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.

Acknowledgment.—The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

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

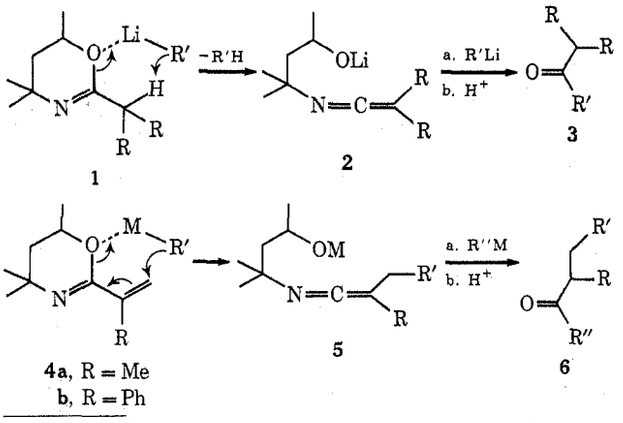
A. I. MEYERS,*[2] A. C. KOVELESKY, AND A. F. JURJEVICH

Department of Chemistry, Louisiana State University in New Orleans, Lakefront, New Orleans, Louisiana 70122

Received February 6, 1973

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.



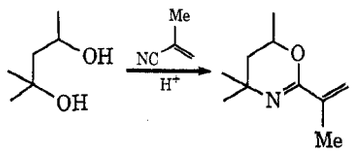
The oxazines chosen for this study were the 2-isopropenyl (**4a**) and the 2-(α-styryl) (**4b**) derivatives prepared from methacrylonitrile and the diol (eq 1) and condensation of the benzyloxazine with formaldehyde (eq 2), respectively. Organometallic addition to the 2-vinyloxazine **4** (R = H) were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

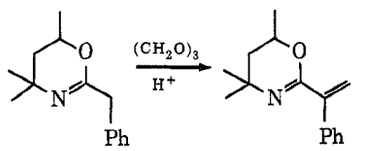
(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

(3) A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973).

(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).



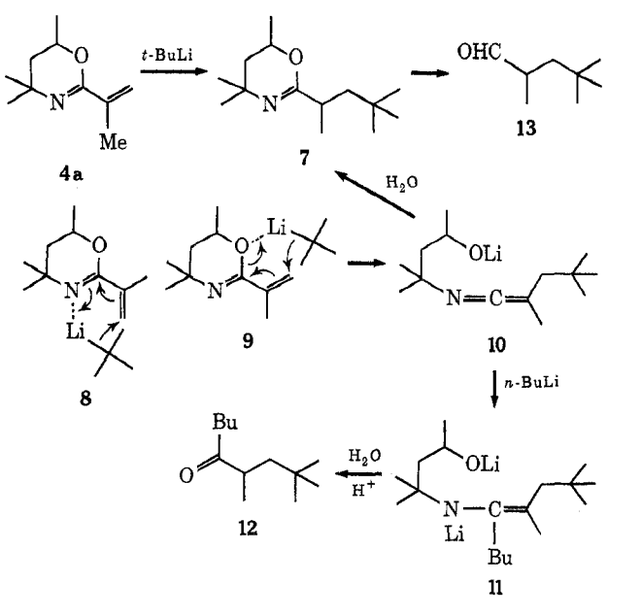
4a (1)



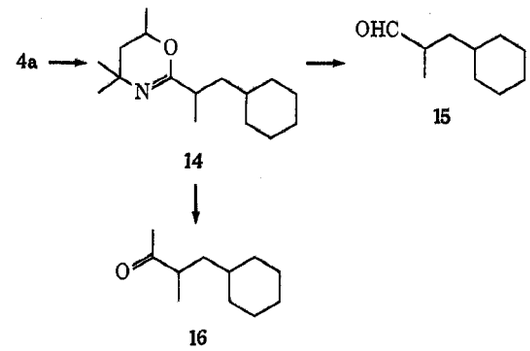
4b (2)

Results and Discussion

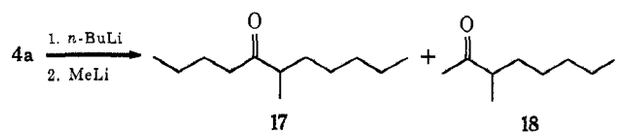
The addition of 1.0 equiv of *tert*-butyllithium to **4a** in THF at −78° produced after quenching a high yield of an oxazine which was characterized as the *tert*-butyl adduct **7**. Although the product may be assumed to merely arise by the familiar 1,4-conjugate addition (**8**), this was not in keeping with the alkylation mechanism in other oxazine systems.[3] A more reasonable mechanism should involve the initial complex **9** followed by ring opening to the ketenimine **10**. Hydrolysis then results in recyclization to the oxazine **7**. In order to confirm this mode of reaction, *tert*-butyllithium was again added to **4a** at −78° and, after 1 hr, 1.2 equiv of *n*-butyllithium was introduced. If the ketenimine **10** is indeed an intermediate, the presence of *n*-butyllithium should convert it to the adduct **11**. The latter is most easily characterized by hydrolysis to the corresponding ketone **12**. This was found to be the case, as the ketone **12** was isolated in 77% overall yield (from **4a**). These data confirm that the oxazines **4a** may be smoothly alkylated and transformed into the ketenimine by addition of organometallics. The initial goal of the study was therefore achieved. Furthermore, the oxazine **7** was readily reduced ($NaBH_4$) and hydrolyzed (oxalic acid) to the aldehyde **13** by the previously described technique.[4] It was now



necessary to determine whether Grignard reagent addition to **4a** would lead to similar results. Treatment of **4a** with cyclohexylmagnesium bromide at −60° in THF provided the cyclohexyloxazine **14**, which was transformed into the aldehyde **15** in 78% overall yield. If the addition of the Grignard reagent was followed by methyllithium, the corresponding ketone **16** was ob-



tained in 82% overall yield. Thus, it is clear that, without the necessity of a strong base, the alkenyloxazines may also serve as useful precursors to carbonyl compounds by utilizing Grignard reagents, organolithiums, or a combination of both. A serious limitation of this method soon became apparent when a primary organometallic (*n*-BuLi, −78°) was added to **4a** followed by methyllithium. The product isolated was found to contain both the *n*-butyl (**17**) and methyl (**18**) ketones



in approximately a 1:1 ratio. This behavior is consistent with the fact that relatively unhindered organometallics will readily add to the newly formed ketenimines (*i.e.*, **10**) giving rise to precursors which lead to **17**. The methyllithium, added subsequently, then must compete with the *n*-butyllithium still present. This result further suggested that the use of 2 equiv of organometallic introduced into a solution of **4a** should lead to a more efficient synthesis of **17**. This was indeed found to be the case, as 2 equiv of *n*-butylmagnesium bromide gave **17** in 79% yield upon addition to **4a**. When 2 equiv of *tert*-butyllithium was added to **4a** under reflux conditions, in an attempt to form **19**, the major product recovered was **7** (40%) along with **19** (6%) and **20** (31%). It may be concluded from this experiment that the bulky *tert*-butyllithium reacts only at "elevated temperatures" (>20°) with the ketenimine, and prolonged heating (or standing at room temperature) results in attack by the base upon the solvent. Tetrahydrofuran is converted to its anion **21** by butyllithium, which is known to cleave to

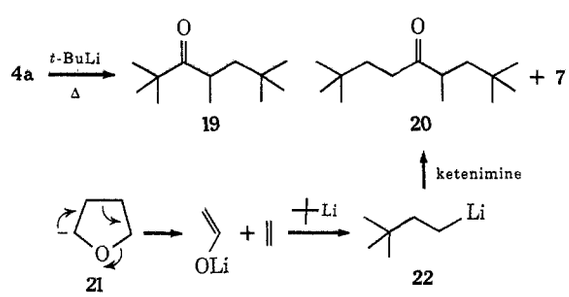
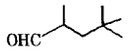
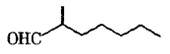
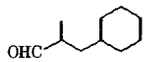
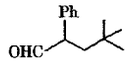
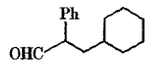
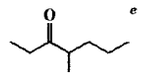
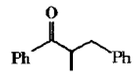
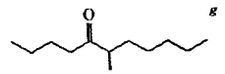
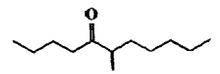
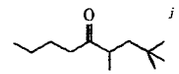
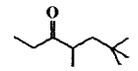
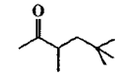
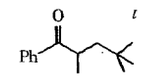
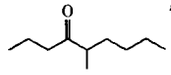
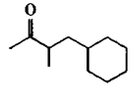
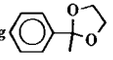
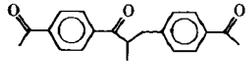
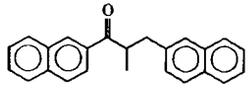
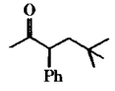
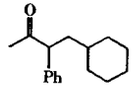
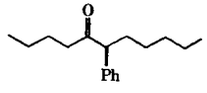
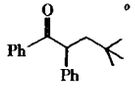
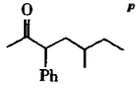
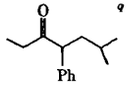


TABLE I

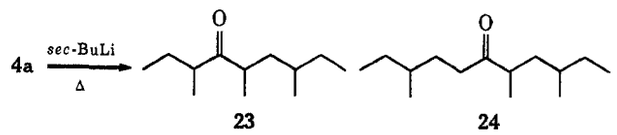
ALDEHYDES AND KETONES FROM 2-ALKENYLDIHYDRO-1,3-OXAZINES 4a AND 4b

Entry	Oxazine	RM	Registry no.	R′M	Carbonyl compd[a]	Registry no.	Yield, %	2,4-DNP mp, °C	2,4-DNP registry no.	Mp or bp, °C (mm)	M+	ν, cm⁻¹ (film)
1	4a[r]	*t*-BuLi	594-19-4	$NaBH_4$		17414-46-9	43	145–146[b]	39575-80-9	44–46 (20)	128	1720, 2695
2	4a	*n*-BuLi	109-72-8	$NaBH_4$		16630-91-4	32	104–105[c]	39576-31-9	50–52 (20)	128	1720, 2697
3	4a	$C_6H_{11}MgBr$	931-50-0	$NaBH_4$		20514-52-7	78	146–148[d]	20514-53-8	106–109 (20)	154	1720, 2699
4	4b[s]	*t*-BuLi		$NaBH_4$		25387-09-1	71	172–173[d]	25387-10-4	64–66 (0.1)	190	1722, 2701
5	4b	$C_6H_{11}MgBr$		$NaBH_4$		25387-11-5	94	155–157[d]	25387-12-6	95–97 (0.08)	216	1720, 2699
6	4a	EtMgBr	925-90-6	EtMgBr		6137-11-7	67	47–48[d]	14807-81-9	52–55 (25)	128	1707
7	4a	PhMgBr	100-58-3	PhMgBr		4842-43-7	47	131–133[f]	17282-48-3	113–115 (0.05)	224	1675
8	4a	*n*-BuLi		*n*-BuLi		26825-70-7	23	Oil[h]	39575-84-3	63–64 (0.45)	184	1705
9	4a	*n*-BuMgBr	693-03-8	*n*-BuMgBr			79					
10	4a	*t*-BuLi		*n*-BuLi		26933-75-5	60	86–87[d,i]	39751-38-7	73–76 (2)	184	1709
11	4a	*t*-BuLi		EtMgBr		26825-72-9	67	77–79[d,i]	39575-85-4	77–80 (2)	156	1710
12	4a	*t*-BuLi		MeLi		26825-71-8	73	64–65[k]	39575-75-2	68–70 (25)	142	1710
13	4a	*t*-BuLi		PhMgBr		39575-71-8	31	115–116	39575-76-3	83–85 (0.3)	204	1680

14	4a	*n*-PrMgBr	927-77-5	*n*-PrMgBr		26825-73-0	79	Oil[h]	39575-77-4	90–95 (25)	156	1705
15	4a	$C_6H_{11}MgBr$		MeLi		27206-64-0	82	104–106[d]	39575-78-5	120–123 (25)	168	1705
16	4a	 (3.1 equiv)	39575-67-2			39575-73-0	62	72–73[n]		72–73	308	1680
17	4a	2-NaphthMgBr (3.2 equiv)	21473-01-8			39575-74-1	92	61–63[n]		61–64	324	1672
18	4b	*t*-BuLi		MeLi		25386-99-6	84	120–122[d]	25387-00-2	74–78 (1.5)	204	1712
19	4b	$C_6H_{11}MgBr$		MeLi		25387-01-3	79	126–127[d]	25387-02-4	102–105 (0.05)	230	1708
20	4b	*n*-BuMgBr		*n*-BuMgBr		25387-03-5	68	Oil[d,h]	39575-79-6	96–97 (0.01)	246	1710
21	4b	*t*-BuLi		PhMgBr			<10%			Semisolid		1670
22	4b	*sec*-BuLi	598-30-1	MeLi		25387-05-7	65	84–86[d]	25387-06-8	84–88 (0.2)	204	1710
23	4b	*i*-PrLi	1888-75-1	EtMgBr		25387-07-9	65	93–95[d]	25387-08-0	70–71 (0.2)		1710

[a] All compounds (except entry 41) gave satisfactory elemental analyses (±0.03%). [b] A. Byers and W. J. Hickenbottom, *J. Chem. Soc.*, 1328 (1948). [c] H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959). [d] New compounds, analytical data in *a* above. [e] J. Dubois and R. Luft, *Bull. Soc. Chim. Fr.*, 1184 (1954), report bp 53–54° (10 mm). [f] L. I. Smith and J. R. Holum, *J. Amer. Chem. Soc.*, **78**, 3417 (1956). [g] F. H. Owens, W. L. Myers, and F. W. Zimmerman, *J. Org. Chem.*, **26**, 2288 (1961), report bp 76–78° (0.8 mm). [h] 2,4-DNP derivative was an oil and semicarbazone could not be prepared. [i] Semicarbazone. [j] Distilled product contained 13% of ketone in entry 8. Pure material collected by vpc (10% UC-W98, 130°). [k] M. F. Ansell, W. H. Hickenbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955). [l] H. Riviere-Larramona, *C. R. Acad. Sci.*, **244**, 1653 (1957), reports bp 80–82° (0.5 mm). [m] S. G. Powell and A. T. Nielsen, *J. Amer. Chem. Soc.*, **70**, 3677 (1948), report bp 68–69° (6 mm). [n] Melting point of ketone; no derivative was prepared. [o] Product could not be obtained pure although spectral evidence was consistent with structure. This appears to be a limiting case for this process. [p] Crude product contained 24% lower boiling ketone, which was identified as 3-phenyl-4-pentanone. [q] Distilled ketone contained 16% of another carbonyl compound, presumably 4-phenyl-3-heptanone. Pure material collected by vpc; see ref *j* above. [r] Registry no., 39575-65-0. [s] Registry no., 38709-86-3.

the enolate of acetaldehyde and ethylene.[5] Reaction of *tert*-butyllithium with ethylene gave the homologated alkyllithium **22**, which adds to the ketenimine producing **20**. In a similar reaction, **4a** was treated with 2–2.5 equiv of *sec*-butyllithium and afforded a mixture of ketones, **23** (35%) and **24** (5%). The latter ketone

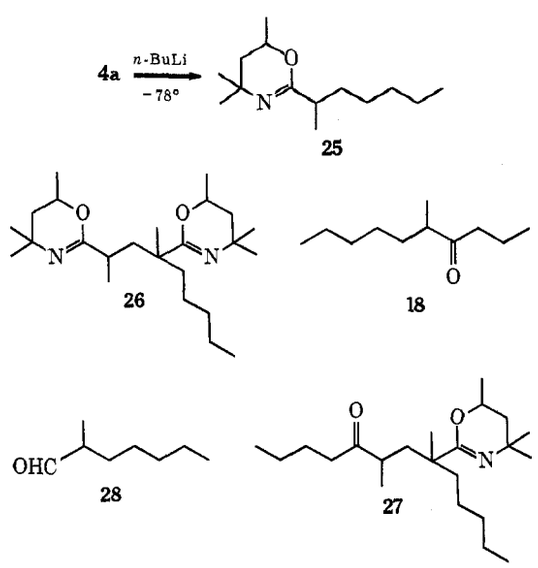


23 **24**

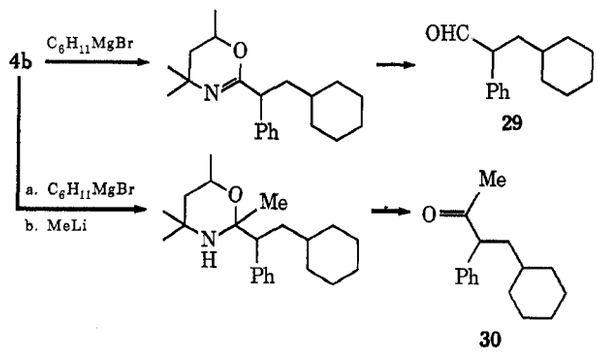
was formed by conversion of *sec*-butyllithium to its ethylene homolog prior to attack on the ketenimine. It should be noted that the "normal" ketone **23** is by far the major product, which implies that *sec*-butyllithium is not so efficient a base as *tert*-butyllithium with regard to proton abstraction on THF. In other studies,[3] it was found that *tert*-butyl- and *sec*-butyllithium were quite useful as nucleophiles for addition to ketenimines. Thus, it is possible to utilize these bulky alkyllithiums to introduce two alkyl groups into the final ketone. By introduction of these reagents at −78°, the likelihood of sequential addition is remote and subsequent treatment with an excess (20–25%) of the more reactive primary organometallic leads to ketones virtually free of isomers.

Several attempts at reaction of 1.0 equiv of a primary organometallic to **4a** were made. Since both *tert*-butyl and cyclohexyl moieties were successfully incorporated into the oxazine (**7** and **14**, respectively), *n*-butyllithium was examined under various conditions in order to obtain **25**. Careful temperature control, rates of addition, orders of addition, and stoichiometric variations all lead to four products (**25**, **26**, **18**, and **27**). The latter two were isolated after oxalic acid hydrolysis. Although **25** was the desired product, its initially formed carbanion (from butyllithium addition to **4a**) undoubtedly was sufficiently long lived to add once again to **4a**, producing **26**. The isolation of ketooxazine **27** must have been the result of the reaction of ketenimine of **26** with butyllithium.

However, **25** could be isolated in 45% yield and transformed by borohydride reduction and oxalic acid

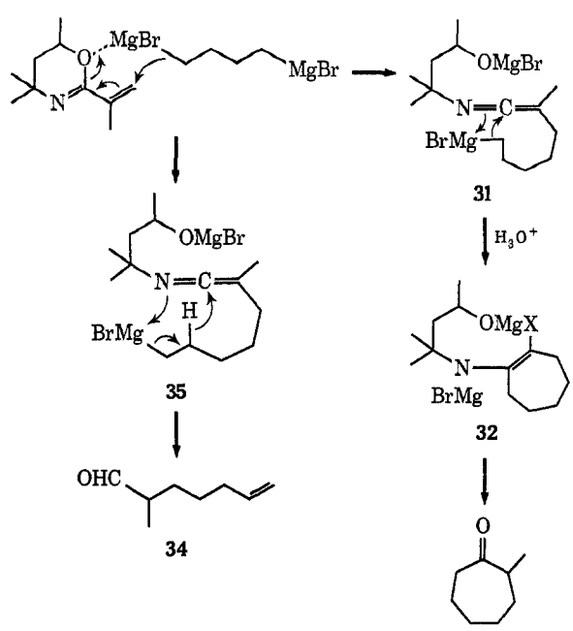


hydrolysis to the aldehyde **28**. Investigation of the 2-(α-styryl)oxazine **4b** as a source of α-phenylaldehydes (**28**) and ketones (**29**) provided the expected results.



The reactions were performed in a manner comparable to those involving **4a** and the limitations encountered were likewise similar. The carbonyl compounds prepared[6] by singular or multiple organometallic treatment with **4a** and **4b** are summarized in Table I. It may be mentioned that the steric retardation to addition of bulky organometallics to the ketenimine intermediate (entries 13 and 21) is manifested in the lower yields of ketones. This effect has already been noted in reactions with other ketenimines.[3]

In an effort to synthesize α-methyl cyclic ketones *via* this method, it was anticipated that a double Grignard reagent would add twice in an intramolecular fashion. Treatment of **4a** in refluxing ether with the *di*-Grignard reagent of 1,4-dibromobutane led to **18** (16.5%), 2-methylcycloheptanone (**33**) (12%), and the unsaturated aldehyde **34** (71.5%). The unexpectedly high percentage of the aldehyde must have arisen *via* reduction of the ketenimine intermediate **35**, whereas the cycloheptanone is derived from the anticipated intermediates **31** and **32**. Changing the solvent to THF and repeating the reaction at room temperature gave the cycloheptanone in 10% yield and **18** in 90%



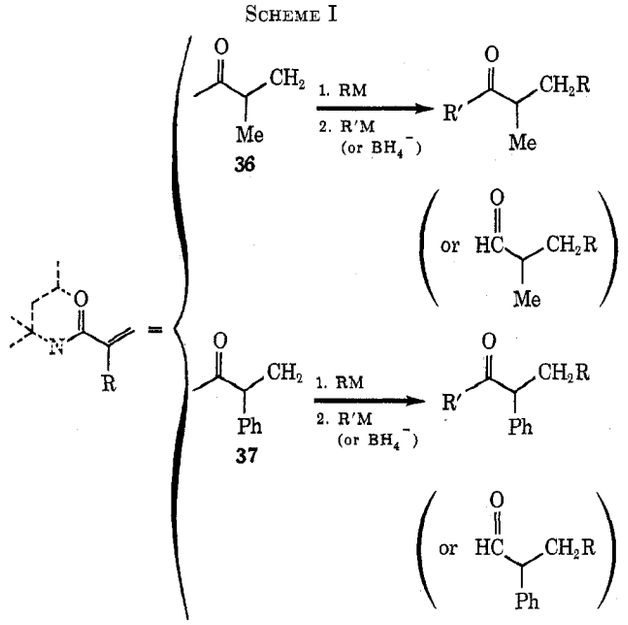
(5) P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955); P. Tamboulian, *et al.*, *J. Org. Chem.*, **38**, 322 (1973).

(6) Preliminary reports have appeared: A. I. Meyers and A. C. Kovelesky, *J. Amer. Chem. Soc.*, **91**, 5887 (1969); A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 4809 (1969).

yield. The aldehyde **34** was present in only trace amounts. Thus, the reduction (*via* **35**) was severely retarded in THF and this could be due to enhanced solvation of the metal in **35** minimizing the need for coordination with the lone pair on nitrogen. Since the goal of this effort was to open a route to α-methyl cyclic ketones and the results in this direction were disappointing, the study was discontinued.

In summary, the synthetic utility of **4a** and **4b** has been demonstrated by their ability to serve as synthons (**36** and **37**) for α-branched ketones and aldehydes. The mode of introduction of substituents into these synthons is outlined in Scheme I.

SCHEME I



Experimental Section[7]

The organolithium reagents used in this study were obtained from The Lithium Corporation of America, Bessemer City, N. C., as the following solutions: methyllithium (1.5 *M* in ether), *n*-butyllithium (1.6 *M* in hexane), *sec*-butyllithium (1.2 *M* in hexane), isopropyllithium (1.6 *M* in hexane), *tert*-butyllithium (1.24 *M* in pentane). All the Grignard reagents were prepared in ether (~3 *M*) just prior to use.

2-Isopropenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (4a) was prepared by the previously described procedure[4] using 118 g (1.0 mol) of 2-methyl-2,4-pentanediol, 74.0 g (1.1 mol) of methacrylonitrile, and 200 ml (96–98%) of sulfuric acid. There was obtained 83.7 g (50.2%) of a colorless liquid: bp 74–76° (25 mm); ir (film) 3100, 1650, 1620 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (br s, 1), 5.2 (br s, 1), 4.1 (m, 1), 1.9 (br s, 3), 1.6 (d of t, 2), 1.2 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.85; H, 10.18; N, 8.38. Found: C, 71.77; H, 10.12; N, 8.29.

2-(α-Styryl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (4b) was prepared by heating a solution of 75.4 g (0.32 mol) of the 2-benzyloxazine[4,8] in 250 ml of toluene to which 12.2 g (0.38 mole) of paraformaldehyde and 2 ml of trifluoroacetic acid had been added. The solution was heated for 24 hr with continuous removal of water *via* an azeotrope trap. The toluene solution was added to water, acidified to pH 2–3, and then shaken vigorously. The toluene layer was withdrawn and discarded. Neutralization of the aqueous solution gave an oil which was taken up in ether, dried (K_2CO_3), and concentrated. Distillation provided 17.5 g (47.2%) of the product: bp 93–95° (0.2 mm); ir (film) 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.1–7.6 (m, 5), 5.9 (d, 1), 5.6 (d, 1), 4.2 (m, 1), 1.7 (m, 2), 1.3 (d, 3), 1.2 (s, 6).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.74; H, 8.26; N, 6.09.

Typical Procedures. 2,4,4-Trimethylpentanal (13).—A solution composed of 10.5 g (63 mmol) of **4a** in 125 ml of dry tetrahydrofuran was cooled to −78° under nitrogen. To the stirred solution was added 55.6 ml of *tert*-butyllithium in pentane (1.24 *M*) in a dropwise manner over a 30-min period. After stirring at −78° for 1 hr, the reaction mixture was decomposed by careful addition of water and the entire mixture was diluted into 250 ml of ice water. The solution was acidified (pH 2–3) and extracted with pentane. The pentane extracts were discarded and the aqueous solution was neutralized with 35% sodium hydroxide. The alkaline solution was extracted with ether, dried (K_2CO_3), and concentrated, leaving 13.3 g of an oil. A portion was distilled, bp 110–113° (25 mm), to give pure **7**, ir (film) 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{27}NO$: C 74.61; H, 12.08; N, 6.21. Found: C, 74.74; H, 11.95; N, 6.18.

The crude oxazine **7** was subjected to borohydride reduction in the following manner. To a 600-ml beaker was added 100 ml of THF, 100 ml of 95% ethanol, and 12.0 g (0.053 mol) of **7**. The mixture was cooled between −35 and −40° with an acetone bath to which Dry Ice was added as needed. Hydrochloric acid (9 *N*) was added to the magnetically stirred solution until an approximate pH of 7 was obtained. The pH was monitored by periodic checks with pH paper. Sodium borohydride solution was prepared by dissolving 2.0 g (0.053 mol) in a minimum amount of water (4–5 ml) to which one drop of 40% sodium hydroxide was added. The sodium borohydride solution and the 9 *N* hydrochloric acid solution were added to the stirred solution alternately so that a pH of 6–8 was maintained. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of this borohydride solution was complete, the solution was stirred with cooling for 2 hr (pH 7 was maintained by the occasional addition of hydrochloric acid solution). The contents were then poured into approximately 100 ml of water and made basic by the addition of 40% sodium hydroxide solution. The layers were separated and the aqueous solution was extracted with three 25-ml portions of diethyl ether. The combined organic extracts were washed with 100 ml of saturated sodium chloride solution and dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give 11.7 g of crude tetrahydro-1,3-oxazine. Only a slight band at 1660 cm^{-1} was evident in the infrared, indicating almost complete reduction. The crude tetrahydro-1,3-oxazine from above (11.4 g 0.051 mol) and an oxalic solution (32.0 g per 100 ml of water) were heated to reflux for 2 hr. The cloudy solution was extracted with diethyl ether (three 50-ml portions) and the extracts were washed with 5% sodium bicarbonate solution and dried (Na_2SO_4). Removal of the solvent and distillation gave 3.1 g (48%) of **13** (43% overall).

1-Methyl-3-cyclohexylpropionaldehyde (15).—Alkylation of **4a** was performed by addition of a solution of cyclohexylmagnesium bromide (prepared in 75 ml of ether from 23.4 ml of cyclohexyl bromide and 5.6 g of triply sublimed magnesium) to 9.9 g (59 mmol) of **4a** in 150 ml of THF at −60°. The solution was allowed to slowly warm to room temperature overnight under a nitrogen atmosphere with magnetic stirring. Isolation of the oxazine **14**, reduction, and cleavage to the ketone **15** were also accomplished as described in the preceding experiment. Pertinent data are presented in Table I.

3-Methyl-4-cyclohexyl-2-butanone (16).—A solution of 10.3 g (61 mmol) of **4a** in 150 ml of THF was cooled to −60° under nitrogen. To the stirred solution was added 75 ml of 2.5 *M* ethereal cyclohexylmagnesium bromide over a 30-min period. After addition was complete, the reaction was slowly allowed to reach room temperature, at which point 49.2 ml of 1.5 *M* ethereal methyllithium was added. The reaction mixture was stirred overnight at room temperature and then the excess Grignard was carefully decomposed by water. Dilution of the mixture in 250 ml of ice–water was followed by acidification with 2 *N* hydrochloric acid. The two-phase mixture was extracted several times with pentane and the pentane solutions were discarded. The aqueous solution was neutralized with 40% sodium hydroxide and subsequently extracted with ether. Drying (K_2CO_3) and concentration of the ethereal extracts provided 16.2 g of crude product whose infrared spectrum displayed only a slight C=N absorption at 1660 cm^{-1}. The oily tetrahydrooxazine (13.7 g)

(7) Microanalyses performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlabs, Atlanta, Ga. Mass, infrared, and nmr spectra were taken on Hitachi RMU-6, Perkin-Elmer 257, and Varian A-60 instruments, respectively. Melting points and boiling points are uncorrected.

(8) R. G. Neville, *J. Org. Chem.*, **24**, 111 (1959).

was added to an oxalic solution (34.3 g in 100 ml of water) and heated to reflux for 2 hr. Ethereal extraction of the cooled solution afforded the ketone, which after distillation provided 8.3 g (82% based on **4a**). Physical data are presented in Table I.

5,5-Dimethyl-3-phenyl-2-hexanone (Table I, Entry 18).—A solution of 6.9 g (30 mmol) of **4b** in 150 ml of THF was cooled to −78° under nitrogen. To the stirred solution was added 20.2 ml (1.8 *M*) of *tert*-butyllithium over a period of 20 min. The reaction was then stirred at −78° for 2 hr, after which 25.0 ml of ethereal (1.5 *M*) methyllithium was added dropwise. The reaction mixture was allowed to warm to room temperature overnight with continual stirring under nitrogen. The excess organolithium reagents were decomposed by careful addition of water (10 ml) and the contents of the flask were poured into 400 ml of ice–water. The solution was acidified (2 *N* HCl) to pH 2–3 and then extracted (3 × 75 ml) with pentane. The latter was discarded and the solution was neutralized, extracted with ether, dried (K_2CO_3), and concentrated. The residue (8.5 g, 93%) was heated for 2 hr in oxalic acid solution (18 g per 150 ml) yielding the ketone, 5.1 g (84.3% based upon **4b**).

2-Methyl-1,3-bis(4-acetylphenyl)-1-propanone (Table I, Entry 17).—A portion of a solution of 5.70 g (0.023 mol) of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane[8] in 10 ml of THF was added to 0.66 g (0.027 g-atom) of triply sublimed magnesium in 10 ml of THF and the resulting mixture was warmed in a hot-water bath with stirring to initiate the reaction. The remainder of the dioxolane solution was added dropwise at a rate sufficient to keep the reaction mixture warm. As the Grignard precipitated after addition of 80% of the solution, an additional 10 ml of THF was added.

To the warm, light yellow slurry was added 1.25 g (7.5 mmol) of **4a** in 10 ml of THF. After 2.5 hr, the mixture had turned deep purple. After stirring for 22 hr at room temperature, the reaction mixture was added to 60 ml of an ice–water mixture. Upon acidification (pH ~2) and extraction with pentane, an insoluble oil separated from the aqueous phase. When the two phases were made alkaline (~pH 8) and extracted with ether, the oil dissolved with difficulty. The ethereal extracts were dried with anhydrous potassium carbonate and the ether was removed on the rotary evaporator to give 3.24 g (87%) of a light yellow, fluorescent oil. The above residue was refluxed for 2.5 hr with 14.8 g (0.12 mol) of oxalic acid dihydrate and 120 ml of water under argon. The mixture was cooled, dichloromethane was added, and the material was stirred overnight. The layers were separated and the aqueous phase was extracted further. The combined extracts were dried with anhydrous sodium sulfate and the solvent was removed to give 1.88 g (81%) of a viscous oil which solidified on standing. Recrystallization from petroleum ether (bp 30–60°)–ether gave 1.32 g (57%), mp 72–73°. Pertinent data are given in Table I, ref *a*.

2-Methyl-1,3-bis(2-naphthyl)-1-propanone (Table I, Entry 17).—The procedure of the preceding experiment was repeated with 0.920 g (0.038 g-atom) of magnesium in 5 ml of THF, 6.47 g (0.031 mol) of 2-bromonaphthalene in 10 ml of THF, and 1.65 g (0.010 mol) of 2-isopropenyloxazine in 3 ml of THF. During the isolation of the tetrahydrooxazine, its insoluble solid hydrochloride was collected, washed with pentane, and converted back to the free base by ammonium hydroxide. The crude yield was 4.3 g (102%) of an orange-brown, taffy-like substance.

The cleavage was accomplished with 6.3 g (0.05 mol) of oxalic acid, 20 ml of water, and 30 ml of acetic acid. The dichloromethane extracts were washed with aqueous 5% sodium bicarbonate. The crude yield was 3.2 g (100%). This material was passed through an alumina column with carbon tetrachloride to give an orange oil, 2.94 g (92%), which gradually solidified. The product was purified by passage through an alumina column (pentane–ether), mp 61–64°. Pertinent data are given in Table I, ref *a*.

Reaction of 4a with 1.0 Equiv of *n*-Butyllithium.—A cold solution (−78°) [20 ml of THF and 8.8 ml of 2.25 *M* (0.02 equiv) of *n*-butyllithium in hexane] was added in a steady stream from a syringe to a cold solution (−78°) of 3.35 g (0.02 mol) of **4a** in 50 ml of THF. After stirring at −78° for 0.5 hr, 1 ml of water was added to the reaction solution. Stirring was continued for several minutes and then the mixture was added to ~200 ml of an ice–water mixture. This aqueous mixture was acidified, extracted with low-boiling ligroin, made basic, and extracted with ether. The ether extracts were dried over anhydrous $MgSO_4$, the ether was evaporated, and the residue was distilled at 1.5 mm to give three fractions: (1) 76–81°, 1.865 g; (2) 81–152°, 0.635 g; and (3) 152–155°, 0.885 g. Fraction 1 was mainly **25** (45%); fractions 2 and 3 were mixtures but fraction 3 was mainly **26** (22%). Fraction 3 was redistilled to give 0.410 g of **26**, ir (film) 1660 cm^{-1}. The mass spectrum had a very weak molecular ion at *m/e* 392 and major peaks at *m/e* 226, 168, 155, 86, and 84.

Anal. Calcd for $C_{24}H_{44}N_2O_2$: C, 73.41; H, 11.30; N, 7.14. Found: C, 73.54; H, 11.05; N, 7.28.

Fraction 1 was subjected to the standard borohydride reduction and hydrolytic cleavage to give 2-methylheptanal (**28**) (Table I, entry 2). If the crude ethereal residue obtained above was subjected to oxalic acid hydrolysis, two carbonyl compounds were produced upon distillation: (a) 6-methyl-5-undecanone (**18**, 13%), bp 63–65° (0.4 mm), and (b) **27** (~8%), bp 124–126 (0.25 mm), ir (film) 1707, 1660 cm^{-1}. The mass spectrum did not give a parent ion at *m/e* 351, but only at *m/e* 226, indicating normal ketone fragmentation, loss of *n*-butyl radical, followed by loss of carbon monoxide. This fragmentation pattern was also seen in the mass spectrum of **26**, which also exhibited a base peak at *m/e* 226.

Anal. Calcd for $C_{22}H_{41}NO_2$: C, 75.16; H, 11.75; N, 3.98. Found: C, 74.96; H, 11.86; N, 3.89.

Reaction of 4a with *sec*-Butyllithium under Reflux Conditions.—To a solution of 2.283 g (0.01366 mol) of **4a** in 30 ml of THF at −78° was slowly added 40 ml of 1.1 *M* (0.044 equiv) of *sec*-butyllithium. The resulting solution was refluxed with stirring for 59 hr. Isolation was performed in the normal manner. A crude yield of 2.34 g of ketonic products was obtained. Vpc peak area weight per cents were 80.7 and 19.3 for the desired and unexpected ketones, respectively. This corresponds to crude yields of 75% of **23** and 15.5% of **24**. Distillation from glass wool gave 0.94 g (37%) of the desired compound, **23**, bp 54–56° (0.8 mm), *m/e* 184.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.03; H, 12.99.

The first minor fraction and the material left in the pot were redistilled to give four fractions, the last of which, bp 80–85° (0.8 mm), appeared to be at least 95% higher boiling ketone. The fractions were collected from vpc to give 0.128 g (4.6%) of 3,5,9-trimethyl-6-undecanone (**24**), *m/e* 212.

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 78.99; H, 13.17.

Reaction of 4a with *tert*-Butyllithium under Reflux Conditions.—The same procedure as in the preceding experiment was used. The reaction utilized 37 ml of 1.22 *M* (0.045 equiv) *tert*-butyllithium in pentane–hexane and 2.403 g (0.0144 mol) of **4a** in 30 ml of THF. There was obtained 0.15 g (~6%) of 2,2,4,6,6-pentamethyl-3-heptanone (**19**), bp 54–58° (1.5 mm), $n^{25}D$ 1.4286 [lit.[9] bp 87–90° (16–18 mm), $n^{20}D$ 1.4288–1.4290, *m/e* 184, nmr (CCl_4) δ 0.86 [s, $CH_2C(CH_3)_3$] and 1.13 [s, $COC(CH_3)_3$], ir (neat) 1700 cm^{-1} (C=O), and 0.906 g (~31%) of 2,2,4,8,8-pentamethyl-5-nonanone (**20**), bp ~76–85° (1.5 mm), *m/e* 212, nmr (CCl_4) δ 0.83 [s, $C(CH_3)_3$] and 0.88 [s, $C(CH_3)_3$], ir (neat) 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.30; H, 13.36.

Reaction of 4a with the Di-Grignard Reagent of 1,4-Dibromobutane.—To a refluxing mixture of 2.300 g (0.094 g-atom) of magnesium in 200 ml of ether was added dropwise 9.24 g (0.043 mol) of 1,4-dibromobutane in 200 ml of ether. After an additional 2.5-hr reflux, two liquid phases were present. A solution of 4.27 g (0.025 mol) of **4a** in 150 ml of ether was added dropwise to the refluxing Grignard. The reflux was continued with stirring for an additional 21 hr. The tetrahydrooxazine was isolated and cleaved in the usual manner to give a three-component mixture. Separation on a 10-ft 10% SE-30 vpc column, monitored by ir, showed the major component to have absorption at 3075 (vinyl protons), 2705 (aldehyde proton), and 1725 cm^{-1} (aldehyde carbonyl). The second component had an absorption at 1700 cm^{-1} (cycloheptanone, 1699 cm^{-1}), and the third at 1710 cm^{-1} (straight-chain ketone). The three components were identified as 2-methylcycloheptanone (**33**) (12%), 6-methyl-5-undecanone (**18**)[10] (16.5%), and 2-methyl-6-heptenal (**34**) (71.5%). The latter was characterized by its molecular ion (*m/e* 126) and elemental analysis.

---

(9) F. C. Whitmore, H. S. Whitaker, W. A. Mosher, O. N. Breivik, W. R. Wheeler, C. S. Minor, L. H. Sutherland, R. B. Wagner, T. W. Clopper, C. E. Lewis, A. R. Lux, and A. H. Poppin, *J. Amer. Chem. Soc.*, **63**, 643 (1941).

(10) G. Stork and S. Dowd, *ibid.*, **85**, 2180 (1963).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.93; H, 11.09.

This reaction was repeated in pure THF at room temperature with 2.29 g (0.094 g-atom) of magnesium in 175 ml of THF, 8.80 g (0.041 mol) of 1,4-dibromobutane in 200 ml of THF, and 3.81 g (0.023 mol) of **4a** in 175 ml of THF. The products isolated consisted of 2-methylcycloheptanone (10%) and 6-methyl-5-undecanone (90%) which were compared with authentic samples. Only a trace (0.2%) of the unsaturated aldehyde **34** was detected.

Registry No.—**7**, 39575-86-5; **19**, 25368-59-6; **20**, 39575-88-7; **23**, 39575-89-8; **24**, 39575-90-1; **25**, 36871-42-8; **26**, 39575-92-3; **27**, 39575-93-4; **33**, 932-56-9; **34**, 17206-63-2; 2-benzyl-4,4,6-trimethyloxazine, 26939-22-0; paraformaldehyde, 30525-89-4.

Acknowledgment.—The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

Correlation of Configuration and ^{19}F Chemical Shifts of α-Methoxy-α-trifluoromethylphenylacetate Derivatives[1]

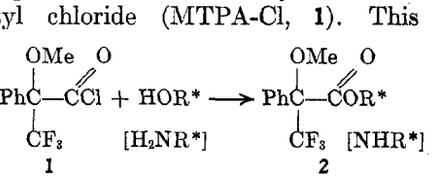
GLENN R. SULLIVAN, JAMES A. DALE,[2] AND HARRY S. MOSHER*

Department of Chemistry, Stanford University, Stanford, California 94305

Received October 31, 1972

An empirically derived correlation of configuration of diastereomeric α-methoxy-α-trifluoromethylphenylacetic (MTPA) esters and amides with the ^{19}F chemical shifts has been developed. The data have been rationalized in terms of a configuration-correlation model **5**. The inherently large ^{19}F chemical shifts ($CDCl_3$ solvent, external trifluoroacetic acid) and their location in an otherwise uncongested region of the nmr spectrum makes this correlation of considerable value in connection with stereochemical studies involving chiral secondary alcohols and primary amines. Of the 25 examples studied, 19 MTPA esters and 6 MTPA amides, 18 clearly group themselves in a general pattern which is discussed in terms of the configuration-correlation model. Three MTPA esters showed no significant chemical shift nonequivalence for the ^{19}F α-CF_3 signals between *R,R–S,S vs. R,S–S,R* diastereomers. Of the four cases which might be considered exceptions to this nmr configurational correlation model, namely isobutyl-*tert*-butylcarbinol, *n*-butyl-*tert*-butylcarbinol, trifluoromethyl-*tert*-butylcarbinol, and borneol, the first three can be rationalized while only borneol stands as a clear exception to the model. All of the 6 MTPA diastereomeric amides studied conform to the same model.

The nonequivalence of various diastereomeric esters and amides has been utilized for the quantitative determination of enantiomeric composition of chiral alcohols and amines.[3] These studies recently have been extended to include correlations of configurations with proton nmr chemical shift differences of these diastereomers.[4] We now report on an empirically derived correlation of configuration and ^{19}F nmr chemical shift differences for esters and amides of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) which are readily prepared from α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl, **1**). This derivative was chosen because of its availability in optically active forms,[3c,5] stability to racemization, and proven utility in earlier proton nmr studies.[4]



1 2

This method has the inherent advantage that the ^{19}F nmr chemical shift differences for the α-CF_3 group of such diastereomeric derivatives (**2**) are generally greater than those of the corresponding proton signals in the same compounds. With the usual substrates the ^{19}F signals are found in a completely unobstructed region of the spectrum. If there are other fluorine substituents on the carbinyl moiety of the MTPA esters or amides, their signals are generally discernible by spin–spin coupling patterns.

The ^{19}F chemical shifts for the diastereomers in this study are listed in Table I. They are recorded in parts per million downfield relative to external trifluoroacetic acid (TFA) in deuteriochloroform solvent. From these data are obtained the diastereomer chemical shift differences ($\delta_X - \delta_Y$). These values are also compared to those reported previously[3c] using internal TFA as a reference standard (Table I, last three columns). In our previous studies we had noted that internal TFA, as well as solvent, had a pronounced effect on the position of the α-CF_3 resonances and on the chemical shift differences of the α-CF_3 signals of diastereomeric MTPA esters. We further observed that in some cases there was no diastereomer chemical shift difference for these α-CF_3 until TFA was added. These initial observations had discouraged us from seriously considering a correlation scheme based upon the nonequivalence of these α-CF_3 resonances. We now find that, in spite of the fact that some MTPA diastereomers give coincident α-CF_3 signals in the absence of TFA (3 out of 25 examples in Table I), very significant nonequivalences are observed in most cases. In the present study all values were obtained using external TFA.

(1) We acknowledge with gratitude support of these studies by the National Science Foundation, Grant GP 27448.

(2) Taken in part from the Ph.D. Thesis of James A. Dale, Stanford University, 1970.

(3) (a) M. Raban and K. Mislow, *Tetrahedron Lett.*, 4249 (1966); (b) *Top. Stereochem.*, **2**, 199 (1967); (c) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); (d) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968); (e) G. Helmchen, R. Ott, and K. Sauber, *Tetrahedron Lett.*, 3873 (1972).

(4) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **95**, 512 (1973), and references cited therein.

(5) Resolved MTPA[5d] is available from Aldrich Chemical Co., Inc., Milwaukee, Wis., Norse Chemicals, Santa Barbara, Calif., and Fluka AG, Buchs, Switzerland.