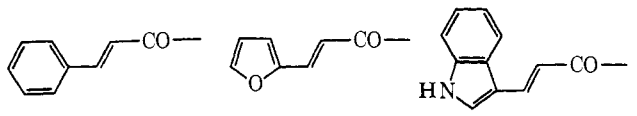
Table I. λ_{max} Values of β-Arylacryloyl Derivatives



A B C

	λ_{max}, nm ($\epsilon_{max} \times 10^4$) for acyl groups[c]		
	A	B	C
O-Acylchymotrypsins[a]			
Native (pH 4.2)	288[b] (1.78[d])	321	359 (1.78[d])
Denatured	280 (1.78[d])	309	334 (1.90[d])
O-Acyl-*N*-acetylserinamides[a]			
H_2O	281 (2.43[d])	309	335 (2.70[d])
10 *M* LiCl in H_2O	285	314	
Methyl esters			
H_2O	279	306	330
10 *M* LiCl in H_2O	280	310	335
Lactones (II, III, IV)			
H_2O	285 (2.28)	314 (2.48)	341 (2.07)
10 *M* LiCl in H_2O	288 (1.85)	320 (2.11)	349 (1.46)
EtOH	280 (2.51)	309 (2.59)	339 (2.14)

[a] See ref 4. [b] Corrected for tyrosine and tryptophan. See M. L. Bender, 143rd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 9–14, 1962; J. F. Wooten and G. P. Hess, *Nature* (*London*), **188**, 726 (1960). [c] A, B, and C are shown above. [d] See ref 12.

chymotrypsins cannot be explained solely on the basis of medium changes.

Binding of dyes and various reporter experiments have been interpreted to show that the active site of chymotrypsin possesses very polar[12] and nonpolar[13] regions. From observations of the ^{19}F chemical shift of chymotrypsin-bound *N*-trifluoroacetylphenylalanine, Zeffren and Reavill[13b] have concluded that either the environment is of polarity approached by *ca.* 10 *M* NaCl or that the fluorine nuclei are situated adjacent to an aromatic ring and subject to its anisotropic effect. Recent nmr experiments[14a,b] provide strong evidence that cinnamate and several *N*-acyltryptophanate ions bind to native α-chymotrypsin in an identical manner, presumably at the "tosyl hole."[15] It seems reasonable to assume that the acyl groups of the chymotrypsin derivatives discussed above occupy this same location in the acylated enzymes. Examination of a model of chymotrypsin shows that this binding site encompasses regions of both polar and nonpolar character, but it is not clear which areas will be dominant in determining the ultraviolet behavior of these chromophores.

We conclude that the "cis hypothesis," if combined with the assumption of a polar binding site, might explain both the reactivity of acylchymotrypsin intermediates and the red shift noted for the β-arylacryloyl reporter groups when esterified to the hydroxyl group of serine-195. However, the cis hypothesis cannot be considered a unique explanation since the chromophore is undoubtedly held in a heterogeneous milieu and chemical or theoretical models for electronic perturbation by a heterogeneous milieu are not available.[16]

(12) (a) R. J. Foster, *Fed. Proc.*, **27**, 784 (1968); (b) J. Kallos and K. Avatis, *Biochemistry*, **5**, 1979 (1966).

(13) (a) M. B. Hille and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **89**, 5945 (1967); (b) E. Zeffren and R. E. Reavill, *Biochem. Biophys. Res. Commun.*, **32**, 73 (1968).

(14) (a) J. T. Gerig and J. D. Reinheimer, *J. Amer. Chem. Soc.*, **92**, 3146 (1970); (b) J. T. Gerig and R. A. Rimerman, work in progress.

(15) T. A. Seitz, R. Henderson, and D. M. Blow, *J. Mol. Biol.*, **46**, 337 (1969).

(16) It should be noted that a trans-to-cis conformational change of substrate bound to chymotrypsin cannot reasonably be employed to explain the facility of the acylation step. Thus, the normal substrates for chymotrypsin are amides, and it is known that amides and lactams exhibit similar rates of alkaline hydrolysis.[17] Lactones II, III, and IV exhibit no appreciable reaction with chymotrypsin. Therefore, a cis configuration of substrate does not impart great lability of substrate to attack by chymotrypsin.

(17) M. Gordon, Ph.D. Thesis, Manchester, 1950.

* To whom inquiries should be addressed.

Thomas C. Bruice,* P. Gilmer Kury, Diane M. McMahon

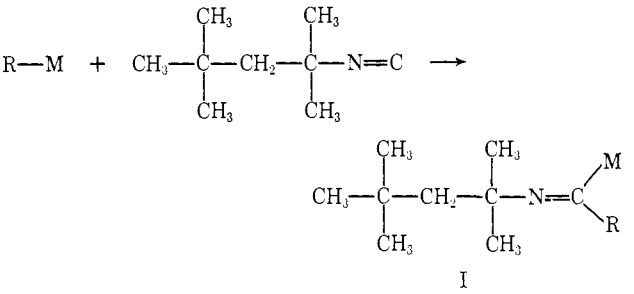
Department of Chemistry
University of California at Santa Barbara
Santa Barbara, California 93106

Received June 27, 1970

Metallo Aldimines. II. A Versatile Synthetic Intermediate[1]

Sir:

We have previously reported on the preparation of lithium aldimines and their use as intermediates for the preparation of aldehydes, C-1-deuterated aldehydes, and α-keto acids.[2] We now wish to report that aliphatic Grignard reagents[3a] also add to 1,1,3,3-tetramethylbutyl isocyanide (TMBI)[3b] to yield the corresponding metallo aldimine (I).



I

M = Li, MgBr

The aldimine I (M = MgX) is prepared by the addition of 1 equiv of TMBI to the desired alkylmagnesium halide in tetrahydrofuran.[4] Hydrolysis of I with D_2O or H_2O followed by steam distillation from a solution of oxalic acid yields the desired aldehyde in yields of 48–67%. Carbonation provides the corresponding α-keto acid. The results are summarized in Table I.

Although the yields of aldehydes and α-keto acids prepared from I (M = MgX) are lower than those prepared using the lithium aldimine reagent[2] (I, M = Li), the use of a Grignard reagent may be more expedient whenever the alkyllithium reagent is not readily available. However, we have observed that when C-1 deu-

(1) The support of this work by grants from the National Science Foundation and Public Health Service Grant No. 04064 from the National Cancer Institute is gratefully acknowledged.

(2) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).

(3) (a) For other attempts to add Grignard reagents to isonitriles see I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 2239 (1961), and references cited therein. (b) Available from Columbia Organic Chemicals, Columbia, S. C.

(4) The Grignard reagent is standardized using the method of Gilman prior to the addition of the isocyanide (H. Gilman, E. H. Zoellner, and J. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).

Table I. Aldehydes and Keto Acids from Alkyl Grignard Reagents and TMBI

RMgBr[b]	T, °C	Time, hr	Aldehyde, %	α-Keto acid, %
sec-Butyl	25	3	67 (96)[a]	47
tert-Butyl	66	24	48	
n-Hexyl	66	1.5	62	26
2-Phenylethyl	66	1.5	63 (80)[a]	
Cyclopentyl	66	1.5	66 (89)[a]	
n-Butyl	66	1.5		34

[a] Per cent deuterium at C-1 as determined by nmr. [b] Concentrations of Grignard reagents were *ca.* 0.1 *M*.

terioaldehydes are prepared using the Grignard route, one does not obtain 100% deuterium incorporation at C-1.[5] In this respect the lithium aldimine reagent would be the method of choice for the preparation of pure C-1 deuterioaldehydes as well as aromatic aldehydes since aromatic Grignard reagents do not add well to TMBI.

In addition we would like to report on the versatility of the lithium aldimine reagent. As shown in Chart I, besides providing a convenient synthesis of aldehydes and α-keto acids, the lithium aldimine I (R = *n*-butyl) can be alkylated with ethyl bromide to yield after hydrolysis an 87% yield of 3-heptanone. An 86% yield of 3-methyl-2-pentanone was also realized by alkylating, with methyl iodide, the aldimine prepared by the addition of *sec*-butyllithium to TMBI (see Table II). Attempts to alkylate I with isopropyl halides were abortive due to the preference for an elimination pathway. The elegant Meyers[6] synthesis of ketones suffers from a similar difficulty in the introduction of bulky groups.

Chart I. Reactions of Lithium Aldimine

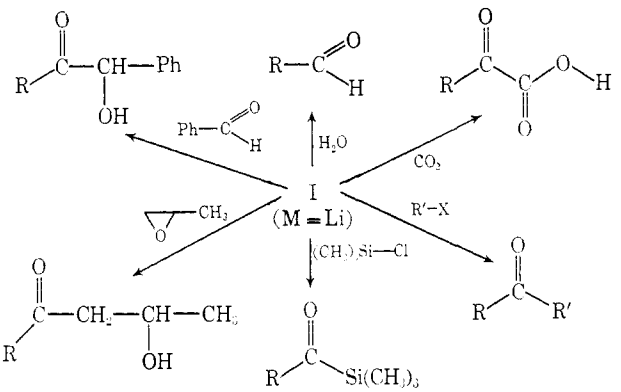


Table II. Reactions of Various Lithium Aldimines

R-Li	R''-NC	R-X	Product	Yield, %
sec-Butyl	TMBI	CH_3I[a]	3-Methyl-2-pentanone	86
n-Butyl	TMBI	C_2H_5Br[a]	3-Heptanone	87
n-Butyl	TMBI	Propylene oxide	2-Hydroxy-4-octanone	90
Ethyl	TMBI	Benzaldehyde	1-Phenyl-1-hydroxy-2-butanone	81
Ethyl	TMBI	$(CH_3)_3$-Si-Cl	Trimethylsilyl ethyl ketone	40[d]
Ethyl	DMPI[b]		1-(*N*-Propylideneamino)-2,6-dimethylbenzene	50
n-Butyl	TBI[c]		2-(*N*-Pentylideneamino)-2-methylpropane	92

[a] Reaction run at −78° in THF. [b] 2,6-Dimethylphenyl isocyanide. [c] *tert*-Butyl isocyanide. [d] Better conditions for the hydrolysis of the imine precursor are being investigated.

(5) The reason for this is currently under investigation and will be reported in our full paper.

Alkylation using propylene oxide yields a β-hydroxy ketone in very good yield. Under the reaction conditions used very little, if any, dehydration occurs. This reaction shows promise in providing a convenient means for preparing mixed aldols. As should be noted, α-hydroxy ketones can also be prepared by the condensation of I with benzaldehyde.[7]

It should also be noted that silyl ketones[8] can be very conveniently prepared by the use of lithium aldimines. The yield of trimethylsilyl ethyl ketone prepared by this method was 40% (nmr analysis). The intermediate imine can also be isolated (in 80–94% yield) if desired.[9]

Further exploration of these intermediates is being continued.[10]

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

(7) The scope and limitations of these reactions are currently under investigation and will be discussed in our full paper.

(8) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Amer. Chem. Soc.*, **89**, 431 (1967); E. J. Corey, D. Seebach, and R. Freedman, *ibid.*, **84**, 434 (1967).

(9) The preparation of other metallic ketones is under investigation.

(10) Solvent effects have been noted in the addition reaction. Moreover, the structure of the isocyanide is important. We have prepared and evaluated a large number of isocyanides which do not have α hydrogens. For reactions of α-hydrogen containing isocyanide swith organometallics, see U. Schöllkopf and G. Fritz, *Angew. Chem., Int. Ed. Engl.*, 7, 805 (1968).

* Address correspondence to this author.

H. M. Walborsky,* W. H. Morrison, III, G. E. Niznik
Chemistry Department, Florida State University
Tallahassee, Florida 32306

Received August 5, 1970

Syntheses *via*-2-Oxazolines. I. The Formylation of Grignard Reagents in the Presence of Hexamethylphosphoramide

Sir:

In the course of a study to evaluate the synthetic utility of 2-oxazolines which have been found to be useful precursors to a variety of aliphatic and aromatic carboxylic esters and acids,[1] we examined the readily obtainable 4,4-dimethyl-2-oxazoline (**1**)[2] as a potential formylating reagent for organometallics. In a previous report[3] we described the addition of organolithium reagents to the dihydro-1,3-oxazine system producing the homologated aldehyde precursor **4**. Although this process proceeded in satisfactory yield the difficulty in obtaining the requisite dihydro-1,3-oxazine detracted from the utility of this method. The ease and quantity with which the 2-oxazoline could be prepared suggested that the five-membered ring system would be a more attractive route to aldehydes from

(1) A. I. Meyers and D. L. Temple, Jr., *J. Amer. Chem Soc.*, **92**, 6644 (1970).

(2) This hitherto unknown compound was prepared in 70% yield by heating an equimolar mixture of 90% formic acid and 2-methyl-2-aminopropanol to 130–140° for 45 min, followed by distillation into cold ether. The aqueous distillate layer was removed, saturated with salt, and extracted with ether, and the combined ethereal solution dried and concentrated. Distillation gave pure **1** [bp 99–100°; ir (neat) 1630 cm^{-1}; nmr (CCl_4) δ 6.55 (s, 1 H), 3.77 (s, 2 H), 1.19 (s, 6 H)]. P. Allen and J. Ginos [*J. Org. Chem.*, **28**, 2759 (1963)] have reported a synthesis of 2-oxazolines upon which this experiment was based.

(3) A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).