formed in this solvolysis reaction by making appropriate structural modifications.

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Syntheses *via* Dihydro-1,3-oxazines. X. A Versatile Ketone Synthesis Involving Stepwise Alkyl or Aryl Introduction

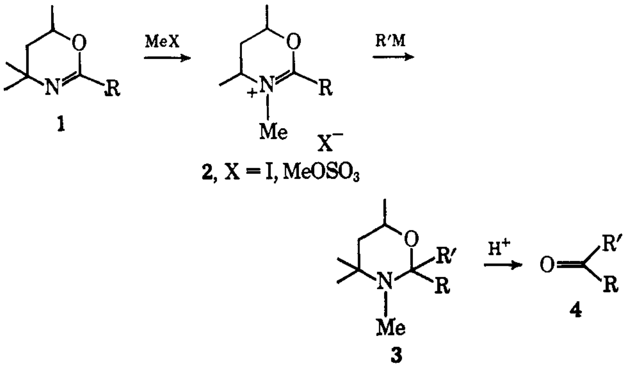
Sir:

We report a synthesis of alkyl and aryl ketones (**4**) originating from the versatile dihydro-1,3-oxazine system[1] (**1**) which involves addition of organometallics to the N-methyl quaternary salts **2** followed by hydrolytic cleavage. It was recently demonstrated that the dihydro-1,3-oxazine ring is inert to organometallics[2] and that this property afforded a novel protecting group against such reagents. It appeared to us that the facile elaboration of the 2-alkyl substituent in dihydro-1,3-oxazines by use of strong bases (*e.g.*, butyllithium) and alkyl halides[4] would provide considerable scope in constructing various ketones if the C=N link in the oxazine could be induced to add an appropriate organometallic. Various attempts to increase the reactivity of the C=N bond toward nucleophillic reagents (RMgX, RLi) by the use of BF_3, R_3B, or Et_3Al failed to provide the adduct in any appreciable amount.[5] The desired result was finally realized by addition of methyl iodide to **1** followed by introduction of the organometallic which was allowed to react at room temperature. In this fashion, the N-methyl quaternary salts[6] were indeed receptive to organometallic addition to the C=N link, and some typical examples of ketones prepared are given in Table I. The dihydro-1,3-oxazines utilized in this study were all prepared by techniques previously described for synthesizing aldehydes.[7] There were differences in behavior noted between several Grignards and their corresponding lithium derivatives. The Grignard generally gave higher yields of the adducts **3** than their organolithium counterpart, whereas phenyl and *t*-butyl Grignard reagents failed to react at all. On the other hand, *t*-butyllithium added successfully to the oxazine quaternary salts producing, after hydrolysis, the corresponding *t*-butyl ketones. The phenyl ketones could be obtained by employing the 2-phenyloxazine (**1**, R = Ph) and an appropriate organometallic. A study to extend this method to the synthesis of α,β-unsaturated ketones is currently under way.[3]

Table I. Formation of Ketones from Dihydro-1,3-oxazines

Dihydro-1,3-oxazine (**1**), R	R′M	Yield of ketone **4**, %[a,k]	2,4-DNP mp, °C (lit.)
$PhCH_2CH_2$	EtMgBr	78	108–115[b]
$PhCH_2CH_2$	*n*-BuMgBr	71[c]	118–120 (130)[d]
	n-BuLi	51	
$PhCH_2CH_2$	*t*-BuLi	29[e]	175–176 (179)[f]
Ph	EtMgBr	70	190 (191)[g]
$CH_2{=}CHCH_2C(Ph)H$	MeMgBr	56	121–123 (123)[h]
Cyclopropyl	*n*-BuMgBr	35[i]	108–110 (112)[j]

[a] Yields are based on 2-substituted 5,6-dihydro-1,3-oxazine. [b] Semicarbazone derivative, I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1965, reports mp 82, 132, 100–135°. [c] Mass spectrum, found: M 190; $C_{13}H_{18}O$ requires M 190. [d] I. N. Nazarov and L. I. Shmonina, *Zh. Obshch. Khim.*, **20**, 1114 (1950); *Chem. Abstr.*, **44**, 9460*i* (1950). [e] Mass spectrum, found: M 190; $C_{13}H_{18}O$ requires M 190. [f] E. Berliner and F. Berliner, *J. Am. Chem. Soc.*, **72**, 222 (1950). [g] A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co. Ltd., London, 1957. [h] M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. France*, 346 (1957). [i] Mass spectrum, found: M 126; $C_8H_{14}O$ requires M 126. [j] M. Julia, S. Julia, and T. S. Yu, *Bull. Soc. Chim. France*, 1849 (1961). [k] All products exhibited ir and nmr spectra in total agreement with assigned structure.



A typical procedure for this ketone synthesis is illustrated by the preparation of 1-phenyl-3-pentanone (**4**, R = CH_2CH_2Ph; R′ = Et). A mixture of 2-phenethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine[7] (2.31 g)

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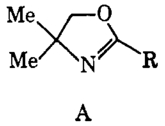
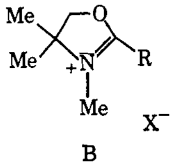
(1) Dihydro-1,3-oxazines have been reported as vehicles for the synthesis of various aldehydes, ketones, and carboxylic acids: A. I. Meyers and A. C. Kovelesky, *J. Am. Chem. Soc.*, **91**, 5887 (1969), and references cited therein.

(2) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *ibid.*, **91**, 5886 (1969). The 2-oxazolines[3] are also useful and, in some respects, superior to the dihydro-1,3-oxazines as protecting groups.

(3) Further investigation into the chemistry of related systems (*i.e.*, the 2-oxazoline A and its N-methyl derivative B) have proven that they have comparable synthetic utility toward the synthesis of ketones, acids, esters, and aldehydes. This work will be reported at a later date.



A



B

(4) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.*, **91**, 763 (1969).

(5) In most cases trace amounts of the 2,2-dialkyltetrahydro-1,3-oxazine (**3**) were detected, but the major paths were usually reaction with the complexing moiety.

(6) It was found that the *in situ* preparation of the methiodide or N-methyl methosulfate were of approximately equal value and that neither derivative had to be removed from the reaction vessel or purified before addition of the organometallic.

(7) For example, **1** (R = $PhCH_2CH_2$) was obtained in 95% yield from the lithio salt of **1** (R = Me) and benzyl bromide; **1** (R = CH(Ph)-$CH_2CH{=}CH_2$) was obtained from the lithio salt of **1** (R = CH_2Ph) and allyl bromide; **1** (R = cyclopropyl) was obtained from **1** (R = Me), 1-chloro-2-bromoethane, and 2.0 equiv of butyllithium; **1** (R = Ph) was obtained using 2-methyl-2,4-pentanediol, benzonitrile, and 96% sulfuric acid. Preparative details for these transformations have been published (A. I. Meyers, *et al.*, *Org. Proc. Prep.*, **1**, 193, 213 (1969); J. J. Ritter and E. J. Tillmanns *J. Org. Chem.*, **22**, 839 (1957)).

and methyl iodide (5 ml) was stirred at room temperature (nitrogen) overnight. The excess methyl iodide was removed *in vacuo* and the quaternary salt was washed twice by successive addition and pipetting-out of dry ether.[8] To the original reaction vessel containing the quaternary salt was added 10 ml of ethylmagnesium bromide (25 mmol); the slurry was stirred for 48 hr at room temperature.[9] The resulting homogeneous reaction mixture was poured into 30 ml of cold water, and the ethereal solution was combined with several ether extracts from the aqueous solution and concentrated. The crude dialkyltetrahydro-1,3-oxazine (**3**) was heated at reflux for 1 hr in 40 ml of water containing 5 g of oxalic acid, the aqueous solution was extracted with ether, and the extracts were washed with dilute (5%) sodium bicarbonate, dried (K_2CO_3), and concentrated to give 1.26 g (78%) of the desired ketone.[10]

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[8] Addition of 1.1 equiv of methyl sulfate to an ethereal solution of the dihydro-1,3-oxazine and stirring for 3 hr afforded a quantitative yield of the N-methyl methosulfate salt which was purified only by washing excess methyl sulfate away with ether.

[9] In some cases examined, comparable yields of ketone were realized after a reaction time of 4–18 hr.

[10] Vpc analysis of this crude product as well as the other ketones prepared showed only trace contamination.

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Concerning the P–N Rotational Barriers in Aminophosphines[1]

Sir:

There is considerable current interest in the stereochemistry of aminophosphines.[2] However, there appears to be some confusion in the literature regarding the measurement of P–N rotational barriers by the nmr method. The present communication is concerned with two papers[3,4] where erroneous conclusions have been drawn.

Greenwood, Robinson, and Straughan[3] observed that the 25° pmr spectrum of methylaminobis(trifluoromethyl)phosphine, $CH_3NH\cdot P(CF_3)_2$ (I), consists of two doublets with identical coupling constants (10.3 Hz) but unequal intensities (Figure 1a). This spectral observation was ascribed to the presence of unequal amounts of two rotational isomers. It was further noted that the pmr spectrum collapsed to a doublet at 88°. Together with the signal separation at coalescence (*ca.* 5 Hz) this would imply a P–N rotational barrier of *ca.* 20 kcal/mol in I. Since this is appreciably higher than the usual range of 10–15 kcal/mol for this barrier[2b,4] and since one would expect the two PNCH couplings in I to be different, we have reinvestigated the matter. It now appears that the doublet of doublets in the pmr spectrum of I at ambient temperature is, in fact, due to coupling of the methyl protons to both the phosphorus atom and the imino proton (J_{PNCH} = 11.5 Hz; J_{HNCH} = 4.9 Hz) and *not to restricted P–N bond rotation.* This conclusion is based on the following experimental observations: (1) the splitting of the four proton lines (in hertz) of I at 44° is the same at 60 MHz and 100 MHz, indicating that the splittings arise from spin-coupling effects; (2) the ^{19}F spectrum of I at ambient temperature consists of a single doublet (J_{PCF} = 82 Hz), thus providing no evidence for the presence of rotational isomers; and (3) the pmr spectrum of N-deuterated I, $CH_3ND\cdot P(CF_3)_2$, consists of a doublet at ambient temperature (Figure 1b) with J_{PNCH} = 11.5 Hz. The collapse of the four-line pmr spectrum of I to a doublet above 88° is therefore presumably due to exchange of the imino proton with concomitant loss of H–N–C–H coupling. The unsymmetrical appearance of the doublet of doublets, together with the temperature dependence of their relative intensities, can be ascribed to the proximity and temperature sensitivity of the broad N–H resonance.[5]

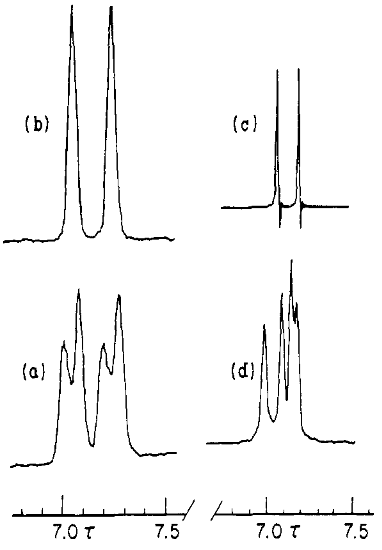

Figure 1. ^{1}H nmr spectra of aminophosphines: (a) 60-MHz spectrum of $CH_3NH\cdot P(CF_3)_2$ (I) at 44°; (b) 60-MHz spectrum of $CH_3ND\cdot P(CF_3)_2$ at 44°; (c) 100-MHz spectrum of $(CH_3)_2NPCl_2$ (II) in $CHFCl_2$ solution at −50°; (d) 100-MHz spectrum of II in $CHFCl_2$ solution at −120°.

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[1] This work was supported by the Air Force Office of Scientific Research, Grant No. AF-AFOSR-1050-67, the National Science Foundation (Grant GP 9518), and the Robert A. Welch Foundation.

[2] (a) M. P. Simonnin, J. J. Basselier, and C. Charrier, *Bull. Soc. Chim. Fr.*, 3544 (1967); (b) A. H. Cowley, M. J. S. Dewar, and W. R. Jackson, *J. Amer. Chem. Soc.*, **90**, 4185 (1968); (c) H. Goldwhite and D. G. Roswell, *Chem. Commun.*, 713 (1969); (d) W. E. Slinkard and D. W. Meek, *Inorg. Chem.*, **8**, 1811 (1969).

[3] N. N. Greenwood, B. H. Robinson, and B. P. Straughan, *J. Chem. Soc., A*, 230 (1968).

[4] D. Imbery and H. Friebolin, *Z. Naturforsch.*, **23b**, 759 (1968).

[5] The N–H resonance occurs at 0.43 ppm upfield from the methyl signals. The HNCH coupling constant is therefore of the same order of magnitude as the chemical-shift separation and leads to a relative enhancement of the high-field components of the doublet of doublets. The distortion is less evident in the spectra of I at 100 MHz owing to the increase in δ/J. The width of the NH signal can be ascribed to coupling with the methyl group and phosphorus atom together with the quadrupolar effect of the nitrogen nucleus.