References and Notes

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Isocyanides. Dissociation of Metallo Aldimines

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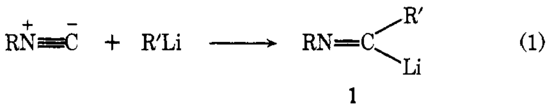
Metallo aldimines were prepared by the addition of organolithium reagents to *tert*-butyl isocyanide, 1,1,3,3-tetramethylbutyl isocyanide, 2-phenyl-2-butyl isocyanide, and triphenylmethyl isocyanide. The reactions of organolithium reagents, Grignard reagents, and organocopper reagents with triphenylmethyl isocyanide are discussed in detail. A new synthetic route for the formation of secondary and tertiary nitriles is described as is a simple and convenient method for the preparation of ketones. The lithium aldimines were converted to copper aldimines by treatment with cuprous iodide. Studies on the dissociative nature of metallo aldimines indicated that both relief of steric crowding (steric effect) and formation of stable intermediates (electronic effect) are the driving forces for the dissociation.

Recent reports on the reaction of isocyanides with organometallic reagents have shown that the chemistry of isocyanides can provide new synthetic pathways to a variety of molecules. It has recently been reported[1] that the α addition of an organolithium reagent to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) yields lithium aldimine (1), which can be used for the preparation of aldehydes, ketones, α-keto acids, and α- and β-hydroxy ketones (eq 1).

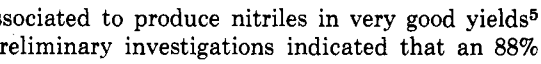


$$\overset{+}{RN}\equiv\overset{-}{C} + R'Li \longrightarrow RN{=}C\begin{smallmatrix}R'\\ Li\end{smallmatrix} \qquad (1)$$

1

The reactions of α-metalated isocyanides are being investigated by Schöllkopf and others.[2,3] In addition, the synthetic applications of copper-isocyanide complex catalyzed reactions for the preparation of a variety of compounds have been explored by Saegusa.[4]

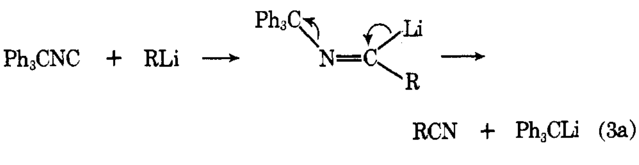
During the course of investigating the synthetic utility of lithium aldimines it was discovered that certain aldimines dissociated to produce nitriles in very good yields[5] (eq 2). Preliminary investigations indicated that an 88% yield of *tert*-butyl cyanide could be achieved by the addition of the *tert*-butyllithium to triphenylmethyl isocyanide (TPMI). However, the use of other lithium reagents produced the corresponding symmetrical ketones which apparently results from the addition of RLi to the nitrile formed (eq 3b).



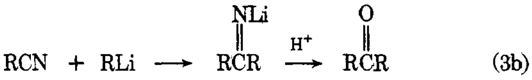
$$RN{=}C\begin{smallmatrix}R'\\ Li\end{smallmatrix} \longrightarrow R'CN + RLi \qquad (2)$$

A detailed study, with an aim of establishing the scope and limitations of this "isocyanide-metal exchange" reaction[5] was undertaken and is the subject of this paper.

Isocyanide-Metal Exchange Reaction. The isocyanide-metal exchange reaction (eq 3a) showed promise as a new method for the preparation of nitriles and ketones. An investigation of the scope and limitation of this reaction was undertaken. The results obtained in Table IV clearly point to triphenylmethyl isocyanide (TPMI) as the isocyanide of choice, and it was therefore selected for our studies.



$$Ph_3CNC + RLi \longrightarrow Ph_3C{-}N{=}C\begin{smallmatrix}Li\\ R\end{smallmatrix} \longrightarrow RCN + Ph_3CLi \qquad (3a)$$



$$RCN + RLi \longrightarrow \overset{NLi}{\overset{\|}{RCR}} \xrightarrow{H^+} \overset{O}{\overset{\|}{RCR}} \qquad (3b)$$

Reactions with Organolithium Reagents. The results of the reactions of a representative set of organolithium reagents with TPMI are given in Table I.[5] It is evident that this reaction provides a convenient method for the preparation of symmetrical ketones and hindered nitriles such as *tert*-butyl cyanide in high yield. Unsymmetrical ketones can also be prepared by the simple expediency of first adding 1 equiv of the more hindered lithium reagent to permit the exchange reaction (eq 3a) to occur, followed by the addition of the less hindered lithium reagent. Using this procedure, *tert*-butyl *sec*-butyl ketone was prepared in 83% yield. It is worth mentioning that by careful work-up of the reaction mixture (see Experimental Section) one can isolate the precursor ketimine in excellent yields. For example, di-*tert*-butyl ketimine was obtained in 77% yield.[6] Lithium phenylacetylide, owing to an unfavorable equilibrium, did not add to TPMI.

The associated nature of organolithium reagents[7,8] may increase the probability of the immediate availability of lithium reagents for further addition to the nitrile as it is formed in the reaction. The observation that the yield of nitrile increased on going from primary to tertiary lithium reagent indicates that steric hindrance also becomes an important factor so that α addition of *tert*-butyllithium to TPMI is favored over its addition to the nitrile formed in

Table I
Reactions of Triphenylmethyl Isocyanide with Organolithium Reagents

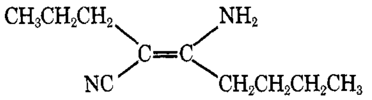
No.	RLi	RLi: Ph_3CNC	Yield,[a] % Nitrile	Ketone
1	*n*-Butyl	1:1	8.5	48.5[b]
		2:1	9	59
2	*sec*-Butyl	1:1	14	55[b]
		2:1	24	63
3	*tert*-Butyl	1:1	88	
		2:1	2	75
4	Phenylethynyl	1:1		
5	Cyclopropyl	1:1	1.5	20
6	Phenyl	1:1		93[b]
		2:1		94
7	Mesityl	1:1		14[c]

[a] Yields determined by glpc analysis. [b] Yields based on theoretical yield of ketone. [c] Isolated as ketimine.

the reaction. The lower yield of dimesityl ketimine is probably due to the steric hindrance experienced in the α addition of the lithium reagent to isonitrile.

Reaction with Grignard Reagents. The availability of organohalides and the ease of preparation of Grignard reagents prompted us to study the reactions of Grignard reagents with TPMI. Although reactions of aromatic and tertiary Grignard reagents were unsuccessful, the results (Table II) with primary and secondary Grignard reactions are significant from a synthetic point of view.

When 1 equiv of *n*-butylmagnesium bromide was treated with TPMI, work-up of the reaction mixture gave neither *n*-valeronitrile nor 5-nonanone. The ir spectrum of the reaction mixture exhibited, in addition to the unreacted isocyanide band at 2140 cm^{-1}, a strong band at 2190 cm^{-1}, absorption in the 3300-3500-cm^{-1} region, and an intense band at 1632 cm^{-1}. These data indicated the presence of an amino and a cyano group in addition to a double bond in conjugation with them. The product was identified as 5-amino-4-cyano-4-nonene (2) by isolation and comparison of its ir and nmr spectra with that of an authentic sample prepared in 49% yield by the reaction of *n*-butylmagnesium bromide with *n*-valeronitrile.[9] Conversion of 2 to the known 4-cyano-5-nonanone by mild acid hydrolysis confirmed the structural assignment.



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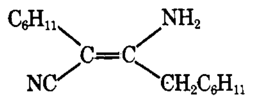


3

When 2 equiv of *n*-butylmagnesium bromide was treated with 1 equiv of TPMI, depending upon the reaction conditions, a 10-20% yield of *n*-valeronitrile was realized, along with a 50-60% yield of 2. Under similar conditions cyclohexylmethylmagnesium bromide gave a 26% yield of cyclohexylacetonitrile and a 55% yield of 3. It is evident that this reaction, although not satisfactory for the preparation of primary nitriles, provides a facile and convenient synthetic route for making α-cyano ketones or the corresponding precursors in good yields. The mechanism of the condensation that occurs during the reaction of Grignard reagents with primary nitriles has been discussed elsewhere.[10]

Table II
Reactions of Grignard Reagents with Triphenylmethyl Isocyanide

RBr[a]	RMgBr: Ph_3CNC	Yield[b] RCN, %
n-Butyl bromide	1:1	Trace[c]
	2:1	10-20[c]
Cyclohexylmethyl bromide	2:1	26[c]
Benzyl bromide	2:1	78
2-Bromobutane	1:1	70
	3:2	98
2-Bromohexane	1:1	79
Cyclopropyl bromide	1:1	17
	2:1	27
Cyclohexyl bromide	1:1	94
	2:1	100
Cycloheptyl bromide	1:1	70
tert-Butyl bromide	1:1	7-10
Bromobenzene	1:1	Trace
p-Methoxybromobenzene	1:1	Trace
p-Bromotoluene	1:1	Trace
Mesityl bromide	1:1	17

[a] Grignard reagent was prepared by standard procedure and titrated whenever it was necessary. [b] Yields determined by glpc. [c] Other products were isolated. Refer to the discussion section.

Table III
Reactions of Triphenylmethyl Isocyanide with Organocopper Reagents

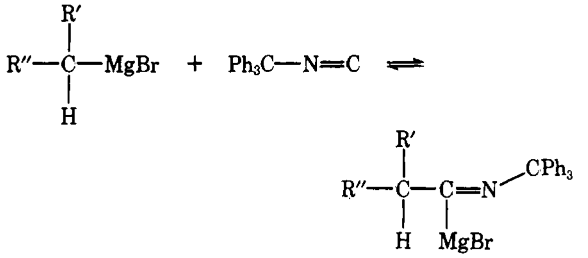
No.	RCu R		Yields,[a] % RCN	Ph_3CH	Conditions Time, hr	Temp, °C
1	*n*-Butyl		38		6.5	34
2	*tert*-Butyl		<5		6.5	34
3	Phenyl		1		6.5	34
	RR′CuLi R	R′				
4	*n*-Butyl	*n*-Butyl	49	62	1	25
5	*n*-Butyl	*n*-Butyl	40	84	6	25
6	*n*-Butyl	*n*-Butyl	17	85	12	10
7	*tert*-Butyl	*tert*-Butyl	31	40	3	36
8	*n*-Butyl	*tert*-Butyl	24[b]	62	0.5	25

[a] Yields determined by glpc. [b] No *tert*-butyl cyanide was formed.

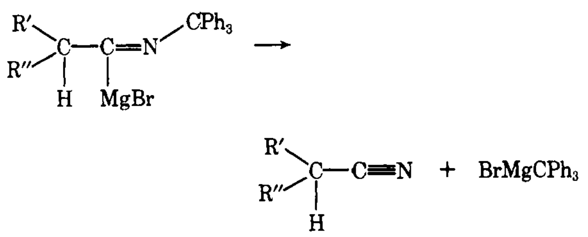
As can be seen from Table II, reactions of secondary Grignard reagents with TPMI gave the corresponding nitriles in excellent yields. When Grignard reagent and isocyanide were allowed to react in 1:1 ratio, the yield of nitrile was of the order of 70-95%. The reaction was complete in 5 min with a quantitative yield being obtained when 2 equiv of cyclohexylmagnesium bromide was treated with 1 equiv of TPMI. Similarly, a 98% yield of 2-cyanobutane was obtained from the reaction of 3 equiv of *sec*-butylmagnesium bromide with 2 equiv of TPMI. The important synthetic application of this reaction should be recognized from the fact that ordinarily unsatisfactory yields of nitriles are obtained by the usual S_N2 displacement of *sec*-acyclic and cyclic halides by cyanide ions.[11]

However, treatment of *tert*-butylmagnesium bromide with TPMI at 36° for 10 hr gave only a small yield of *tert*-butyl cyanide (~10%). Also, reactions with phenylmagnesium bromide, *p*-methoxyphenylmagnesium bromide, and *p*-methylphenylmagnesium bromide did not yield the corresponding nitrile. In the case of mesitylmagnesium bromide, 2,4,6-trimethylbenzonitrile was obtained in 17% yield, which could be increased to 39% yield when the reaction mixture was refluxed for 18 hr at 65° (THF).

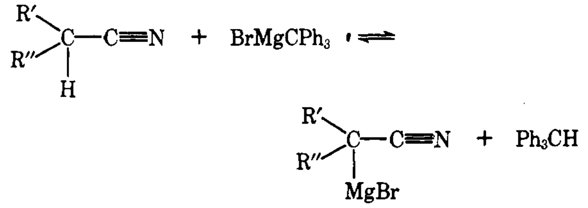
In contrast to the results with lithium reagents (Table I) we note in the case of Grignard reagents that tertiary and aromatic Grignard reagents do not react with TPMI to any appreciable extent. This effect has previously been observed in the reaction of phenylmagnesium bromide with 1,1,3,3-tetramethylbutyl isocyanide (TMBI) and the lack of reactivity was ascribed to an unfavorable equilibrium.[1b,12] A similar situation seems to obtain in the reaction of Grignard reagents with TPMI.



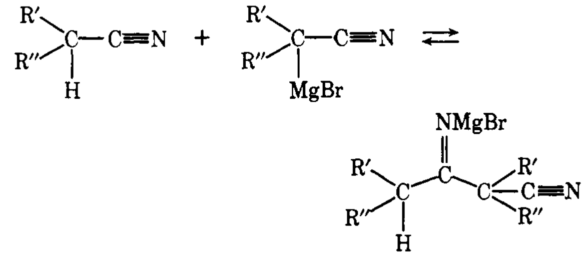
(4a)



(4b)



(4c)



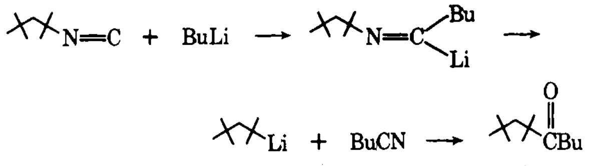
(4d)

In the case when R″ = H the α-metalated nitrile can undergo further condensation to give products of the type of 2 and 3. When both R′ and R″ are alkyl groups, one then obtains good yields of nitrile, since the reaction with tritylmagnesium bromide represents a less favorable equilibrium[10b] (eq 4c) and the propensity for condensation is reduced for steric reasons. However, when R′ = phenyl and R″ = H, the equilibrium (eq 4c) will be almost completely to the right, leading to a stable phenylacetonitrile anion, and therefore benzylmagnesium bromide gives good yields of phenylacetonitrile.

Copper Aldimines. Reaction with Organocopper Reagents. One of the aims in the study of the reaction of organometallics with TPMI was to stop the reaction at the nitrile stage and isolate them free of side products. We have seen that by a judicious choice of organometallic reagent such as tertiary organolithium and secondary Grignard reagents one is able to obtain good yields of the corresponding nitriles. In the case of primary organometallic reagents the nitrile formed in the first step reacted further with both organolithium and Grignard reagents to give ketones and α-cyano ketones, respectively. Since organocopper reagents have been reported to be unreactive toward nitriles,[13] it was felt that the use of these reagents might circumvent the secondary reactions previously encountered. The results of this study are shown in Table III.

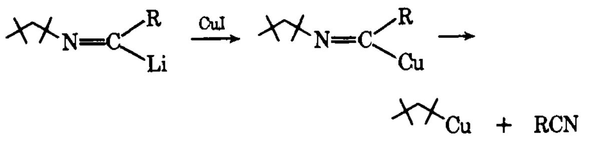
The reaction of alkyl- and phenylcopper reagents with TPMI to give nitriles did not proceed to any appreciable extent. The use of lithium dialkylcuprate reagents improved the yield of nitrile somewhat. Although, as anticipated, no ketone or condensation products were formed, the low yields obtained in these reactions mitigate its use as a synthetic tool.

Conversion of Lithium Aldimines to Copper Aldimines. Initial investigations were focused on the effect of the structure of the isonitrile on the course of the reaction. It was hypothesized that the driving force for the dissociation of the lithium aldimine formed by the α addition of *tert*-butyllithium to TPMI was due to the stabilized trityl anion behaving as a good leaving group. It was therefore surprising to observe the formation of 5–10% yield of *n*-butyl 1,1,3,3-tetramethylbutyl ketone, as a minor product, from the addition of *n*-butyllithium to TMBI. Formation of this ketone suggested that the aldimine dissociated to give *n*-butyl cyanide and 1,1,3,3-tetramethylbutyllithium, which upon further reaction furnished the observed ketone (eq 5).

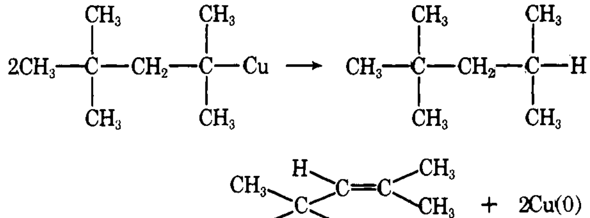


(5)

Based on these observations it was felt that the conversion of lithium aldimine to copper aldimine, by the addition of cuprous iodide, should produce 1,1,3,3-tetramethylbutylcopper (eq 6). Since organocopper reagents do not add to nitriles,[13] one should be able to avoid the formation of ketone and thereby identify the nitrile. Indeed, the copper aldimine obtained from the reaction of cuprous iodide with the lithium aldimine formed from TMBI and *tert*-butyllithium gave a 61% yield of *tert*-butyl cyanide. The formation of 1,1,3,3-tetramethylbutylcopper was also indicated by the identification of its disproportionation products, 2,4,4-trimethylpentane, 2,4,4-trimethyl-2-pentene, and metallic copper (eq 7).



(6)



(7)

Having established that the lithium or copper aldimines from both triphenylmethyl isocyanide (TPMI) and 1,1,3,3-tetramethylbutyl isocyanide (TMBI) dissociated to produce alkyl cyanides, it became apparent that electronic factors alone could not account for the driving force for this dissociation. Although the former produced the highly delocalized trityl anion, the latter formed a tertiary alkyllithium or alkylcopper reagent, neither of which possess any favorable stabilizing factors. Steric interactions, however, may also be playing an important role in this reaction. To evaluate this possibility a study of the copper aldimine intermediate was undertaken, the results of which are given in Tables IV and V. The copper aldimines were chosen for this investigation since this reaction produces solely nitriles and is not complicated by ketone formation.

The results, shown in Table IV, show the effect of varying the alkyl group (R′ in R′NC) upon the dissociation of metallo aldimines (eq 8). It has been recognized that non-

$$\mathrm{R'NC} \xrightarrow[\text{2. CuI}]{\text{1. \textit{tert}-butyllithium}} \mathrm{R'N{=}C}\begin{smallmatrix}t\text{-Bu}\\ \\ \mathrm{Cu}\end{smallmatrix} \longrightarrow t\text{-BuCN} \qquad (8)$$

Table IV
Reactions of Copper Aldimines. Effect of Changing R′ Group in Isocyanides

No.	R′NC	RLi	Solvent[a]	Temp, °C	Reaction period, hr	Yield[b] RCN, %
1	*tert*-Butyl	*tert*-Butyl	Et_2O	*f*	2.5	10.5[c]
2	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	Et_2O	*f*	2.5	61[d]
3	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	THF	*f*	2.5	29
4	2-Phenyl-2-butyl	*tert*-Butyl	THF	0	2.5	35
5	Trityl	*tert*-Butyl	THF	−78	0.25	88[e]

[a] *tert*-Butyllithium in pentane or hexane was used. [b] Yields determined by glpc analysis. [c] 43% yield of *N*-*tert*-butyl-2,2-dimethylpropanamide was observed. [d] A small amount of *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide was noticed. [e] No CuI was added. [f] Room temperature.

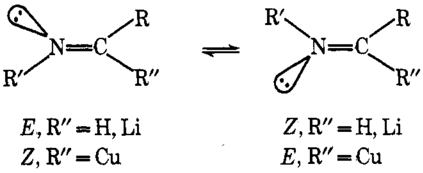
Table V
Reactions of Copper Aldimines. Effect of Changing R Group in Organolithium Reagents

No.	R′NC	RLi	Solvent[a]	Temp	Reaction period, hr	RCN	R′NHC(=O)R, % yield[b]
1	1,1,3,3-Tetramethylbutyl	Methyl	Et_2O	*f*	2.5	Trace[c]	<5
2	1,1,3,3-Tetramethylbutyl	*n*-Butyl	Et_2O	*f*	2.5	Trace[d]	27
3	1,1,3,3-Tetramethylbutyl	*sec*-Butyl	Et_2O	*f*	2.5	<2	>90
4	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	Et_2O	*f*	2.5	61	*e*
5	*tert*-Butyl	*tert*-Butyl	Et_2O	*f*	2.5	10.5	43

[a] RLi in pentane was used. [b] Yields determined by glpc analysis using authentic sample. [c] Corresponding aldimine was the major product (>90%). [d] Corresponding aldimine was the major product; a 10–12% yield of *n*-butyl 1,1,3,3-tetramethylbutyl ketone was also observed. [e] A small amount of *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide was detected. [f] Room temperature.

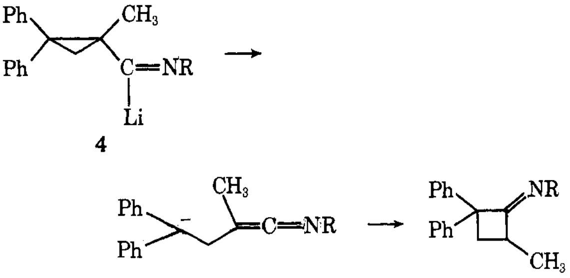
Chart I

E-*Z* Isomerization of Metallo Aldimines



bonded interactions between the substituent on nitrogen and the substituent on carbon in imines have a pronounced effect on the *E* to *Z* isomer ratio in these systems.[14] A similar situation should be obtained in the case of the metallo aldimines (Chart I). One should expect that with copper aldimines the most favored configuration would be *Z*, which would place both alkyl groups in a trans relationship to each other. Boyd, *et al.*,[15] have shown that interactions involving the nitrogen lone pair of electrons are important in determining the imine stereochemistry. The localized electron pair or valence shell electron pair repulsion theory assumes that a nonbonding or lone pair of electrons is larger in volume and takes up more space on the surface of an atom than a bonding pair.[16] It seems reasonable that even in their most favored configuration *Z* copper aldimines are inherently sterically crowded systems and will try to minimize their nonbonded interactions, if possible, by dissociation. Under identical conditions copper aldimines obtained by the addition to *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide (TMBI) gave *tert*-butyl cyanide in 10.5 and 61% yields, respectively. The copper aldimine obtained from TMBI at room temperature in THF rather than ether dissociated to give only a 29% yield of *tert*-butyl cyanide. The lower yield could be attributed to the greater stability of organocopper reagents in THF.[17] However, at 0° in THF, 2-phenyl-2-butyl isocyanide gave a 35% yield of *tert*-butyl cyanide. The observed increase in yield of *tert*-butyl cyanide at a lower temperature (0°) from 2-phenyl-2-butyl isocyanide than from TMBI at room temperature suggests that in addition to a steric factor, electronic effects are also operating through the formation of the benzylic anion.

Moreover, the replacement of both alkyl groups in 2-phenyl-2-butyl isocyanide by two phenyl groups caused the aldimine to dissociate very rapidly (−78°, less than 15 min) largely owing to the stability of the trityl anion produced. These results are consistent with the postulate that both relief of steric strain and the formation of a stable anion are the driving forces for the dissociative ring opening of the lithium aldimine intermediate 4 obtained by the addition of 2,2-diphenyl-1-methylcyclopropyllithium to TMBI (eq 9).[18]

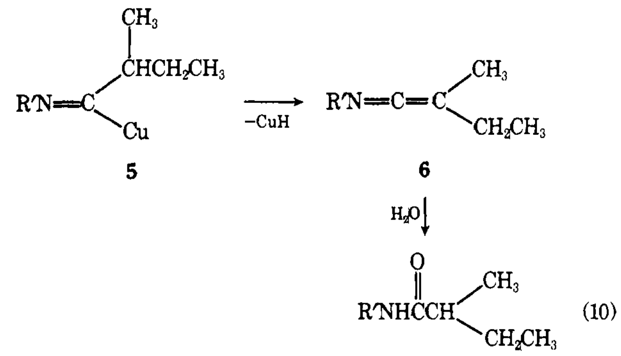


(9)

R = 1,1,3,3-tetramethylbutyl

The effects of varying the organolithium reagent upon the reaction product composition resulting from the dissociation of metallo aldimines are given in Table V. It should be pointed out that all of the reactions are conducted under an *argon atmosphere*. It is interesting to note that in addition to the formation of corresponding alkylnitriles, in most cases, the formation of an amide was observed to be the major product. From the addition of methyllithium and *n*-butyllithium to TMBI, followed by addition of cuprous iodide, the major product was shown to be the corresponding aldimine and only a trace of alkylnitrile was formed. In the case of *sec*-butyllithium neither the alkylnitrile nor the aldimine was the major product, but a 90% yield of *N*-(1,1,3,3-tetramethylbutyl)-2-methylbutanamide was observed. However, when *tert*-butyllithium was used, the *tert*-butyl cyanide was formed in 61% yield, with *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide as a minor product.

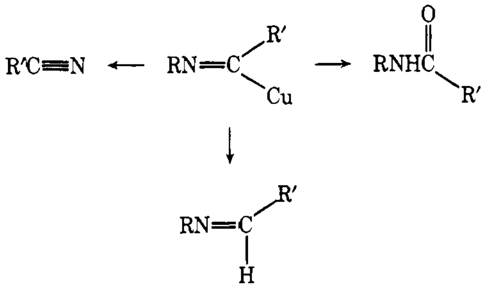
It was noted that the normal work-up (addition of the reaction mixture to aqueous acid) of the copper adimine 5 did not give the corresponding aldimine. This indicated that either the metallo aldimine 5 was stable to acidic conditions or a "ketenimine" (6) was the intermediate which upon addition of water gave the amide in high yield[19] (eq 10). However, since the work-up of the reaction



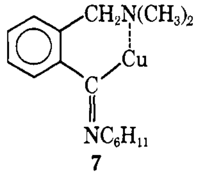
(10)

R′ = 1,1,3,3-tetramethylbutyl

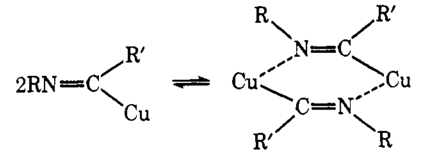
mixture with D_2O or CH_3OD did not incorporate deuterium at the α position of the amide formed, the possibility of a ketenimine as a viable reaction intermediate was ruled out. It was also observed that the addition of water to the copper aldimine **5** followed by refluxing for 5 hr *under argon* (35°) produced the corresponding aldimine in >90% yield. However, replacing the argon atmosphere by an *oxygen atmosphere* resulted in the formation of amide (49% yield). It therefore appears that the reaction of copper aldimine **5** is very much faster with oxygen than with water and it is this reaction that produces amide. The reaction of a copper aldimine with oxygen to yield amides has also been observed by van Koten and Noltes.[20] It is evident that all of the observed products (Table V), namely aldimine, amide, and nitrile, result from a common copper aldimine intermediate. The question to be answered is why, under identical conditions, these different products are formed in different proportions as one changes R′.



Of significance is the observation of van Koten and Noltes[20] that the copper aldimine **7** is dimeric in benzene solution. They proposed a six-member ring complex formed by intermolecular coordination of two copper aldimines. One might then expect that the metallo aldimines reported in Table V would exist in equilibrium with the dimeric structure and that the position of the equilibrium would be sensitive to the structure of R′ such that when favorable steric conditions exist the equilibrium may be completely over to the dimer (eq 11). As one proceeds from methyl to *sec*-butyl (Table V), it was observed that the yield of aldimine decreased considerably and the formation of amide increased rapidly. It is suggested that as the bulkiness of the organolithium reagent is increased, the stability of the copper aldimine toward hydrolysis increases. A close analysis of the dimer (Chart II) of, for example, the copper aldimine **5** would indicate that the approach of the protonated water molecule (which is solvated) to the Cu–C bond is highly sterically prohibited by the hydrophobic alkyl groups but that its reaction with gaseous oxygen molecule to give amide is not retarded. With a methyl or *n*-butyl group present, the steric crowding around the Cu–C bond is not critical enough to prevent the hydrolysis and hence the aldimine was observed to be the major product. In the case of a *tert*-butyl group the nonbonding interaction between the *tert*-butyl group and the 1,1,3,3-tetramethylbutyl group is very severe and formation of the dimer becomes energetically unfavorable; the copper aldimine would therefore exist mostly as monomer. This conclusion would equally apply to the copper aldimines reported in Table IV. As we have discussed earlier, depending upon the steric and electronic factors, the monomeric copper aldimines dissociated to give nitriles as one of the major components of the products.



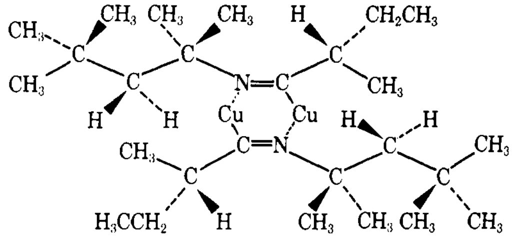
7



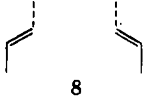
(11)

R = 1,1,3,3-tetramethylbutyl; *tert*-butyl
R′ = methyl; *n*-butyl; *sec*-butyl; *tert*-butyl

Chart II
Dimeric Structure of Copper Aldimine 5



A number of studies have established the thermal disproportionation of alkylcopper(I) reagents to alkane, alkene, and metallic copper (eq 7), with practically no dimerized hydrocarbon product.[21] However, in the case of vinylcopper reagents Whitesides and his coworkers[22] have observed that these reagents decomposed at ambient temperature (4 hr, 25°) to give metallic copper and high yields of dimers with >95% stereospecificity. They concluded that free vinylic radicals are not involved as intermediates and proposed mechanisms which would not involve free radicals. One of the suggestions involved a four-center mechanism and the other a "σ–π" interconversion to an intermediate containing a vinyl radical π bonded to a copper atom cluster, **9**. It is seen that the transition state for either of these mechanisms would require the carbon atoms forming the new σ–σ bond (in the product) to face each other. The copper aldimines under discussion did not give any detectable amount of dimeric products. Also, van Koten and Noltes observed that the thermal degradation of **7** in quinoline at 200° yielded the corresponding Schiff's base in 61% yield instead of the expected symmetrical dimer.[20] As we have discussed earlier, the copper aldimines (1, 2, and 3 in Table V) and **7** would be expected to exist in dimeric forms in which the carbon atoms that would form the new σ bond are far away from each other in the six-membered ring structure, and therefore neither of the two proposed transition states (**8** and **9**) would be attained, and therefore no dimeric products would be formed. In the case of copper aldimines existing predominantly in monomeric form, the unfavorable steric crowd-



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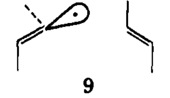


9

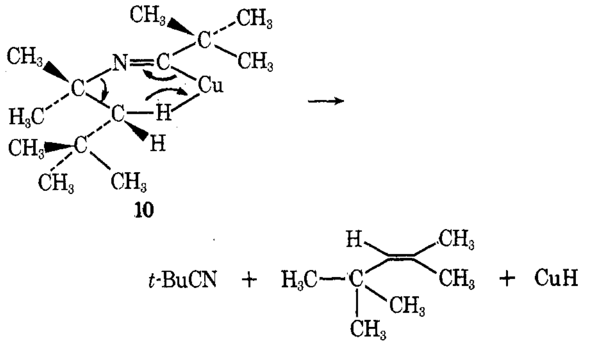
Table VI
Product Distribution from the Decomposition of 1,1,3,3-Tetramethylbutylcopper(I) Reagent

		Time,	Yield, %[b]		
No.	Solvent[a]	min	t-BuCN	Alkane[c]	Alkene[d]
1	Et_2O	15	12	2.5	12
2	Et_2O	30	46	18	32
3	Et_2O	480	55	23	33
4	THF	150	29	3.7	27.8

[a] Organolithium in pentane was used. [b] Yields determined by glpc analysis using authentic samples. [c] 2,4,4-Trimethylpentane. [d] 2,4,4-Trimethyl-2-pentene.

ing that would develop in transition states **8** or **9** would be severe enough to prevent the coupling reaction. In these cases an alternate reaction occurs, that of dissociation, due in part to relief of steric strain.

Finally, we would like to comment on the mechanism for the dissociation of copper aldimines to alkylnitriles and alkylcopper. One of the probable mechanisms involves the cleavage of copper aldimines to give alkylnitrile and organocopper. The latter reagent disproportionates to yield equal amounts of alkane, alkene, and metallic copper (eq 6 and 7). However, as can be seen in Table VI, the yield of 2,4,4-trimethyl-2-pentene was higher than that of 2,4,4-trimethylpentane. Moreover, in the decomposition of the 2-phenyl-2-butylcopper intermediate, 2-phenyl-2-butene was formed in about 25–30% higher yield than *sec*-butylbenzene. To account for the increase in olefin yield we would like to suggest that the copper aldimine, besides dissociating to give nitrile and alkylcopper (eq 6), can also dissociate *via* transition state **10** (eq 12) to yield nitrile and olefin.


10

$$t\text{-BuCN} + (CH_3)_3C\text{—}CH{=}C(CH_3)_2 + CuH \quad (12)$$

Experimental Section

Melting points were measured with a Mel-Temp apparatus and both melting and boiling points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or Brucker 90-MH spectrophotometer; chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Low-resolution mass spectra were obtained on a Nuclide electron impact mass spectrometer. Glpc analyses were carried out on F & M Model 500 gas chromatograph under reported conditions. Microanalyses were performed by the Beller Laboratories, Gottingen, Germany.

Solvents. Reagent-grade tetrahydrofuran (THF) and diethyl ether were distilled from lithium aluminum hydride under nitrogen and stored over 3A Molecular Sieves. Bulk solvents were distilled before use. Industrial grade dimethylformamide (DMF) was purified by distilling from barium oxide and discarding a forecut.

Reagents. Isocyanides were synthesized using a recent procedure.[23] Cuprous iodide was dried in an oven (120°) for 6 hr and cooled in a desiccator just before use. Organolithium reagents purchased from Foote Minerals Co. were titrated before use.[24] Grignard reagents were prepared using standard procedures and analyzed whenever it was necessary. Established procedures were used to prepare organocopper reagents.[25] All other reagent-grade materials were purified by distillation.

General Procedure for Preparing Metallo Aldimines. The following procedure is typical of compounds reported in Tables IV–VI.

To 2.085 g (15 mmol) of TMBI dissolved in 15 ml of dry ether at room temperature, under an argon atmosphere, was added 15.5 mmol of *tert*-butyllithium (in pentane) over a period of 2–3 min. After stirring for 10 min at room temperature, 3.04 g (16 mmol) of CuI was added and the mixture was stirred for 2.5 hr at ambient temperatures. The mixture was poured onto a mixture of ice and hydrochloric acid, under argon, and extracted with ether after separating inorganic material by filtration. The ether extract was washed with aqueous ammonia, dilute hydrochloric acid, and water, and dried over anhydrous sodium sulfate. Glpc analysis using an authentic sample on a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS on 60/50 AWCP column at 90° indicated that *tert*-butyl cyanide was formed in 61% yield.

Glpc analysis using authentic samples on the above column at 40° showed the yield of 2,4,4-trimethylpentane and 2,4,4-trimethyl-2-pentene to be 18 and 32%, respectively, when the yield of *tert*-butylnitrile was 46% (entry 2, Table III).

Identification of *n*-Butyl 1,1,3,3-Tetramethylbutyl Ketone. *n*-Butyl 1,1,3,3-tetramethylbutyl ketone was identified by ir, nmr, and mass spectral analysis: bp 79–80° (3 mm); ir (CCl_4) 1702 (s) and 1368 cm^{-1}; nmr (CCl_4) δ 0.87 (12, s), 1.11 (6, 2), 1.78–1.11 (4, broad), 1.62 (2, s), 2.42 (2, t, J = 7 Hz); mass spectrum parent ion m/e 198.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.8; H, 13.22. Found: C, 78.76; H, 13.13.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)pentanamide. *N*-(1,1,3,3-tetramethylbutyl)pentanamide was identified by ir, nmr, and mass spectral analysis: bp 108–110° (4 mm); ir (CCl_4) 3440, 3360–3330, 1685 (s), 1508, and 1376 cm^{-1}; nmr (CCl_4) δ 0.99 (12, s), 1.36 (6, s). 1.79 (2, s), 1.78–1.11 (4, broad), 2.09 (2, t, J = 7 Hz), 6.8 (1); mass spectrum m/e 213, 198, 171, 156, 142, 114, 102, 72, 58, 57.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; O, 7.50. Found: C, 73.20; H, 12.73; O, 7.48.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)-2-methylbutanamide. *N*-(1,1,3,3-Tetramethylbutyl)-2-methylbutanamide was identified by ir, nmr, and mass spectral analysis: mp 86–88°; ir (CCl_4) 3435, 1685 (s), 1505, and 1372 cm^{-1}; nmr (CCl_4) δ 0.86–1.07 (14, m), 1.36 (6, s), 1.72 (3, d, J = 8 Hz), 1.57–2.08 (3, broad), 5.22 (1, broad); mass spectrum m/e 213, 198, 156, 142, 114, 102, 97, 58, 57.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; N, 6.56. Found: C, 73.33; H, 12.70; N, 6.54.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)-2,2-dimethylpropanamide. *N*-(1,1,3,3-Tetramethylbutyl)-2,2-dimethylpropanamide was identified by ir, nmr, and mass spectral analysis: mp 85–86°; ir (Cl_4) 3440, 1670 (s), 1505, and 1370 cm^{-1}; nmr (CCl_4) δ 1.0 (9, s), 1.10 (9, s), 1.33 (6, s), and 1.71 (2, s); mass spectrum m/e 213, 198, 156, 142, 112, 97, 85, 57, 55.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; N, 6.56. Found: C, 73.31; H, 12.64; N, 6.63.

General Procedure for the Reaction of Organolithium Reagent with TPMI. The following procedures A and B are typical of reactions run in 1:1 and 2:1 ratios, respectively (Table IV).

A. To a stirred solution of 2.69 g (10 mmol) of TPMI dissolved in 20 ml of dry THF at −78° under a dry argon atmosphere was added 10 mmol of *tert*-butyllithium (in pentane) over a period of 2–3 min. After stirring for 30 min at −78°, the mixture was poured onto an ice–water, extracted with ether, and dried over anhydrous sodium sulfate. Glpc analysis indicated the yield of *tert*-butyl cyanide to be 88%.

B. To a stirred solution of 5.38 g (20 mmol) of TPMI dissolved in 30 ml of dry THF at −78° under an argon atmosphere was added 40 mmol of *tert*-butyllithium (in pentane) over a period of 8–10 min. After stirring for an additional period of 30 min, the mixture was brought to room temperature and stirred for 2 hr. The reaction mixture was worked up as above, and after the ether extract was concentrated, the crude ketimine was refluxed with dilute hydrochloric acid for 2 hr. The ether extraction was concentrated and distilled to give 2.13 g (~75%) of di-*tert*-butyl ketone, bp 150–151°.

Di-*tert*-butylketimine. The above procedure was repeated but omitting the acid hydrolysis step. The reaction mixture was poured into an ice–water mixture and extracted with either. Distillation of the crude reaction product gave 2.18 g (77.4% yield) of di-*tert*-butylketimine:[6] bp 163–163.5°; ir (neat) 1610 and 1372 cm^{-1}; nmr (CCl_4) δ 1.24 (18, s), 0.95 (1, broad); mass spectrum parent ion m/e 141.

Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56. Found: C, 76.57; H, 13.66.

Identification of Dimesitylketimine. Dimesitylketimine was identified by ir, nmr, and mass spectral analysis: mp 124-125.5°; ir ($CHCl_3$) 3540-3260 (broad), 1620, 1600 (s), 910, and 855 cm^{-1} (s); nmr (CCl_4) δ 2.29 (12, s), 2.44 (6, s), and 9.11 (1, broad); mass spectrum *m/e* 265.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.98; H, 8.74. Found: C, 85.86; H, 8.76.

General Procedure for the Reaction of Grignard Reagent with TPMI. Primary Grignard Reagent. To a stirred solution of 35 mmol of freshly prepared *n*-butylmagnesium bromide in ether at room temperature and under an argon atmosphere was added 4 g (15 mmol) of TPMI dissolved in dry THF over a period of 2-3 min. The reaction mixture was refluxed for 2 hr, poured onto a mixture of ice-dilute hydrochloric acid, and extracted with ether. Glpc analysis on a 6 ft × 0.25 in. XE-60 column indicated a 10-20% yield of *n*-valeronitrile. Concentration of solution followed by elution through alumina column with a mixture of ether-pentane as eluent gave 0.72 g (58% yield) of 5-amino-4-cyanononene-4 (**2**) whose spectral properties were identical with that of an authentic sample, prepared as below.

5-Amino-4-cyanononene-4 (2). To 2.9 g (35 mmol) of *n*-valeronitrile dissolved in 5 ml of dry THF at 0° under an argon atmosphere was added 20 mmol of *n*-butylmagnesium bromide over a period of 10 min. The mixture was refluxed for 3 hr and the resin-like material along with solvent was poured onto a dilute hydrochloric acid-ice mixture. The ether extract was washed once with water and twice with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Vacuum distillation of the concentrated crude product gave 1.45 g (49% yield) of pure product: bp 142-143° (5 mm) [lit.[9] bp 125-126° (3 mm)]; ir (CCl_4) 3490, 3390, 3360 (m), 2190 (s), and 1632 cm^{-1} (vs); nmr (CCl_4) δ 4.72 (s, 2, position concentration dependent), 2.35 (t, 2), 1.97 (t, 2), 1.47 (complex, 6), 0.95 (t, 6); mass spectrum parent ion *m/e* 166.

Hydrolysis of 5-Amino-4-cyanononene-4. An aqueous solution of 2.85 g of **2** in dilute hydrochloric acid was refluxed for 6 hr and evaporation of the ether extract gave about 2.86 g (~100%, crude) of product, which was then distilled: bp 100-101° (5 mm) [lit.[9] bp 127-128° (18 mm)]; ir (CCl_4) 2245 (m), 1728 cm^{-1} (vs); nmr (CCl_4) δ 3.43 (t, 1), 2.72 (t, 2), 1.25-2.0 (complex, 8), 1.06 (t, 6).

Identification of 2-Amino-1-cyano-1,3-dicyclohexylpropene (3). 2-Amino-1-cyano-1,3-dicyclohexylpropene was identified by its ir and nmr analysis: mp 134-136°; ir (CCl_4) 3475, 3380, 2190 (s), 1620 cm^{-1} (vs); nmr ($CDCl_3$) δ 4.11 (2, broad), 2.27 (2, d, J = 7 Hz), 2-2.26 (1, t, overlapping with cyclohexyl protons), 1-2 (21, complex).

Anal. Calcd for $C_{16}H_{26}N_2$: C, 78.0; H, 10.54. Found: C, 77.7; H, 10.62.

Secondary Grignard Reagent. To 35 mmol of cyclohexylmagnesium bromide in ether at 0° under an argon atmosphere was added 8.07 g (30 mmol) of TPMI dissolved in 40 ml of dry THF. The mixture was refluxed for 1.5 hr, poured onto an ice-dilute hydrochloric acid mixture, and extracted with ether. The ether extract was washed with water, saturated with sodium chloride solution, and dried over anhydrous sodium sulfate. Glpc analysis in a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS and 60/50 AWCP column showed that cyclohexyl cyanide was formed in 94% yield.

After removing the solvents the mixture was distilled to give 2.55 g (78% yield) of cyclohexylnitrile, bp 44-45° (4 mm) [lit.[26] bp 72-75° (12 mm)], ir (CCl_4) 2248 cm^{-1} (m).

Tertiary Grignard Reagent. To 15 mmol of *tert*-butylmagnesium bromide in ether at room temperature under an argon atmosphere was added 2.5 g (10 mmol) of TPMI dissolved in 15 ml of dry THF over a period of about 90 sec. The mixture was refluxed for 2 hr and poured onto ice-dilute hydrochloric acid mixture. Glpc analysis of the ether extract showed that *tert*-butyl cyanide was formed in 6-7% yield. The unreacted trityl isocyanide was recovered.

In a like manner, the Grignard reagent was prepared in THF and the reaction mixture was refluxed for 10 hr. Infrared analysis of the reaction product indicated the absence of TPMI. The major product was observed to be triphenylmethyl cyanide with less than 5% yield of *tert*-butyl cyanide.

Aromatic Grignard Reagent. To 2.42 g (9 mmol) of TPMI dissolved in 10 ml of dry THF at 0° under an argon atmosphere was added 9 mmol of mesitylmagnesium bromide over a period of 5 min. After refluxing for 2 hr, the reaction mixture was worked up as usual. Glpc analysis using an authentic sample indicated the yield of 2,4,6-trimethylbenzonitrile to be 17%.

The above reaction was repeated but refluxed for 18 hr before work-up. The yield of 2,4,6-trimethylbenzonitrile was observed to be 39%.

General Procedure for the Reaction of Organocopper Reagent with TPMI. Reaction of *n*-Butylcopper with TPMI. To 3.82 g (20 mmol) of dry cuprous iodide in 15 ml of dry ether at −20° under an argon atmosphere was added 20 mmol of *n*-butyllithium (in hexane) drop by drop over a period of 20-25 min, giving a black solution. After the cold bath was removed, 2.69 g (10 mmol) of TPMI dissolved in 20 ml of dry THF was added over a period of 1-2 min at a rate such that the temperature of the mixture was brought to 25°. The mixture was refluxed for 6.5 hr and then poured onto cold water under an argon atmosphere. After the inorganic residue was filtered off, the ether extract was washed with ammonia solution followed by dilute acid and finally with water. Glpc analysis of the dried (Na_2SO_4) reaction mixture indicated a 38% yield of *n*-valeronitrile. After solvents were removed, the mixture was refluxed for 3 hr with dilute hydrochloric acid and extracted with ether. Glpc analysis indicated <2% yield of 5-nonanone.

Reaction of Lithium Di-*n*-butyl Cuprate with TPMI. To an ether solution of 25 mmol of *n*-butyllithium (in pentane) and 2.38 g (10.5 mmol) of cuprous iodide was added 2.69 g (10 mmol) of TPMI in 20 ml of THF. The reaction was stirred for 6 hr at 25° and worked up in the usual manner. Glpc analysis on a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS and 60/50 AWCP column indicated a 40% yield of *n*-valeronitrile. The yield of triphenylmethane was found to be 84% from glpc analysis on a 4 ft × 0.25 in. SF-96 column. The inorganic residue was stirred with 20 ml of THF for 30 min over a steam bath. Filtration followed by addition of petroleum ether (bp 30-60°) gave <0.1 g of triphenylcarbinol, mp 161-163°; ir was found to be identical with that of an authentic sample.

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Registry No.—**2**, 49689-62-5; **3**, 49633-70-7; TPMI, 1600-49-3; TMBI, 14542-93-9; *n*-butyl 1,1,3,3-tetramethylbutyl ketone, 49633-72-9; *N*-(1,1,3,3-tetramethylbutyl)pentanamide, 49633-73-0; *N*-(1,1,3,3-tetramethylbutyl)-2-methylbutanamide, 49633-74-1; *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide, 49633-75-2; di-*tert*-butyl ketone, 815-24-7; di-*tert*-butylketimine, 29097-52-7; dimesitylketimine, 49633-78-5; 4-cyano-5-nonanone, 49633-79-6.

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

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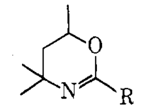
Treatment of the 2-chloromethyloxazine **2** with lithium hexamethylsilazane produces the α-chloromethyloxazine carbanion **12** which, upon alkylation, leads to the elaborated oxazine. The latter may be reduced and hydrolyzed to α-chloro aldehydes or directly hydrolyzed to α-chlorocarboxylic acids.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

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

DHOR ≡



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

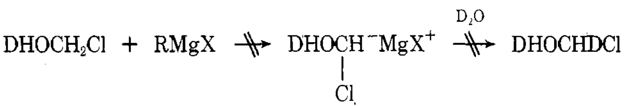
Results and Discussion

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

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

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

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



2 **7**

$$\underset{\mathbf{2}}{DHOCH_2Cl} + RMgX \not\longrightarrow \underset{\mathbf{7}}{DHO\underset{\displaystyle Cl}{\underset{|}{C}}H^-MgX^+} \overset{D_2O}{\not\longrightarrow} DHOCHDCl$$

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