine whether it was feasible to couple the 2-chloromethyloxazine with Grignard reagents was initiated solely for the purpose of obtaining elaborated oxazines **3** that would then serve as precursors to the substituted acetaldehydes **4**. If successful, this sequence would possess three distinct advantages: (a) eliminate the use of *n*-butyllithium to form the anion **5**; (b) provide an alternative route to the elaborated oxazine **3**; and (c) overcome the lack of nucleophilic displacement of aryl halides with **5** and provide a method for arriving at arylmethyl oxazines **6** (and ultimately to arylacetaldehydes). By placing an electrophilic site on the oxazine and utilizing organometallics as the nucleophilic moiety, the roles of the reagents would essentially be reversed from the original oxazine–aldehyde synthesis.

$$\underset{\mathbf{2}}{DHOCH_2Cl} + RMgX \longrightarrow \underset{\mathbf{3}}{DHOCH_2R} \longrightarrow \underset{\mathbf{4}}{O{=}CHCH_2R}$$

$$\underset{\mathbf{5}}{DHOCH_2Li} + ArX \not\longrightarrow \underset{\mathbf{6}}{DHOCH_2Ar}$$

The reactions of **2** with methyl, ethyl, and phenyl Grignard reagents, as suitable models, were surveyed under a variety of conditions. Treatment of **2** with 1.0 equiv of the above Grignard reagents led mainly to recovery of starting materials (~70–80%) when either ether or THF was used as solvent. This implies that a complex between **2** and the Grignard was formed initially without any subsequent transformation. The possibility that proton abstraction from **2** occurred, producing the anion **7**, was precluded when the recovered chloromethyloxazine was found to be devoid of deuterium upon quenching in deuterium oxide.

$$\underset{\mathbf{2}}{DHOCH_2Cl} + RMgX \not\longrightarrow \underset{\mathbf{7}}{DHOCH(Cl)MgX^+} \xrightarrow{D_2O} \not\longrightarrow DHOCHDCl$$

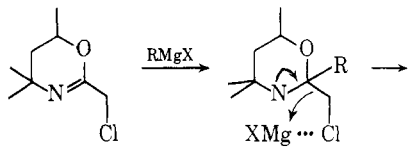
When 2.5 equiv of Grignard reagent was added to **2** and the ethereal solution was heated overnight at reflux, mixtures of products were obtained (Table I). In all instances coupling products were obtained in poor to moderate yields (10–30%) accompanied by starting material and intractable tars. For the reaction of **2** with ethyl and methyl Grignard, the 2-methyloxazine was found to accompany the coupling products. These probably arose from "functional exchange"[5] between **2** and the Grignard reagent prior to quenching. The most interesting product observed was the 2-ethyloxazine **8** from ethyl Grignard and the 2-phenyloxazine **9** from 2-phenyl Grignard. Both of these compounds have been prepared previously[6] and comparison confirmed their identity. Formation of these oxazines may be rationalized by an addition–elimination

Table I
Reaction of RMgX + 2-Chloromethyloxazine (2) in Ether (35°, 16 hr)

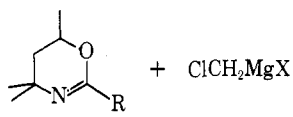
Grignard (equiv)	Products[a]		
CH_3MgI (2.5)	$DHOCH_3$ (20%)	$DHOCH_2CH_3$ (20%)	
CH_3CH_2MgBr (2.5)	$DHOCH_3$ (20%)	$DHOCH_2CH_3$ (5%)	$DHOCH_2CH_3CH_3$ (20%)
C_6H_5MgBr (2.5)	$DHOCH_2Ph$ (30%)	DHOPh (70%)	

[a] Separated by glc (SE-31 on Diatoport S) and collected for structure verification. Unidentifiable materials accounted for 40–60% of the total material balance.

pathway on the chloromethyloxazine **2** producing the chloromethylmagnesium halide. No products derived from this species could be detected. The presence of **8** and **9**



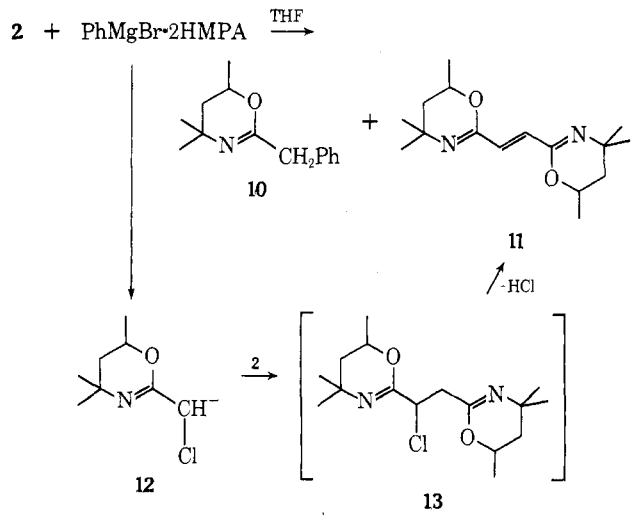
2



8, R = Et
9, R = Ph

was unexpected in view of the fact that the C=N link in oxazines has repeatedly been shown to be inert to Grignard reagents.[3] The presence of the electronegative halogen-containing substituent, however, might render the C=N link in **2** sufficiently electrophilic to allow Grignard addition. These results indicate that direct coupling of Grignard reagents with **2** is not a synthetically feasible process. Changing solvents from ether to THF provided comparable mixtures of products and, thus, proved equally disappointing.

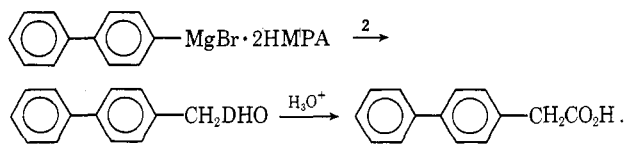
In light of the remarkable solvating properties of hexamethylphosphoramide[7] [HMPA = $(Me_2N)_3PO$] and its effect upon coupling of Grignard reagents with alkyl halides,[8] its use in this study was evaluated. Treatment of **2** with phenylmagnesium bromide in THF previously complexed with 2.0 equiv of HMPA gave the coupling product **10** in 65% yield along with 5% of the 1,2-bis(oxazinyl)ethylene **11** and 12–15% of starting material. The appearance



10 **11** **12** **13**

of the ethylene derivative was not surprising in light of previous studies[9] which showed that Grignard reagents tend to become stronger bases in the presence of HMPA. Thus, **11** would arise from proton abstraction from **2** leading to the anion **12** which displaces choride ion from unreacted **2** forming the bischloro adduct **13**. The latter would be expected to eliminate hydrogen chloride in the presence of the basic medium or upon aqueous work-up. To confirm that **11** does indeed arise from the enhanced base strength of the Grignard reagent, the reaction was repeated using 1:1 THF–HMPA. The large excess of HMPA now present led to an 80% yield of **11** and only traces of the coupled product **10**. When **2** was treated with ethyl or methyl Grignard reagents complexed with 2.0 equiv of HMPA, only **11** was produced. This result is consistent with previous observations[9] that Grignard reagents containing sp^3 carbon bonded to the magnesium become more basic than their sp^2- or sp-bonded counterparts. In other words, alkyl Grignard reagents are stronger bases than aryl, benzyl, vinyl, or acetylenic Grignard when complexed with HMPA.[10]

In order to evaluate the scope of aryl Grignard coupling, *p*-biphenylmagnesium bromide was added as its HMPA complex in THF to an ethereal solution of the chloromethyloxazine. The coupled adduct was then hydrolyzed, without purification, to *p*-biphenylacetic acid (**15**)

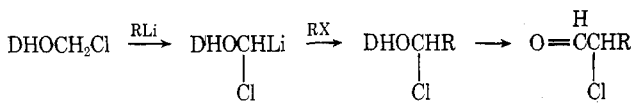


14 **15**

in 48% overall yield. Similarly, phenylmagnesium bromide was transformed into phenylacetic acid in 57% overall yield. It, therefore, seems reasonable to conclude that aryl Grignard reagents may be homologated to their acetic acid derivative by simple coupling with the chloromethyloxazine. Two-carbon homologation of vinyl, benzyl, and acetylenic Grignard reagents should likewise take place, although these experiments have not been performed.

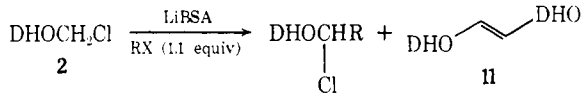
Reaction of Chloromethyloxazine 2 with Organolithium Reagents. In view of the fact that the HMPA-complexed Grignard reagents removed the α proton of the chloromethyloxazine leading to the bis(oxazinyl)ethylene **11**, it was desirable to evaluate the more basic organolithium reagents which might lead to a stable oxazine carbanion. If this could be realized, then a route to α-chloro aldehydes and α-chloro aicds would be cleared (Scheme I).

Scheme I



Treating **2** with *n*-butyllithium in THF or ether, at −78°, followed by addition of ethyl iodide, produced a mixture of products, the major one being the desired 2-(α-chloropropyl)oxazine **16**. Also found were the ethyleneoxazine **11** and varying amounts of dialkylated chlorooxazine **17**. Varying the quantities of *n*-butyllithium from 1.0 to 2.0 equiv effected only slight changes in the composition of the mixture. When 1.0 equiv of *n*-butyllithium was employed, little or no dialkylated product **17** was formed. In contrast to these results, the use of *tert*-butyllithium followed by introduction of methyl iodide gave generally lower yields of the desired alkylated prod-

Table II
Alkylation of 2-Chloromethyloxazine with Lithium Bis(trimethylsilyl)amide (LiBSA) in Tetrahydrofuran

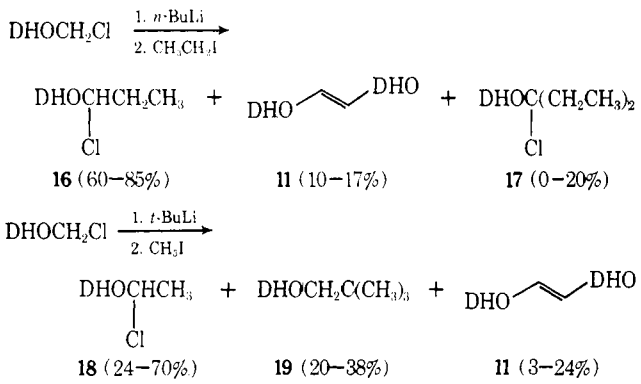


18, R = CH_3
16, R = C_2H_5

Entry	Equiv	RX	Temp,[a] °C	Time, hr[b]	% 2	% 16 or 18	% 11[f]
1	1	CH_3I	−78	0.5	40	60	0
2	2	CH_3I	−78	0.5	3	97	0
3	2	CH_3I	−78	2.0	2	97	1
4	2	CH_3I	−30	2.0	2	68	30
5	2	CH_3I	0	1.0	2	36	62
6	2	CH_3I	−78	*c*	2	98	0
7	2	CH_3CH_2I	−78	0.5	0	100[d]	0
8	2	CH_3CH_2Br	−78	0.5	1	93[e]	6
9	2	CH_3CH_2Cl	−78	0.5	16	7	77

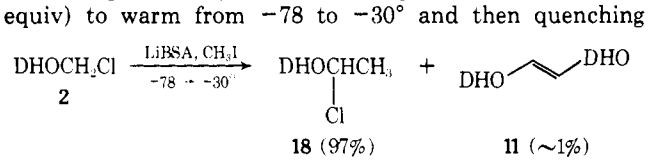
[a] Temperatures at which **2** and base were mixed. [b] Time elapsed prior to addition of alkyl halide at the temperatures indicated. Reaction solutions were allowed to gradually warm to room temperature. [c] Methyl iodide added to solution of base followed by addition of **2**. [d] Contained 7% dialkylated material, **17**. [e] Contained 3% dialkylated material, **17**. [f] Product ratios were determined by vpc; isolated yields of **16** or **18** were slightly lower.

uct **18** along with the coupling product **19**. The disappointing results obtained with alkyllithium reagents, namely coupling, polyalkylation, and reactions between **2** and its lithio salt, rendered the feasibility of Scheme I questionable.



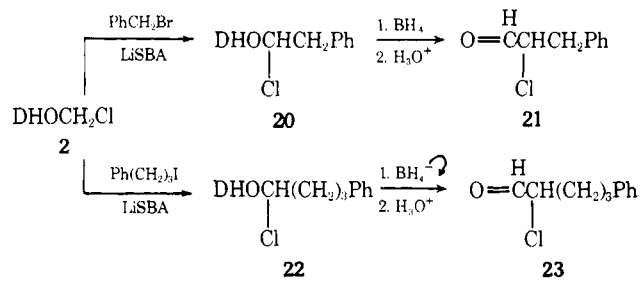
Attention was then focused on an alternative base, lithium bis(trimethylsilyl)amide (LiBSA), as a suitable reagent which might minimize both coupling and polyalkylation owing to its steric bulk and poor nucleophilic character. This base has been successfully used by Rathke[11] in his elegant alkylation of acetic esters. Furthermore, the base is conveniently prepared from hexamethyldisilazane[12] and is a stable, easily handled reagent soluble in both polar and nonpolar solvents.

Addition of **2** to a solution of LiBSA at −78° in THF, followed by introduction of D_2O–DCl at this temperature, gave the chloromethyloxazine devoid of any deuterium incorporation. It thus became evident that a proton is not abstracted from **2** at this temperature. This implied that it should be possible to introduce **2**, the lithium base, and the alkyl halide all together at −78° and allow the reaction to warm slowly. When the proton is removed at some elevated temperature, the presence of the alkyl halide should allow alkylation in a style more competitive than that observed with *n*-butyl- and *tert*-butyllithium. This, indeed, proved to be the case. Allowing a THF solution containing **2**, methyl iodide (1.1 equiv), and LiBSA (2.0 equiv) to warm from −78 to −30° and then quenching gave **18** in 97% yield along with a trace of the ethylene **11**. A study was carried out to assess the stoichiometry, temperature, and nature of the halide. The results are presented in Table II.

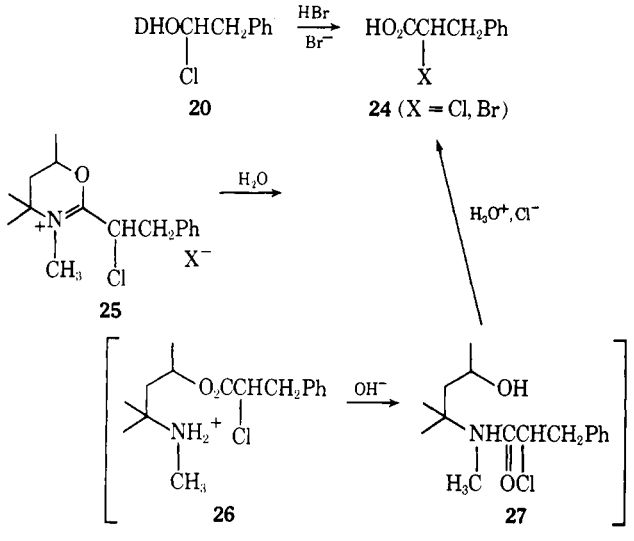


As seen from the tabulated results, 2.0 equiv of LiBSA was required to effect efficient alkylation (entry 1 and 2). Presumably, the base and chloromethyloxazine anion are in equilibrium and the excess base produced a higher concentration of the oxazine anion. The amount of ethylene product **11** becomes significant at temperatures above −30° (entries 3–5), which means that the anion is forming very rapidly at these temperatures and coupling with **2** is facile. It is also evident from Table II that the order of introduction of the reactants at −78° is of no consequence (entry 2 and 6), since, as already mentioned, no reaction takes place at this temperature. Varying the halogen from Cl to Br to I gave the expected results (entries 7–9). Reaction with ethyl chloride was poor as seen by the 7% yield of alkylated product. The anion undoubtedly preferred reaction with the chloromethyloxazine, producing the ethylene product in 77% yield. The small quantity of diethylated material in entries 7 and 8 was readily removed by distillation and presented no difficulties in preparative runs.

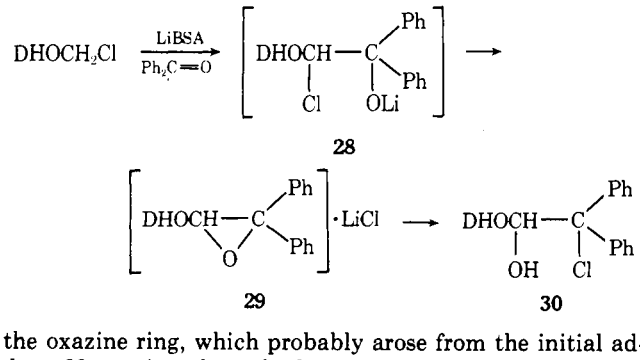
In order to demonstrate that this technique was indeed useful for the preparation of α-chloro aldehydes, **2** was alkylated with benzyl bromide and 3-phenylpropyl iodide, giving the elaborated oxazines **20** and **22**, respectively. Subjecting these oxazines to the usual borohydride reduction[13] and acidic hydrolysis furnished the α-chloro aldehydes **21** and **23** in overall yields (from **2**) of 55 and 53%, respectively. This synthesis of α-chloro aldehydes, therefore, provides a useful alternative to the existing methods which involve direct chlorination.[14] The addition of dichloromethyllithium to carbonyl compounds[15] is also noteworthy.



Since oxazines have been hydrolyzed to carboxylic acids, this sequence should be applicable to α-chlorocarboxylic acids. Heating **20**, for example, with aqueous hydrobromic acid–sodium bromide did produce the carboxylic acid **24** in good yield, but as a mixture of the chloro and bromo derivatives. The poor results obtained on hydrolysis using hydrochloric acid[16] precluded its use. A milder, more efficient oxazine cleavage was achieved by converting **20** to its methosulfate salt **25** (X = $OSO_3CH_3^-$) and treating it with water. This gave the open-chain amino ester **26** in good yield. The latter was stirred in a weakly alkaline solution for a few minutes, which afforded the amide **27**. Reacidification with 9 *N* hydrochloric acid resulted in amide cleavage and furnished the α-chloro acid **24** (X = Cl) in 82% yield. The entire cleavage operation was carried out in a single vessel without isolation of any of the intermediates.[17] The methiodide salt **25** (X = I) could not be employed in this sequence owing to its instability. Upon standing, the iodide ion in **25** reacts with the chlorine substituent, generating copious amounts of iodine vapor.



In an effort to vary the nature of the electrophile that could react with the chloromethyloxazine carbanion, it is unfortunate that enolizable carbonyl compounds must be excluded. This is due to the fact that current conditions require all the reactants to be present simultaneously at −78°. For nonenolizable carbonyl compounds, reactions with LiBSA have also been reported.[18] Nevertheless, when a solution of **2**, benzophenone, and 2.0 equiv of LiBSA was allowed to warm slowly from −78 to 0° and quenched, the chlorohydrin **30** was obtained in 65% yield. Of interest is the fact that the hydroxy group in **30** is α to the oxazine ring, which probably arose from the initial adduct **28** passing through the epoxide **29**. The latter rearranged either under the influence of lithium chloride[19] or during the aqueous work-up which involved dilute hydrochloric acid.



In summary, the 2-chloromethyloxazine appears to possess the potential for elaborating aryl Grignard reagents by two carbons to their acetic acid derivatives and further provides a route to α-chloro aldehydes and carboxylic acids. In the accompanying paper, the chloromethyloxazine is shown to serve as a useful precursor to phosphorus ylides and carbanions whose synthetic utility will be demonstrated.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., Midwest Microlabs, Inc., Indianapolis, Ind., and Atlantic Microlabs, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. The nmr spectra were measured with Varian A-60A and T-60 instruments using carbon tetrachloride or deuteriochloroform as solvent containing tetramethylsilane (~1%) as the internal standard. Mass spectra were obtained on an Atlas CH-4 spectrometer at 70 eV. Thin layer chromatography (tlc) was carried out on silica gel G (PF_{254}). The chromatograms were developed in an iodine chamber. Preparative thick layer chromatography (plc) was performed on silica gel G (PF_{254}) and visualization of the chromatogram was effected by exposure to short-wave uv light (Blak-Ray UVL-21). Vapor phase chromatography (vpc) analyses were performed on an F & M Model 810 (thermal conductivity) chromatograph with column A, 10 ft × 0.25 in. o.d. copper tubing containing 7% (w/w) Silicone Fluid SE-30 on Chromosorb P; a Hewlett-Packard Model 5750 (flame ionization) chromatograph with column B, 6 ft × 0.125 in. o.d. stainless steel UCW 98, 80–100 mesh, column C, 18 ft × 0.125 in. o.d. UCW 98; or a Hewlett-Packard Model 5750 (thermal conductivity) chromatograph with column D, 6 ft × 0.25 in. o.d. copper tubing containing 10% (w/w) Silicone Fluid SE-31 on Diatoport S. Hexamethylphosphoric triamide (HMPA) was dried over molecular sieves (Linde) and distilled onto molecular sieves for storage under argon.

2-Chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2). To a 500-ml flask equipped with a thermometer, a stirrer, and a 125-ml addition funnel was added 100 ml of concentrated sulfuric acid. The acid was cooled to 0–5° with an ice–acetone bath and 41.6 g (0.55 mol) of chloroacetonitrile was added at such a rate that the temperature was maintained at 0–5°. After the addition of the nitrile was completed, 59 g (0.4 mol) of 2-methyl-2,4-pentanediol was added at such a rate that the same temperature (0–5°) was maintained. The mixture was stirred for an additional 1 hr and then poured onto 400 g of crushed ice. The aqueous solution was extracted with four 50-ml portions of methylene chloride (and the methylene chloride extracts were discarded). The cold aqueous acid solution was carefully poured into a cooled (0°) beaker containing 400 g of sodium bicarbonate and 300 ml of diethyl ether. Upon becoming neutral a red-yellow oil appeared that was taken up in the ether layer. The aqueous layer was extracted with four 200-ml portions of diethyl ether (water was added as needed) and the combined ether extracts were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation and the residue was distilled through a 20-cm fractioning column to give 47–57 g (55–63%) of a colorless liquid: bp 41° (1.0 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 1.2 (s, 6), 1.3 (d, 3), 1.7 (d of t, 2), 3.9 (s, 2), 4.2 (m, 1).

The product can be stored indefinitely under nitrogen at −20° over a few grains of potassium carbonate.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.92; H, 7.98; N, 7.76.

Treatment of 2-Chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2) with Various Grignard Reagents in Ether or in THF. In general, coupling reactions attempted between **2** and excess Grignard reagents gave mixtures as described in the discussion. The mixtures were analyzed on vpc volumns B and D and by tlc and nmr. Assignments of structure were made by comparison of isolated materials with authentic samples prepared by alternate routes.[3] The following procedure is a typical one.

Treatment of 2 with 2 Equiv of Phenylmagnesium Bromide in Ethyl Ether. Phenylmagnesium bromide was prepared in the usual way from magnesium (3.14 g, 0.02 mol) in ether (30 ml). It was then added slowly to **2** (1.76 g, 0.01 mol) in ether (20 ml) and heated to reflux for 16 hr. The dark mixture was then cooled in an ice bath, 5 ml of cold 1 *N* hydrochloric acid was added slowly, and the mixture was poured over ice and made acidic (pH ~3). The acidic mixture was extracted with ether (3 × 50 ml) and the

ether extracts were discarded. The aqueous solution was neutralized with sodium bicarbonate and the neutral mixture was extracted with ether (4 × 50 ml). The neutral ether extracts were dried over potassium carbonate and evaporated to give 1.49 g of brown liquid. The nmr and ir spectra were consistent with a 70:30 mixture of 2-phenyl-1,3-oxazine **9** and 2-benzyl-1,3-oxazine **10**.[3] The products did not separate on vpc columns B, C, or D. The mixture was separated by elution on a silica gel (28–200 mesh) column with ether. The oxazine **9** was the first component to elute from the column, followed by **10**.

Treatment of 2 with 1 Equiv of Phenylmagnesium Bromide in the Presence of 2 Equiv of HMPA. Preparation of 10 from 2. Phenylmagnesium bromide was prepared from magnesium (0.3 g) and bromobenzene (1.57 g, 0.01 mol) in THF (20 ml). To the Grignard solution was added HMPA (3.58 g, 0.02 mol), which became warm on mixing. The solution was added slowly to **2** (1.76 g, 0.01 mol) in ether (35 ml) *via* syringe and the resultant solution was refluxed for 18 hr. The solution was poured into ice water, made acidic (pH ~3), and extracted with ether, and the ether extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate and extracted with ether, and the neutral ether extracts were dried and evaporated to yield an amber product (1.66 g) which consisted of **10**[3] (85%) and recovered **2** (15%).

Reaction of 2 with 1 Equiv of Phenylmagnesium Bromide in 50:50 HMPA–THF. Preparation of 11. Phenylmagnesium bromide was prepared as described above. To the Grignard solution was added HMPA (3.58 g, 0.02 mol). On mixing, some heat was liberated. The resultant solution was then added slowly to **2** (1.76 g, 0.01 mol) in a mixture of THF (25 ml) and HMPA (25 ml) and heated to reflux for 18 hr. The product was isolated as in the previous reaction. The crude product (1.20 g) was recrystallized from cold ethyl ether, giving 1.12 g (80%) of **11**: white needles, mp 161°; ir 1631 cm^{-1}; nmr (CCl_4) δ 6.4 (s, 2), 4.1 (m, 2), 1.32 (d, 6), 1.2 (s, 12); mass spectrum *m/e* (rel intensity) 278 (20), 180 (100).

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.97; H, 9.52; N, 10.13.

***p*-Biphenylacetic Acid (15).** *p*-Biphenylmagnesium bromide was prepared from magnesium (0.6 g) and *p*-bromobiphenyl (5.12 g, 0.022 mol) in THF (50 ml). To the biphenylmagnesium bromide solution was added HMPA (8 ml). The resultant solution was added slowly to a solution of **2** (3.5 g, 0.02 mol) in ethyl ether (100 ml). The mixture was refluxed for 18 hr and the product, a thick yellow liquid, was isolated as in the previous experiment. The nmr spectrum of the crude material showed a mixture of starting material **2**, the desired oxazine adduct **14**, and traces of HMPA. The crude product was then added to a hydrobromic acid solution (0.08 mol of HBr in 30 ml of H_2O saturated with NaBr); this refluxed for 18 hr. The acidic mixture was extracted with chloroform and the organic layer was washed with brine. Benzene (10 ml) was added to the chloroform solution and the solution was evaporated to give a tan solid (2 g, 47%), which was recrystallized from ethyl ether to give pure *p*-biphenylacetic acid **15** (1.7 g, 41%), white needles, mp 165° (lit.[20] mp 164°).

Reaction of 2 with *tert*-Butyllithium. To 40 ml of THF at −78° under nitrogen was added *tert*-butyllithium (0.011 mol in pentane) followed by **2** (1.76 g, 0.01 mol) in 10 ml of THF. The mixture was stirred for 30 min and methyl iodide (1.41 g, 0.01 mol) was then added *via* syringe. The mixture was allowed to stir for 2 hr, poured into cold 1 *N* hydrochloric acid (~25 ml), and extracted with pentane, and the pentane extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate, extracted with ether, and concentrated to yield a yellow liquid (1.4 g), which was analyzed by vpc on column B (100–250°). The material recovered was found to be a mixture with the following composition: **18** (24%), **19** (38%), **11** (24%), and recovered **2** (3%). Products were identified by comparison of their physical properties to those of authentic samples. Oxazine **19**, which had not been previously prepared, was isolated by preparative layer chromatography using ether–pentane (3:1) as the eluent, R_f 0.75. Another sample was collected from the vpc instrument, column C, 135°: ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.1 (m, 1), 2.0 (s, 2), 1.5 (m, 2), 1.3 (d, 3), 1.1 (s, 6), 1.0 (s, 9).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.84; H, 11.66; N, 7.24.

Lithium Bis(trimethylsilyl)amide (LiBSA). The procedure of Amonoo-Neizer[12] was followed. *n*-Butyllithium (0.3 mol) in hexane (2.56 *M*) was added slowly to a stirred solution of freshly distilled hexamethyldisilazane (51.5 g, 0.32 mol) in ether (100 ml). The mixture was heated to reflux, the solvents were evaporated, and the residue was dried under vacuum. The residue was then dissolved in THF to obtain a 2 *M* solution and used in the subsequent reactions.

2-(1-Chloroethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (18). A 50-ml portion of a 2 *M* solution of LiBSA, prepared as above and cooled to −78° in Dry Ice–acetone under nitrogen, was treated with 8.8 g (0.05 mol) of **2** in 10 ml of THF. MeI (8.46 g, 0.06 mol) in 10 ml of THF was slowly added *via* syringe. The resultant solution was allowed to slowly warm to 0° (3–3.5 hr) and poured into cold 6 *N* hydrochloric acid solution (40 ml). The acid solution was extracted with petroleum ether and the extracts were discarded. The acid solution was then neutralized using sodium bicarbonate and extracted with ether. The ether extracts were evaporated and the residue was distilled, furnishing 8.14 g (85%) of **18**: bp 44° (1.3 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.3 (q, 1), 4.2 (m, 1), 1.7 (d of t, 2), 1.6 (d, 3), 1.3 (d, 3), 1.1 (s, 6). Vpc analysis on column C (135°) indicated that the material contained less than 1% of **2**.

Anal. Calcd for $C_9H_{16}NOCl$: C, 56.99; H, 8.50; N, 7.33. Found: C, 57.04; H, 8.43; N, 7.08.

2-(1-Chloropropyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (16) was prepared in the same manner as **18**, using ethyl iodide. Oxazine **16** was obtained in 92% yield (distilled), bp 45° (0.4 mm); vpc analysis on column B (135°) indicated the absence of **2** and less than 1% dialkylated material (**17**); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.2 (m, 1), 4.0 (t, 1), 1.9 (m, 2), 1.7 (m, 2), 1.3 (d, 3), 1.1 (s, 6), 0.9 (t, 3); mass spectrum *m/e* (rel intensity) 205 (6), 203 (16), 168 (48), 84 (100).

2-(1-Chloro-2-phenylethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (20). Using the above procedure, **2** was treated with benzyl bromide or benzyl chloride and the reaction was quenched at −30°. A 72 and 68% yield, respectively, of **20** was obtained: bp 98° (0.15 mm); solidified mp 65–66.5° (pentane); ir (film) 3080–3020, 1665, 1605 cm^{-1}; nmr (CCl_4) δ 7.2 (s, 5), 4.3 (t, 1), 4.1 (m, 1), 3.2 (d of d, 2), 1.5 (d of t, 2), 1.3 (d of d, J = 1 Hz, 3), 1.1 (d, J = 1 Hz, 3), 0.9 (s, 3).

Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.80; H, 7.60; N, 5.26. Found: C, 67.54; H, 7.77; N, 5.32.

2-Chloro-3-phenylpropanal (21). The oxazine **20** was reduced with sodium borohydride according to the general procedure previously described.[3] The excess sodium borohydride was destroyed at −45° with 3 *N* hydrochloric acid solution to avoid halogen removal. The crude isolated aldehyde, after oxalic acid hydrolysis, gave a single peak on vpc analysis (column B, 155°). Distillation afforded pure material: bp 112° (13 mm); $n^{25}D$ 1.5358 (lit.[21] $n^{14}D$ 1.5375); ir (film) 1735 cm^{-1}; nmr (CCl_4) δ 9.63 (J = 2 Hz, d, 1); semicarbazone mp 199°.

2-(1-Chloro-4-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (22). Using the above procedure, **2** was treated with 1-iodo-3-phenylpropane and the reaction was quenched at 0°. Oxazine **22** was obtained in 83% yield: bp 115° (0.05 mm); ir 3080–3020, 1665, 1605 cm^{-1}; nmr (CCl_4) δ 7.2 (s, 5), 4.2 (m, t, 2), 2.6 (t, 2), 1.4–2.2 (m, 4), 1.3 (d, 3), 1.2 (s, 6); mass spectrum *m/e* (rel intensity) 293 (5), 295 (16), 258 (27), 175 (100), 141 (27).

2-Chloro-5-phenylpentanal (23). Oxazine **22** was reduced with sodium borohydride and the aldehyde **23** was released[3] after oxalic acid hydrolysis. Distillation furnished pure α-chloro aldehyde: bp 77° (0.075 mm); ir (film) 1730 cm^{-1}; nmr (CCl_4) δ 9.4 (d, J = 2 Hz, 1), 7.2 (m, 5), 4.1 (m, 1), 2.7 (t, 2), 1.4–2.2 (m, 4); semicarbazone mp 204°.

Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.11; H, 6.65. Found: C, 67.39; H, 6.73.

2-Chloro-3-phenylpropionic Acid (24). To 25 ml of ether, under nitrogen, was added dimethyl sulfate (2.52 g, 0.02 mol) and **20** (2.66 g, 0.01 mol). The solution was stirred overnight, during which time an oil separated from solution. The ether was evaporated, cold water was added, and the resulting acidic solution was made basic (pH ~10 for 5 min). The mixture was again made acidic by addition of 9 *N* hydrochloric acid (pH ~1) and the solution was heated to reflux overnight. The mixture was extracted with chloroform, and the chloroform extracts were dried (sodium sulfate) and evaporated. The residue was distilled, giving 1.52 g (82%) of **24**: bp 170° (2 mm) [lit.[22] bp 170–174° (25 mm)]; ir 3500–2400, 1745, 1605 cm^{-1}; nmr ($CDCl_3$) δ 11.9 (b, 1), 7.15 (s, 5), 4.4 (t, 1), 3.3 (d of t, 2).

2-(2-Chloro-1-hydroxy-2,2-diphenylethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (30). Using the above procedure, **2** was treated with benzophenone and the reaction was quenched at 0°. Oxazine **30** was obtained in 63% yield: mp 130° (hexane); ir (KBr) 3110, 1665 cm^{-1}; nmr (CCl_4) δ 7.0–7.8 (m, 10), 6.8 (s, 1, exchangeable with D_2O), 5.0 (s, 1), 4.0 (m, 1), 0.6–1.7 (m, 1); mass spectrum *m/e* (rel intensity) 322, 182, 140, 105 (100).

Anal. Calcd for $C_{21}H_{24}NO_2Cl$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.62; H, 6.84; N, 3.71.

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The Chemistry of 2-Chloromethyloxazines. Formation of Phosphoranes and Phosphonates. The Use of α,β-Unsaturated Oxazines as a Common Intermediate for the Synthesis of Aldehydes, Ketones, and Acids[1]

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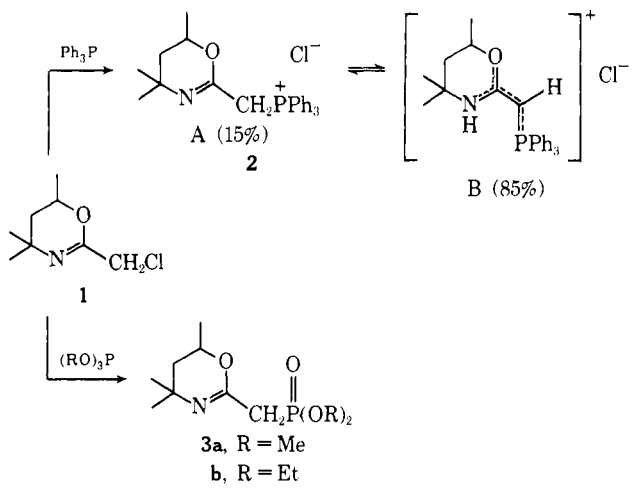
The 2-chloromethyloxazine **1** has been found to yield phosphonium salts **2** and phosphonates **3** which serve as "Wittig-type" reagents upon reaction with carbonyl compounds. The resulting α,β-unsaturated oxazines **5**, in turn, have been shown to serve as a common precursor to unsaturated aldehydes, ketones, and acids by (a) sodium borohydride reduction of **5** or their *N*-methyl quaternary salts **24**, (b) addition of organolithium reagents to the *N*-methyl quaternary salts **24**, and (c) hydrolysis of **24** in aqueous medium.

The availability of the 2-chloromethyloxazine **1** and its successful use of an electrophile[1] has prompted an investigation into its potential role as a precursor to oxazine "Wittig-type" reagents. Reaction of **1** with triphenylphosphine provided a 75% yield of the phosphonium salt **2** as a 1:5.7 mixture of tautomers A and B. The infrared spectrum of **2** (chloroform) showed only weak absorption at 1660–1670 cm^{-1} for the C=N link in A and strong absorption at 1603 cm^{-1}, whereas the ultraviolet spectrum (ethanol) exhibited bands at 273, 267, and 263 nm resulting from extended delocalization in B. The nmr spectrum of **2** showed a doublet at δ 4.22 (J = 15 Hz, 0.85 H) and a broad signal at δ 10.2 (0.85 H) attributable to the vinyl and NH protons, respectively, in the B tautomer. A small, broad signal at δ 2.48 was present due to the α-methylene protons in tautomer A. The highly delocalized structure in B was further confirmed by a single-crystal X-ray analysis.[3] The chloromethyloxazine also underwent a smooth Michaelis–Arbuzov reaction with trialkyl phosphites, furnishing the oxazine phosphonates **3a** (40%) and **3b** (80%). Both **2** and **3b** were allowed to react with a variety of carbonyl compounds in order to assess their ability to form olefinic derivatives.



When a suspension of **2** in THF was treated with potassium *tert*-butoxide, a yellow solution of the phosphorane **4** formed immediately. The phosphorane reacted rapidly and exothermally with aldehydes, giving good yields of the *trans*-vinyl oxazines **5** (R_2 = H). Reactions with ketones were more sluggish, requiring overnight heating and resulting, where possible, in mixtures of geometric isomers