15); mass spectrum (70 eV) *m/e* (rel intensity) 164 (42), 41 (100). An analytical sample was prepared by glpc.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.01; H, 9.77.

Again the shift (δ 2.63) of the bridgehead hydrogen adjacent to the ketone in **18** confirmed the structural assignment, but the deuterium experiment was carried out, giving a product containing 3 mol % $C_{11}H_{16}O$, 14 mol % $C_{11}H_{15}DO$, 83 mol % $C_{11}H_{14}D_2O$, no $C_{11}H_{13}D_3O$, and no $C_{11}H_{12}D_4O$ and confirming the structural assignments.

Registry No.—**1a**, 39837-99-5; **2**, 39832-73-0; **3**, 39832-74-1; **4**, 22118-00-9; **5a**, 24097-40-3; **5b**, 39832-76-3; **5c**, 39832-77-4; **5d**, 39832-78-5; **6**, 18631-96-4; **7a**, 39832-80-9; **7b**, 39832-81-0; **7c**, 39832-82-1; **7d**, 39832-83-2; **8**, 22118-01-0; **9a**, 39832-85-4; **9b**, 39832-86-5; **9d**, 39832-87-6; **10**, 39832-88-7; **11**, 39832-89-8; **13**, 24736-69-4; **15**, 39832-91-2; **16**, 39832-92-3; **17**, 39832-93-4; **18**, 39832-94-5; bicyclo[4.3.0]non-1(6)-en-7-ol, 39832-95-6; bicyclo[4.3.0]non-1(6)-en-7-yl vinyl ether, 39832-96-7; methanesulfonyl chloride, 124-63-0.

Acknowledgment.—Generous support of this research by the National Science Foundation and valuable assistance in preparation of vinyl ethers and precursors by Mr. Gary Hanwell are gratefully appreciated.

The Synthesis of α-Branched Ketones from Dihydro-1,3-oxazines *via* the Ketenimine Intermediate. α-Substituted Ketones from a Stable Ketenimine[1]

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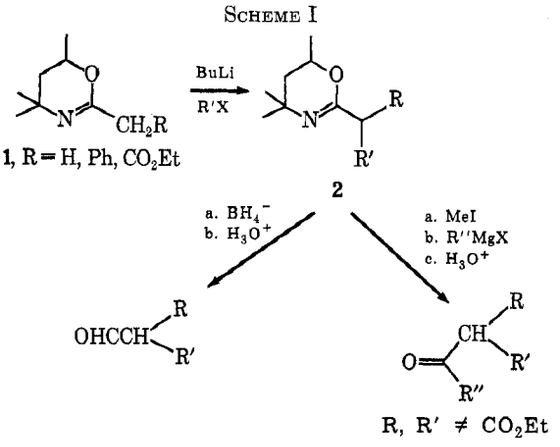
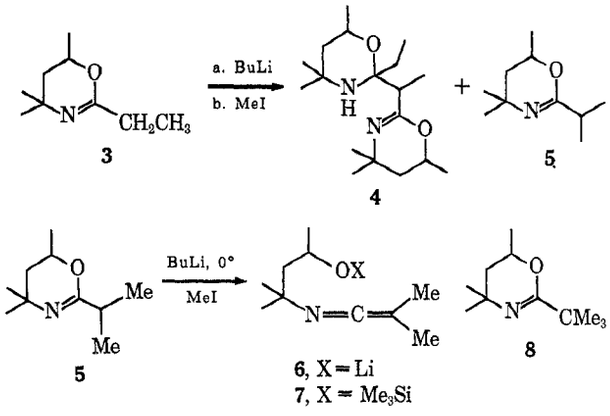
The tertiary proton abstraction from 2-isoalkyloxazines (**12**) by organolithiums leads to rapid ketenimine rearrangement. The ketenimines are shown to be useful precursors to a variety of highly substituted ketones by virtue of successive alkylations. The ketenimine intermediate was verified by isolation as its trimethylsilyl ether (**7**) and also used as a precursor to substituted ketones by addition of Grignard or organolithium reagents.

The readily available tetramethyldihydro-1,3-oxazine **1** (R = H) has been shown to serve as a useful precursor to aldehydes[4] and ketones[5] by the equations set forth in Scheme I. In addition, the corresponding

SCHEME I



2-benzyl (R = Ph) and 2-carboethoxy (R = CO_2Et) derivatives led to substituted oxazines by virtue of alkylation of their respective carbanions. These, in turn, were transformed into carbonyl compounds by similar manipulations. Among the limitations noted for these methods[4,5] was the failure of oxazines possessing *n*-alkyl (**1**, R = Me, Et, Pr, etc.) or isoalkyl (**2**, R, R′ = Me, Et, etc.) substituents to form a stable carbanion capable of further alkylation. For example, the 2-ethyloxazine **3** gave mainly the dimer **4** upon treatment with butyllithium (or other comparable bases) and methyl iodide under a variety of conditions. The expected product **5** was produced in only 10–15% yield. Similar treatment of the 2-isopropyloxazine **5** indicated complete inertness to strong base below ~0°; yet above this temperature (0–25°) it was rapidly transformed into the ketenimine **6**. The latter was trapped by addition of trimethylchlorosilane and **7** was isolated in 35–40% yield. Only a trace of the 2-*tert*-butyloxazine **8** was found among the product. It is evident,



therefore, that secondary and tertiary carbanions α to the oxazine ring are unstable to the temperatures at which they are formed, rearranging to open-chain ketenimines which react further with nucleophiles present. This oxazine–ketenimine rearrangement thus prohibits the synthesis of α-alkylaldehydes *via* Scheme I but was deemed sufficiently novel that a study to assess its potential was undertaken.[6]

(1) Part XX of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).

(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

(3) Postdoctoral Fellow of the Medical Research Council of Canada, 1968–1970.

(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).

(5) A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972).

(6) The synthesis of α-alkylaldehydes was accomplished, nevertheless, using the 2-vinyloxazine and successive addition of Grignard reagent and alkyl iodides (see ref 4).

Results and Discussion

The reaction of **5** with 1.0 equiv of *n*-butyllithium (0°, THF) gave the tetrahydro-1,3-oxazine **10**, which, upon hydrolysis in aqueous oxalic acid, afforded the ketone **11** in ~30% yield. This result may be explained by the slow rate of tertiary proton removal followed by rapid rearrangement of the unstable α carbanion and addition of unreacted *n*-butyllithium leading to **9**. Introduction of trimethylchlorosilane subsequent to the addition of *n*-butyllithium leads to **7** and **9a** after quenching. The tetrahydro-1,3-oxazine **10** was not obtained pure and was probably contaminated with **9a** (Me_3Si singlet in nmr of crude **10**). Nevertheless, both **10** and **9a** would lead to the ketone **11** on hydrolytic cleavage. It was a simple matter to render this process more efficient by adding 2.0 equiv of *n*-butyllithium to the isopropyloxazine, **5**. In this fashion there was sufficient base to abstract completely the tertiary proton and also allow addition to the resulting ketenimine. The yield of ketone **11** rose to 75% after this modification. A series of ketones **13** were prepared *via* this route (Scheme II) using various isoalkyloxazines **12** and organolithium reagents (Table I, entries 1–12). A significant extension to this process was developed by taking advantage of the *in situ* formation of the lithioenamine intermediate **14**. If, prior to quenching, the solution containing **14** is treated with an alkyl halide, **15** is produced by a nucleophilic attack of the lithioenamine upon the alkyl halide. This provides the quaternary carbon adduct, which, after quenching and oxalic acid hydrolysis, leads to the α-quaternary carbon ketones **16**. Thus, a stepwise technique based upon four alkyl groups being introduced in sequence is available for the formation of highly substituted ketones (Table I, entries 13–17).[7] The relationship of the alkylation step (**14** → **15**) to that reported by Stork[8] is obvious. Transformation of aldehydes and ketones to their imine derivative, followed by salt formation with a Grignard reagent, leads to the magnesioenamine **17**, which similarly alkylates at the β carbon, affording, after hydrolysis, the α-alkylated ketone **18**. It is noteworthy that only the magnesioenamine **17** is formed and not the more highly substituted isomer, **19**. This confirms the absence of an equilibrium between the two metalated enamines **17** and **19** and this was also observed in the enamine salts derived from ketenimines. Furthermore, both methods complement each other nicely in that Stork's procedure leads to ketones containing the alkyl group on the least substituted carbon, whereas this method produces ketones alkylated at the more highly substituted carbon.

In the case where the oxazine bears a benzyl proton (*e.g.*, **20**) it may be removed at −78° with *n*-butyllithium, since the conjugated effect of the phenyl group assists in stabilizing the carbanion, **21**. At −78° this carbanion may be alkylated smoothly[4] but, if **21** is allowed to warm up, rearrangement to the ketenimine **22** ensues. At this point, other nucleophilic reagents may be introduced (*i.e.*, RMgX), furnishing the magnesioenamine **23** which is ultimately carried on to either the ketone **24** or **25**. This route possesses two distinct advantages: (a) it reduces the necessity for using 2.0 equiv of an organolithium reagent whose availability or carbon skeleton may be either time-consuming or expensive, and (b) allows the preparation of methyl ketones which could not be obtained using 2.0 equiv of methyllithium, since the latter fails to

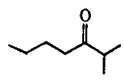
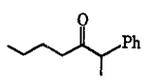
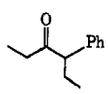
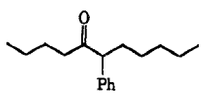
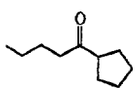
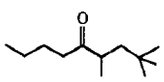
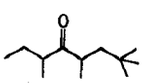
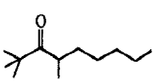
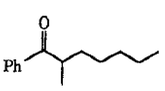
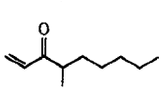
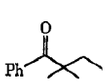
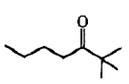
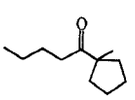
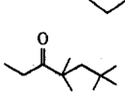
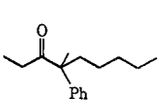
SCHEME II

(7) A Preliminary report has appeared: A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Amer. Chem. Soc.*, **93**, 2314 (1971).

(8) G. Stork and S. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

TABLE I

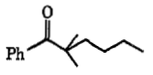
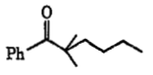
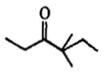
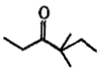
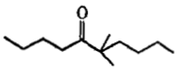
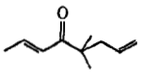
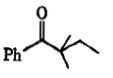
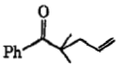
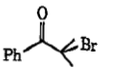
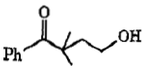
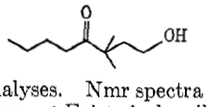
KETONES 16 AND 13 *via* SCHEME II

Entry	Registry no. of 12	Oxazine, 12[a] R1	R2	Organolithium R3	Registry no.	Alkyl iodide R4	Ketone	Registry no.	Yield, %[b]	Registry no.	ν, cm⁻¹ (film)
					Ketones 13[c]						
1	39575-96-7	Me	Me	*n*-Bu	109-72-8			13019-20-0	73		1705
2		Me	Me	*t*-Bu	594-19-4			5857-36-3	49		1700
3		Me	Me	Ph	591-51-5			611-70-1	80		1694
4	39575-97-8	Ph	Me	*n*-Bu				7661-44-1	70[d]	39576-16-4	1709
5	36867-26-2	Ph	Et	Et	811-49-4			6957-17-1	92[e]	39576-17-5	1712
6	30078-61-6	Ph	*n*-Amyl	*n*-Bu				25387-03-5	77		1710
7	39576-00-6			*n*-Bu				6636-80-2	88[f]	39576-18-6	1701
8	39575-86-5	Me	Neopent	*n*-Bu				26933-75-5	61		1709
9		Me	Neopent	*sec*-Bu	598-30-1			39576-08-4	57		1702
10	36871-42-8	Me	*n*-Amyl	*t*-Bu				32557-59-8	63		1703
11		Me	*n*-Amyl	Ph				39576-10-8	47		1685
12		Me	*n*-Amyl	CH_2=CH	917-57-7			32524-99-5	45		1699 1679 1613
					Ketones 16						
13		Me	Me	Ph	75-03-6	Et		829-10-7	51		1681
14		Me	Me	*n*-Bu	74-88-4	Me		19078-97-8	60[g]	39576-19-7	1715
15				*n*-Bu		Me		32524-97-3	63		1709
16		Me	Neopent	Et		Me		32557-57-6	65		1700
17		Ph	*n*-Amyl	Et		Me		39576-15-3	73		1710

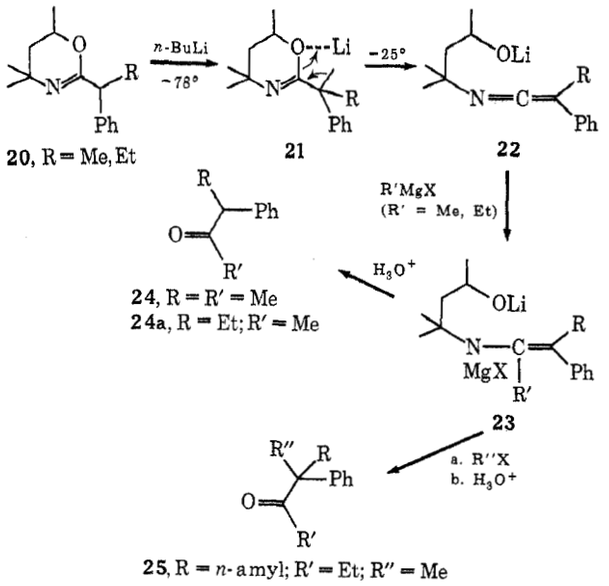
[a] Oxazines were distilled prior to reaction with organolithium reagents. [b] Yields based upon 2-isoalkyloxazines (12). [c] All compounds gave satisfactory elemental (±0.03%) and mass analyses. Nmr spectra were consistent with structures in all cases. [d] Semicarbazone, mp 119–120°. [e] Semicarbazone, mp 138–140°. [f] Semicarbazone, mp 120–121°. [g] Semicarbazone, mp 143–145°.

TABLE II

α-SUBSTITUTED KETONES (27) FROM KETENIMINE O-TRIMETHYLSILYL ETHER (7)

Entry	Registry no.	RMgBr	E	Registry no.	Ketone 27[a]	Registry no.	Yield, %	ν, cm⁻¹ (film)
1	100-58-3	Ph	*n*-BuI	542-69-8		17234-63-8	74	1680
2		Ph	*n*-BuBr	109-65-9			81	
3	925-90-6	Et	EtI			19550-14-2	87	1712
4		Et	EtBr	74-96-4			78	
5	693-03-8	*n*-Bu	*n*-BuI			39576-22-2	79	1704
6	1730-25-2	Allyl	Allyl Br	106-95-6		39576-23-3	70[b]	1683, 1628
7		Ph	EtI				74[e]	1681
8		Ph	Allyl Br			39576-24-4	60	1678
9		Ph	Br_2	7726-95-6		10409-54-8	40	1670
10		Ph	Ethylene oxide	75-21-8		39576-26-6	30[c]	3480
11		*n*-Bu[d]	Ethylene oxide			39576-27-7	65[c]	1688, 3500

[a] All compounds gave satisfactory elemental (±0.03%) and mass analyses. Nmr spectra were consistent with structures in all cases. [b] Obtained as a mixture (9:1) of conjugated and nonconjugated isomer. [c] Exists in hemiketal form. [d] Butyllithium was used since poor yields (~15%) were obtained using *n*-butylmagnesium bromide. [e] Identical with **13** (entry 13) in Table I.



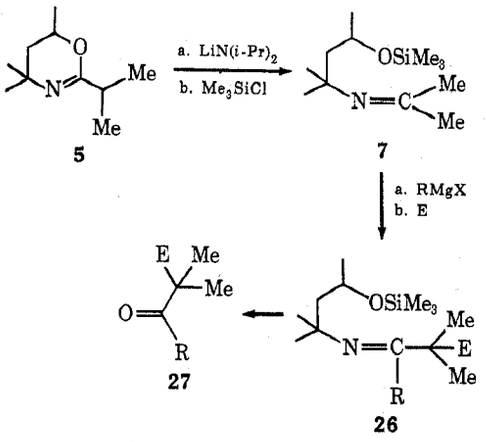
abstract the tertiary proton from the oxazines.[9] Unfortunately, this route was limited to oxazines whose α protons can be removed at low temperatures, thus avoiding interference by the ketenimine.

The use of lithium diisopropylamide as a base provided a partial solution to the problem of employing 2.0 equiv of an organolithium reagent. Treatment of 2-isopropyloxazine **5** with lithium diisopropylamide at 0° in THF, followed by addition of trimethylchlorosilane, gave the ketenimine silyl ether **7** in 80% yield. This was in sharp contrast to the results mentioned earlier using butyllithium. The efficient preparation of **7**, in sufficient quantity to classify it as a suitable starting material, allowed its chemistry to be further evaluated. The ketenimine was found to be completely stable to water and alkali for several hours (25°), but very unstable to aqueous acid.[10]

A variety of Grignard reagents were added to **7** followed by introduction of an electrophile (E) leading to the imine **26**. Hydrolysis of the latter in oxalic acid afforded the ketones **27** in variable yields (Table II). It is seen from Table II that bromine and ethylene oxide also served as electrophilic agents producing α-bromo and γ-hydroxy ketones, respectively. Among the electrophiles which did not add were chlorine, iodine, acyl halides, esters, and epoxides carrying sub-

(9) Methyllithium failed to function as a base at low temperature in all the oxalines studied to date.[4] (However, see ref 13.)

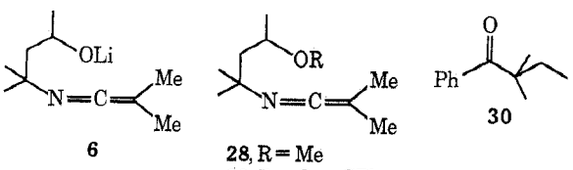
(10) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **75**, 657 (1953).



5 7 27 26

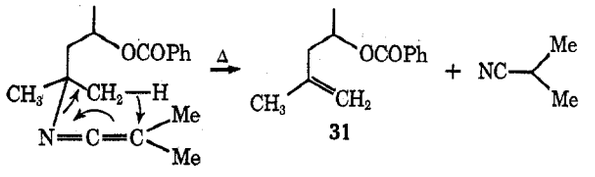
stituents (ethyl, phenyl). *sec*-Butyl and 3-cyclohexenyl bromide also failed to react with the intermediate magnesioenamine. Of further note was the sluggish nature of the Grignard addition to **7**. After these reactants had been stirred at room temperature for 18 hr there was still a considerable quantity of unreacted **7**. This is in contrast to the more facile addition (25°, 8 hr) of Grignard reagents to the *O*-lithioketenimines **6** and **22**. Similarly, the addition of alkyl halides to the magnesioenamine derived from **7** proceeded slowly at room temperature. The yields of ketones in Table II were achieved only after heating the ketenimine and Grignard reagents to reflux (~18 hr) and similarly heating the reaction after introduction of the electrophile (except bromine).

It is difficult to explain the slow reaction rate of **7** as compared to that of the *O*-lithio salt **6** except on steric grounds. Yet the bulky trimethylsilyl group must be hindering attack by both the Grignard and electrophilic agent. Why this should occur in an open-chain compound is not clear. In order to test this hypothesis, the ketenimine *O*-methyl ether **28** was prepared by addition of dimethyl sulfate to the *O*-lithioketenimine **6**. This compound could not be obtained pure since it was accompanied by 10% of the 2-isopropyloxazine, and separation attempts were all fruitless. Nevertheless, **28** was used in ~90% purity in reaction with Grignard reagents and subsequently with ethyl iodide. There was no concern over the presence of 10% oxazine in the ketenimine, since it is now well known that oxazines are completely inert to Grignard reagents.[4] Addition of phenyl Grignard to **28** followed by ethyl iodide proceeded smoothly at room temperature to give, after work-up, the phenyl ketone **30** in 90% yield (based upon



6 28, R = Me 29, R = O=CPh 30

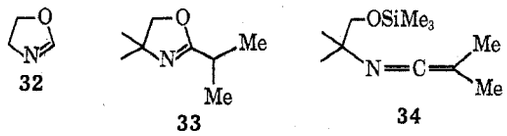
the ketenimine present). Thus, the smaller methoxyl group in **28** results in greater accessibility to the magnesioenamine by ethyl iodide. During attempts to purify **28**, vpc examination above 175° showed several additional highly volatile peaks, one of which was collected and found to be isobutyronitrile. The origin of this material was subsequently determined by subjecting the higher boiling ketenimine benzoate **29** to pyrolysis (160–200°). In addition to isobutyronitrile, the unsaturated ester **31** was isolated in 80% yield.



29 31

While this study was in progress, Ciganek reported the pyrolytic conversion of ketenimines to olefins and nitriles.[11]

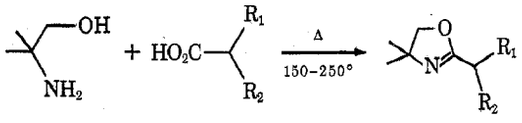
In view of the synthetic utility exhibited by the related 2-oxazoline system **32** as a source of carboxylic acids and esters,[12] it was of interest to examine its behavior in the carbanion–ketenimine rearrangement. As expected, the carbanion of **33** was formed using *n*-butyllithium and in the presence of an excess of the latter base provided *n*-butyl isopropyl ketone **11** in 84% yield. Furthermore, addition of lithium diisopropylamide to **33** followed by trimethylsilyl chloride produced the trimethylsilyl ketenimine **34** in 65% yield.



32 33 34

Several experiments were performed on **34** in order to assess its utility toward the synthesis of ketones. Addition of phenylmagnesium bromide followed by *n*-butyl iodide gave after extended heating the corresponding ketone **26** (Table II, entry 1) in only 40% yield. On the basis of this experiment, it would appear that the trimethylsilyl group is exerting an even greater retarding effect than was observed in the ketenimine derived from the oxazine. In view of these results, no further effort was expended on the 2-oxazoline. A report by Dubois[13] has demonstrated that excellent yields of α-branched ketones were obtained by the use of 2.0 equiv of organolithium reagents on **33** according to the method given in Scheme II. The main advantage to the use of the oxazoline as a precursor to ketones was stated by Dubois to lie in their ease of preparation. Thus, by heating 2-methyl-2-aminopropanol with carboxylic acids according to Scheme III,

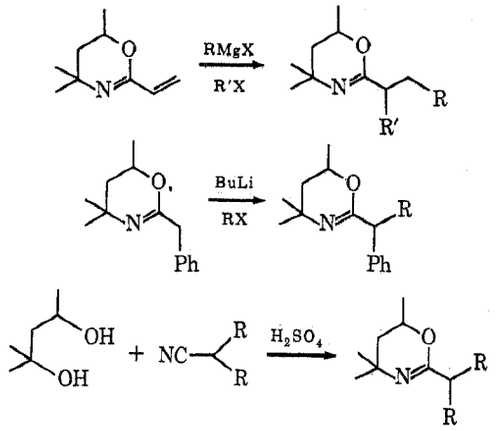
SCHEME III



various 2-isoalkyl-2-oxazolines were obtained in 30–68% yield. Although this may be an efficient route to simple oxazolines ($R_1 = R_2 = Me$), the yields drop off rapidly as the substituents on the carboxylic acid increase in bulk. On the other hand, the use of oxazines as precursors to ketones allows a variety of alkyl substituents to be employed by the efficient elaborative techniques outlined in Scheme IV. The oxazines **12** in Table I

(11) E. Ciganek, *Tetrahedron Lett.*, 5179 (1969).
(12) A. I. Meyers and D. L. Temple, *J. Amer. Chem. Soc.*, **92**, 6644, 6646 (1970).
(13) J. E. Dubois and C. Lion, *C. R. Acad. Sci.*, **274**, 203 (1972).

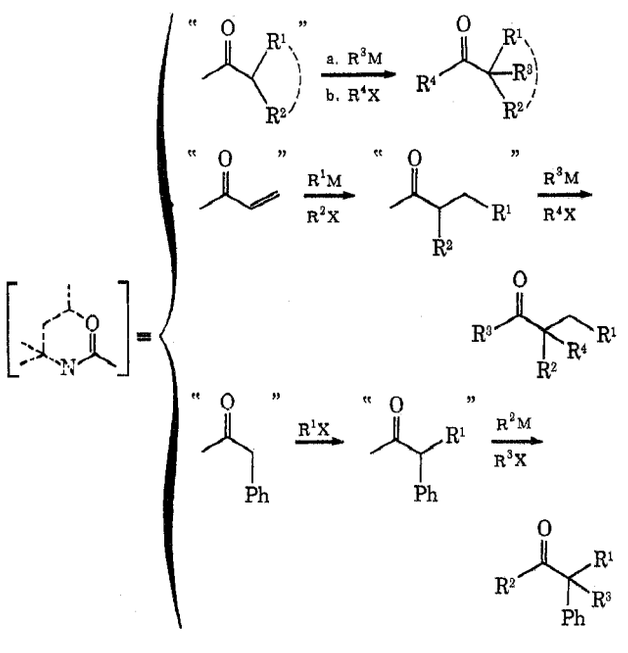
SCHEME IV



were all prepared from these three methods, and except for the last one, involving the glycol–nitrile condensation, are much more versatile than that in Scheme III. It should also be mentioned that the 2-vinyl- and 2-benzyloxazines are easy to prepare in quantity[4] or may be obtained from commercial sources.[14]

In summary, the oxazine ketone synthesis relies on a successive introduction of alkyl groups into the variously substituted oxazines whose carbonyl synthetic equivalents are depicted in quotes in Scheme V. These

SCHEME V



synthons are derived from the readily available oxazines shown in Scheme IV. Although several elegant and useful approaches to highly branched ketones have been recently reported,[15-18] they all involve substrates with preconstructed substituents or the use of bulky organometallic reagents. The oxazine ketone synthesis should provide a useful alternative to a number of these approaches.

(14) Columbia Organic Chemicals, Columbia, S. C.

(15) (a) J. E. Dubois, C. Lion, and C. Moulineau, *Tetrahedron Lett.*, 177 (1971); (b) J. E. Dubois, M. Busso, and C. Lion, *ibid.*, 829 (1971).

(16) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).

(17) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1029 (1971).

(18) H. C. Brown and G. W. Kabalka, *ibid.*, **92**, 714 (1970), and references cited therein.

Experimental Section[19]

2-Substituted 4,4-Dimethyl-5,6-dihydro-1,3-oxazines 12 (Table I). **A. 12 (R_1 = R_2 = Me, 5)** was prepared according to previously described procedures[4] from 76.0 g (1.1 mol) of isobutyronitrile, 118 g (1.0 mol) of 2-methyl-2,4-pentanediol, and 100 ml of concentrated sulfuric acid. The isopropyl oxazine was obtained in 62% yield (105 g): bp 64–65° (2 mm); ir (film) 1666 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1), 2.1 (m, 1), 1.5 (d of t, 2), 1.2 (d, 3), 1.1 (s, 6), 1.0 (d, 6).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.08; H, 11.31; N, 8.33.

B. 12 (R_1 = Ph, R_2 = Me, 20) was prepared according to previously described procedures[4] from the 2-benzyloxazine (10.85 g), methyl iodide (7.81 g), and *n*-butyllithium: yield 11.6 g (99%); bp 85–90° (0.2 mm); ir (film) 1661 cm^{-1}; nmr (CCl_4) δ 7.0–7.4 (m, 5), 4.0 (m, 1), 3.4 (q, 1), 1.5 (d of t, 2), 1.0–1.4 (m, 12).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.00; H, 9.13; N, 5.99.

C. 12 (R_1 = Ph, R_2 = Et, 20) has been previously described.[4]

D. 12 (R_1 = Ph, R_2 = *n*-amyl, 20) was prepared by alkylation of 2-benzyloxazine (10.85 g) with *n*-amyl iodide (10.25 g) with *n*-butyllithium:[4] yield 13.0 g (91%); bp 120° (0.05 mm); ir (film) 1663 cm^{-1}; nmr (CCl_4) δ 7.1–7.4 (m, 5), 4.0 (m, 1) 3.2 (d of d, 1), 1.5 (d of t, 2), 0.8–1.4 (m, 20).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.31; H, 10.21; N, 4.69.

E. 12 (R_1 = Ph, R_2 = *n*-butyl) was prepared by alkylation of 2-benzyloxazine (10.85 g) with *n*-butyl bromide (7.54 g) according to previous procedures:[4] yield 13.4 g (98%); bp 108–110° (0.2 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 7.0–7.4 (m, 5), 4.0 (m, 1), 3.2 (t, 1), 0.8–2.1 (m, 21).

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.17; H, 10.08; N, 5.00.

F. 12 (R_1 = Me, R_2 = neopentyl) has been described elsewhere.[20]

G. 12 (R_1 = Me, R_2 = *n*-amyl) has been previously described.[4]

H. 12 [R_1 = R_2 = $-(CH_2)_4-$] was prepared from cyclopentyl cyanide and 2-methyl-2,4-pentanediol according to the previously described[4] method: yield 62%; bp 54–56° (0.3 mm); ir (film) 1667 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1), 2.5 (m, 1), 1.5–2.0 (m, 10), 1.3 (d, J = 7 Hz, 3), 1.1 (s, 6).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.67; H, 10.95; N, 7.07.

Dimethylketen-*N*-(4-trimethylsiloxy-2-methyl)-2-pentylimine (7).—A solution of lithium diisopropylamide in THF (0.22 mol in 150 ml) prepared from equivalent amounts of *n*-butyllithium and diisopropylamine mixed at 0°, was treated under nitrogen with 33.7 g (0.2 mol) of **5** (**12**, R_1 = R_2 = Me) at 0°. After the dropwise addition was complete, the yellow solution was allowed to warm to room temperature and stirring was continued for 3 hr. Upon recooling to 0°, 22 g (0.2 mol) of trimethylchlorosilane was slowly added and the resulting cloudy solution was stirred for an additional 2 hr at room temperature. The precipitated lithium chloride was removed by filtration and the filtrate was concentrated, leaving a yellow oily residue. Distillation gave 37 g (80%) of a colorless liquid: bp 65–68° (0.3 mm); ir (film) 2020, 843 cm^{-1}; nmr (CCl_4) δ 3.9 (m, 1), 1.5 (s, 6), 1.4 (m, 2), 0.9–1.1 (m, 9), 0.5 (s, 9).

Anal. Calcd for $C_{13}H_{27}NOSi$: C, 64.67; H, 11.27; N, 5.80. Found: C, 64.98, H, 11.17; N, 6.03.

2-Isopropyl-4,4-dimethyl-2-oxazoline (33).[21]—A mixture of 88.1 g (1.0 mol) of isobutyric acid and 89.1 g (1.0 mol) of 2-amino-2-methylpropanol was heated (~220°) in the presence of

(19) Microanalyses were performed by Midwest Microlab, Indianapolis, Ind. The nmr, infrared, and mass spectra were taken on a Varian T-60, Perkin-Elmer 257, and AEI MS-9 instrument, respectively. The organolithium reagents were kindly supplied by the Lithium Corporation, Bessemer City, N. C. The 2-vinyl-, 2-benzyl-, and 2-isopropyloxazines in Scheme IV were purchased from Columbia Organic Chemicals, Columbia, S. C., or prepared as previously described.[4]

(20) A. I. Meyers, A. C. Kovelesky, and A. F. Jurjevich, *J. Org. Chem.*, **38**, 2136 (1973).

(21) Adapted from the procedure reported by P. Allen and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).

a 6-in. Vigreux column until 2.0 mol (~36 ml) of water was visible in the distillate [hexane (~300 ml) was present in the receiving flask to facilitate monitoring of the distilled water]. The temperature of the distillate then rose to 130–140° and the distillate was also collected in the hexane. When distillation ceased, the aqueous layer was separated and extracted repeatedly with fresh hexane, and the latter extracts were combined with the main hexane solution. Drying (K_2CO_3), concentration, and distillation of the hexane residue gave 96 g (68%) of **33**: bp 135–136°; ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 3.8 (s, 2), 2.4 (m, 1), 1.0–1.2 (s, 6; d, 6).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.34; H, 10.94; N, 10.00.

Dimethylketen-*N*-(3-trimethylsiloxy-2-methyl)-2-propylimine (34).—The preparation was the same as that described for **7** using 0.12 mol of lithium diisopropylamide, 14.1 g (0.1 mol) of 2-isopropyl-2-oxazoline (**33**), and 7.68 g (0.12 mol) of trimethylchlorosilane in 70 ml of THF: yield 13.2 g (62%); bp 65–67° (17 mm); ir (film) 2021 cm^{-1}; nmr (CCl_4) δ 3.3 (s, 2), 1.6 (s, 6), 1.05 (s, 6), 0.5 (s, 9).

Anal. Calcd for $C_{11}H_{23}NOSi$: C, 61.97; H, 10.86; N, 6.57. Found: C, 61.69; H, 10.58; N, 6.73.

Ketones 13. General Procedure.—The following procedure is typical for all ketones **13** in Table I listed in entries 1–12.

A 1 *M* THF solution of the 2-isoalkyloxazines **12**, previously cooled to −78° under nitrogen with stirring, was treated in a dropwise manner with 2.1 equiv of the organolithium reagent. After addition was complete, the solution was allowed to warm to room temperature and stirred for 3 hr (overnight stirring was also performed with no detrimental effects). The resulting solution was quenched in 3–4 volumes of water and the aqueous mixture was extracted repeatedly (3–4 times) with ether, dried (K_2CO_3), and concentrated. The crude tetrahydrooxazine (0.02 mol) was dissolved in aqueous oxalic acid (5 g of oxalic acid in 40 ml of water) and heated to reflux for 1.5 hr, after which the aqueous solution was extracted with ether. The latter extracts were washed with 10% sodium carbonate solution, dried (K_2CO_3), and concentrated, affording the crude ketones **13**. Purification was accomplished by distillation and verified by vapor phase chromatography, infrared, nmr, and mass spectra. Known ketones were identified through solid derivatives. (See footnote *c*, Table I).

Ketones 16. General Procedure.—The following procedure is typical for ketones **16** in Table I, entries 13–17.

Prior to the aqueous quenching step in the procedure for **13** above, the solution containing the lithioenamine adduct was cooled to 0–5°. Addition of 1.1 equiv of an alkyl iodide was performed slowly in a dropwise fashion owing to the exothermic nature of the reaction. Stirring was continued after complete addition for 4–12 hr and then the reaction mixture was quenched in water, isolated, and identified as above.

Ketones 24 and 25 Prepared by Successive Addition of *n*-Butyllithium and a Grignard Reagent.—The preparation leading to **24a** is typical of this technique. A 1 *M* solution of **20** (R = Et) in THF was treated with 1.0 equiv of *n*-butyllithium at −78° and the resulting solution was allowed to warm to room temperature under nitrogen and with continuous stirring. The addition of 1.1 equiv of ethereal methylmagnesium bromide followed at room temperature and the mixture was stirred for 12–15 hr. Quenching in water, extraction with ether, drying (K_2CO_3), and concentration left an oil (tetrahydro-1,3-oxazine). The infrared spectrum exhibited medium-intensity bands for NH and OH (3200–3300 cm^{-1}) and C=N (1660 cm^{-1}). The C=N and OH absorptions are due to the open-chain tautomer of the tetrahydro-1,3-oxazine. Hydrolysis in 2 *M* oxalic acid solution (reflux 1.5 hr) gave, after ethereal extraction, the ketone **24a** [60% based upon **20** (R = Et)]: ir (film) 1710 cm^{-1}; nmr (CCl_4) δ 7.2 (br s, 5), 3.4 (t, J = 7 Hz, 1), 1.9 (s, 3), 1.8 (m, 2), 0.8 (t, 3); *m/e* 162; semicarbazone mp 198–199° (lit.[22] mp 189–190°).

The preparation of **24** was accomplished in the same manner using **20** (R = Me), *tert*-butyllithium, and methylmagnesium bromide. The yield based upon **20** was 59.3%: ir (film) 1709 cm^{-1}; nmr (CCl_4) δ 7.3 (br s, 5), 3.7 (q, 1), 1.9 (s, 3), 1.4 (d, 3); *m/e* 148; semicarbazone mp 173–175° (lit.[23] mp 172–173°).

The preparation of **25** was accomplished in a similar manner using a 1 *M* solution of **20** (R = *n*-amyl) and 1.0 equiv of *tert*-butyllithium, followed by 1.0 equiv of ethylmagnesium bromide. After stirring for 12–15 hr, the solution was cooled to 0° and 1.0 equiv of methyl iodide was added dropwise. The solution, containing a pale yellow suspension was stirred for 15 hr at room temperature and quenched in water. Extraction and drying in the usual manner gave 76% of **25** which was identical in all respects with **16** (entry 17 in Table I).

Ketones 27 from the Ketenimine *O*-Trimethylsilyl Ether 7. A. 2-Benzoyl-2-methylhexane (27, Entry 1).—The preparation of this ketone may be considered typical for entries 1–8 in Table II.

A solution containing 0.03 mol of phenylmagnesium bromide in 40 ml of THF was treated with 4.83 g (0.02 mol) of the ketenimine **7** and heated to reflux overnight. The reaction mixture was cooled to 0° and *n*-butyl iodide (4.05 g, 0.02 mol) was added dropwise at this temperature (exothermic reaction). After complete addition, the solution was heated to reflux overnight and then concentrated *in vacuo*. The residue was dissolved in aqueous oxalic acid (80 ml of 10% solution) and heated to reflux for 2 hr. Ether extraction of the aqueous solution, washing of the extracts with saturated sodium bicarbonate, drying (Na_2SO_4), and evaporation left 4.01 g (95%) of crude ketone. Distillation afforded 3.01 g (74%): bp 64–65° (0.2 mm); ir (film) 1680 cm^{-1}; nmr (CCl_4) δ 7.6–7.8 (m, 2), 7.2–7.5 (m, 3), 0.6–1.8 (m, 15).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.03; H, 9.75.

B. 2-Benzoyl-2-bromopropane (27, Entry 9).—A solution containing 0.03 mol of phenylmagnesium bromide in 40 ml of THF was treated with 4.83 g (0.02 mol) of **7** and heated to reflux for 16 hr. Upon cooling to 0°, bromine (4.8 g) was added dropwise and the solution was allowed to stir at room temperature for 15 hr, after which it had solidified. The mass was heated at reflux for 1 hr and then the solvent was removed under rotary evaporation. Hydrolysis of the residue with 80 ml of 10% oxalic followed by ethereal extraction, bicarbonate washing, drying, and concentration gave the bromo ketone:[24] 1.8 g (39.7%); bp 81–83° (0.65 mm); ir (film) 1670 cm^{-1}; nmr (CCl_4) δ 8.0–8.3 (m, 2), 7.4–7.6 (m, 3), 2.0 (s, 6).

Anal. Calcd for $C_{19}H_{11}OBr$: C, 52.86; H, 4.84. Found: C, 52.47; H, 4.69.

C. 1-Hydroxy-3,3-dimethyl-4-octanone (27, Entry 11).—Addition of *n*-butyllithium(0.03 mol) to **7** (4.83 g, 0.02 mol) in 40 ml of THF at room temperature gave a clear solution which was stirred at this temperature for 15 hr. Ethylene oxide (2.64 g, 0.06 mol) was added at 0° and heated to reflux for 3 hr in the presence of a Dry Ice–acetone condenser. Most of the solvent was removed by rotary evaporation and 80 ml of 10% oxalic acid was carefully added. After this exothermic reaction had subsided, the mixture was heated to reflux for 30 min and isolation of the organic material was accomplished in the manner given above. The residual crude product was distilled to yield 1.8 g (60%) of the hydroxy ketone, bp 113–116° (0.5 mm); ir (neat) showed weak carbonyl (1710 cm^{-1}) and enol ether (1688 cm^{-1}) bands as well as a weak OH (3400–3500 cm^{-1}). The nmr spectrum was also indicative of a mixture of ketone, hemiacetal, and enol ether (dehydrated hemiacetal). The mass spectrum (8, 70 eV) gave a parent ion only at *m/e* 154 (dehydrated hemiacetal). The moisture sensitivity of this compound was indicated by its elemental analysis which corresponded to the hydroxy ketone and/or the hemiacetal.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.78; H, 11.63.

Ketone 27 (entry 10) was prepared in the same manner as the ketone above using phenylmagnesium bromide, **7**, and ethylene oxide: yield 30%; mp 119–120°; *m/e* 192; ir (KBr) 3480 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.8 (m, 5), 4.0–4.3 (d of d, 2), 2.6 (s, 1, exchanged with D_2O), 1.4–2.5 (m, 2), 1.2 (s, 3), 0.6 (s, 3). This compound existed solely as the hemiacetal.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.70; H, 8.35.

Dimethylketen-*N*-(4 methoxy-2-methyl)-2-pentylimine (28).—2-Isopropyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (**5**, 16.9 g, 0.1 mol) was added to a solution of lithium diisopropylamide (0.11 mol) in THF at 0°. The reaction mixture was stirred for

(22) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 2709.

(23) A. Witzel, A. Botta, and K. Dimroth, *Chem. Ber.*, **98**, 1465 (1965).

(24) Trimethylphenylsilane was observed as a minor product (15–25%) in this and all other reactions of **7** with phenylmagnesium bromide. Hence the excess of Grignard reagent utilized in these experiments.

3 hr at room temperature, 19.0 g (0.15 mol) of dimethyl sulfate was added, and stirring was continued for an additional 3 hr. After addition of dilute potassium hydroxide solution (1 *M*) at 0–5°, the solution was stirred for 45 min to decompose excess dimethyl sulfate. The aqueous solution was extracted with ether, and the extracts were dried (K_2CO_3) and concentrated. The residue was distilled, producing several fractions: (a) 25–35° (0.4 mm), (b) 35–40° (0.4 mm), and (c) 40–44° (0.4 mm). Fraction c contained the ketenimine ether **28** along with ~10% of starting oxazine **5**. Repeated attempts at column chromatography failed to completely remove **5**. Total ketenimine recovery was 6.6 g (35%), which included 10% oxazine: ir (neat) 2021, 1667 cm^{-1}; nmr ($CDCl_3$) δ 4.0 (m, 0.1 oxazine), 3.4 (m, 0.9), 3.2 (s, 2.7), 1.7 (s, ~6), 0.9–1.4 (m, 11).

Reaction of 28 with Phenylmagnesium Bromide and Ethyl Iodide to Give 30.—Crude **28** (~90% purity) from above was treated in the usual manner with phenylmagnesium bromide (1.5 equiv) at room temperature in THF for 12 hr. This was followed by addition of 1.1 equiv of ethyl iodide to the cooled solution (0°) and the solution was again stirred for 12 hr. The usual isolation procedure led to the ketone **30** in 90% yield, which was identical in every respect with **27** (entry 7, Table II) obtained from **7**.

Dimethylketen-*N*-(4-benzoyloxy-2-methyl)-2-pentylimine (29) and Its Pyrolysis to 31.—The benzoyloxyketenimine **29** was prepared in a manner analogous to **28** by the addition of benzoyl chloride to the lithioketenimine **6** prepared above. The main difference in preparation lies in the fact that the solution was heated to reflux for 1 hr after addition of the benzoyl chloride. The mixture was decomposed in cold 1 *N* potassium hydroxide and rapidly extracted with ether, dried (K_2CO_3), and concentrated. Bulb-to-bulb distillation at 0.2 mm gave a colorless oil (~30%) which was <90% pure: ir (neat) 2020, 1718 cm^{-1}; nmr ($CDCl_3$) δ 8.02 (m, 2), 7.45 (m, 3), 5.0 (m, 1), 1.6 (s, 6), 1.5 (m, 2), 1.2 (d, 3), 1.0 (s, 6). This product contained ~10% of the starting oxazine **5**. Pyrolysis of **29** was accomplished by heating (160–200°) at 0.5 mm until a distillate appeared (110–130°). Vpc examination of the distillate gave three peaks which were collected. The minor peaks were characterized as isobutyronitrile and the 2-isopropyloxazine **5** originally present. The major peak collected was consisted with the unsaturated ester **31**: ir (neat) 1715 cm^{-1}; nmr (CCl_4) δ 8.0 (m, 2), 7.3 (m, 3), 5.3 (sextet, 1), 4.8 (br s, 2), 2.3 (d of t, 2), 1.8 (s, 3), 1.3 (d, 3); *m/e* 204.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.37; H, 7.79.

Registry No.—**7**, 36867-23-9; **12** (R_1 = Ph; R_2 = *n*-Bu), 39576-28-8; **24**, 769-59-5; **24a**, 1528-39-8; **28**, 39576-31-3; **29**, 39576-32-4; **31**, 39576-33-5; **33**, 34575-25-2; **34**, 39575-64-9; isobutyric acid, 79-31-2; 2-amino-2-methylpropanol, 124-68-3.

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1,4 Addition of Organometallics to 2-Alkenyldihydro-1,3-oxazines. A Synthesis of α-Substituted Aldehydes and Ketones[1]

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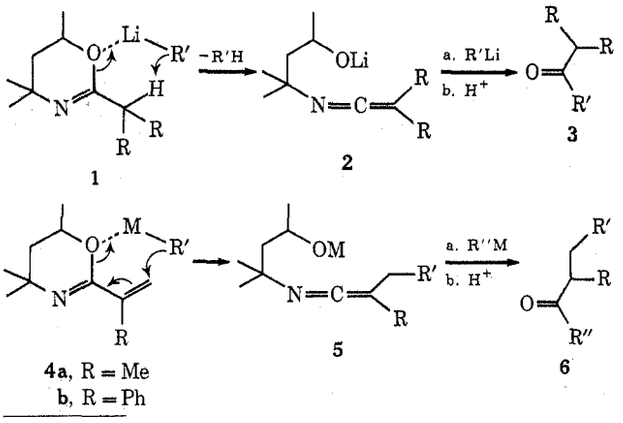
Addition of organolithium and Grignard reagents to 2-alkenyloxazines (**4a** and **4b**) leads to alkylation *via* the ketenimine intermediate (**10**). The latter may be converted to α-methyl- or α-phenylaldehydes or, in turn, may be sequentially alkylated with alkyl halides to the corresponding ketones. The formation of ketenimines may be accomplished by nucleophilic addition to the alkenyloxazines, thus eliminating the necessity of a strong base to effect these transformations. The scope and limitation to this carbonyl synthesis are presented.

The base-induced rearrangement of 2-isoalkyloxazines (**1**) to ketenimines (**2**) following proton abstraction has been shown to lead to a variety of α-branched ketones (**3**).[3] It was of interest to determine if the oxazine–ketenimine rearrangement could be effected by addition of organometallics to 2-alkenylozaxines (**4**). Implementation of this process would further expand the scope of the ketone synthesis by incorporation of an additional β-methylene group in the ketenimine **5** and the resulting ketone **6**. Furthermore, organometallic addition to **4**, since it does not require proton abstraction as in **1**, may be possible with Grignard reagents as well as organolithiums. This, in itself, would be worthwhile modification owing to the more convenient nature of Grignard reagents.



The oxazines chosen for this study were the 2-isopropenyl (**4a**) and the 2-(α-styryl) (**4b**) derivatives prepared from methacrylonitrile and the diol (eq 1) and condensation of the benzyloxazine with formaldehyde (eq 2), respectively. Organometallic addition to the 2-vinyloxazine **4** (R = H) were precluded owing to the polymerization already noted for this system.[4]

(1) Part XXI of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see ref 3.

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