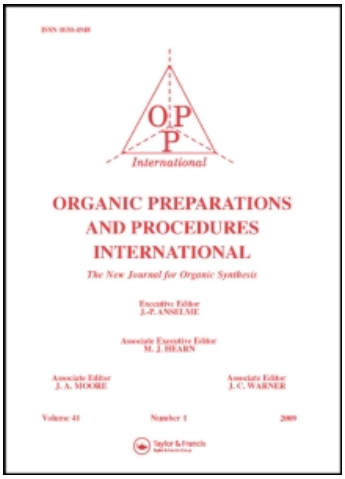

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Periasamy, M. P. and Walborsky, H. M.(1979) 'ISOCYANIDES IN ORGANIC SYNTHESIS. A REVIEW', Organic Preparations and Procedures International, 11: 6, 293 — 311
To link to this Article: DOI: 10.1080/00304947909355415
URL: http://dx.doi.org/10.1080/00304947909355415

ORGANIC PREPARATIONS AND PROCEDURES INT. 11(6), 293-311 (1979)

ISOCYANIDES IN ORGANIC SYNTHESIS. A REVIEW

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INTRODUCTION

Isocyanides, which are isoelectronic with carbon monoxide, are part of a limited class of stable organic compounds formally possessing a divalent carbon.

$$:C::\ddot{O}: \longleftrightarrow :\bar{C}:::\overset{+}{O}$$

$$:C::\ddot{N}\text{-}R \longleftrightarrow :\bar{C}:::\overset{+}{N}\text{-}R$$

They undergo a wide variety of reactions. They behave as nucleophiles, electrophiles, carbenes, radical acceptors and pseudohalogens.[1] The presence of a non-bonding pair of electrons in an sp-hybridized orbital on the terminal carbon enables isocyanides to behave as strong carbon ligands for transition metals.[2] In general, most isocyanides do not exhibit appreciable toxicity to mammals. However, 1,4-diisocyanobutane has been shown to be highly toxic and therefore all isocyanides should be handled with due caution. Volatile isocyanides show their toxic action due to their ability, like carbon monoxide, to block hemoprotein and enzyme systems.[3] Isocyanides, with high vapor pressures, are usually malodorous.

There is an increasing number of naturally occurring molecules containing the isocyanide moiety being isolated. The antiobiotics xanthocillin[4a] and xanthocillin monoethyl ether[4b] have been shown to be 2,3-diisocyanobutadiene derivatives. The structure of a fungal metabolite

isolated from Trichoderma sp. possesses a novel isocyano epoxide group[5] and recently sesquiterpene and diterpene isocyanides have been isolated from marine sponges.[6] Isocyanides have also been proposed as precursors for the synthesis of amino acids in the "prebiotic soup".[7]

In this review we will limit our discussions to the recent developments in the preparation of isocyanides, the synthetic applications of α-addition reactions, and the use of isocyanides for the deamination of primary amines.

I. SYNTHESIS OF ISOCYANIDES

1. Dehydration of N-monosubstituted Formamides

The ready availability of N-monosubstituted formamides, due to their ease of formation, makes them an attractive precursor for the formation of isocyanides. The original dehydration procedure of Ugi[1,8], using phosgene in the presence of a tertiary amine, suffers from the disadvantages inherent in the use of phosgene for large scale preparations. This difficulty may be circumvented by the use of chlorodimethylformiminium chloride (1) (Vilsmeier reagent). This reagent is readily prepared, in situ, from thionyl chloride and N,N-dimethylformamide (DMF). The addition of this dehydration reagent, under controlled conditions, to the formamide leads to excellent yields of isocyanides.[9]

$$(CH_3)_2NCHO + SOCl_2 \longrightarrow [(CH_3)_2N{=}CHCl]^+Cl^- + SO_2$$

$$[(CH_3)_2N{=}CHCl]^+Cl^- + RNHCHO \longrightarrow R{-}N{=}C + (CH_3)_2NCHO + 2HCl$$

Table 1. PREPARATION OF ISOCYANIDES USING VILSMEIER REAGENT (1)

RNC	Yield %	Reaction scale, mol
Aliphatic		
n-Hexyl	82	0.13
Cyclohexyl	87	0.10
t-Butyl	55	0.20
1,1,3,3-Tetramethylbutyl	93	0.53
Benzylic		
Benzyl	63	0.12
(R)-(+)-2-Phenyl-2-butyl	92	0.04
1,1-Diphenylethyl	90	0.08
Trityl	94	0.06
Cyclopropyl		
(R)-(-)-2,2-Diphenyl-1-methylcyclopropyl	88 70	0.019 0.003
Vinyl		
(E)-1,2-diphenylvinyl	84	0.06
Aromatic		
Phenyl	60	0.18
2,6-Dimethylphenyl	74	0.11
p-Methoxyphenyl	82	0.18
1-Naphthyl	72	0.04

As can be seen from Table 1, this procedure provides a general, convenient method for the preparation of cyclic, acyclic, benzylic, cyclopropyl, vinylic and aromatic isocyanides. Recently a variation of the Vilsmeier reagent, 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of triethylamine has been used to dehydrate formamides.[10] Ugi[11] has proposed a modification of his original procedure using diphosgene (perchloro (methyl formate)) in place of phosgene. However, the availability of this reagent is limited.[12]

Preparation of Isocyanides - To a stirred solution of formamide (0.5 mol) in 1L of DMF was added, under a nitrogen atmosphere, a solution of thionyl chloride (0.5 mol) dissolved in 150 ml. of DMF at a rate such that the temperature never exceeded -50°. After addition, the cooling bath was removed momentarily to allow the temperature to rise to -35° (for 1° and 2° aliphatic and for aromatic formamides -45°), then replaced and anhydrous sodium carbonate (1 mol) was added. The cooling bath was removed, and the reaction mixture was heated to 35° with rapid stirring and at ambient temperature for 1 hour. The mixture was diluted with ice-water in a separatory funnel and extracted into pentane. The extract was dried over anhyd. sodium sulfate, evaporated and the residue distilled.

2. Addition of Dichlorocarbene to Primary Amines

Application of phase-transfer catalyses to the Hofmann carbylamine reaction has made this reaction competitive with the dehydration of formamides. Weber and Gokel[13] demonstrated that the reaction of primary amines with chloroform and 50% sodium hydroxide in the presence of a phase-transfer catalyst, benzyltriethylammonium chloride, produced isocyanides in 40-60% yield. Using this procedure, Jakobsen[14] prepared aliphatic N-isocyanoimines from the corresponding hydrazones. Employing a crown ether as a phase-transfer catalyst, Mayer[15] synthesized a number of isocyanides in very good yield (~60%) by reacting N-sulfinylamine with chloroform and solid potassium hydroxide.

In addition, syntheses of a variety of novel isocyanides, namely α-acyloxy isocyanide[16], N-acyl isocyanide[17], N-isocyanoarylamine[18] and 1-isocyano sugars[19] have been reported.

II. REACTIONS OF ISOCYANIDES WITH ORGANOMETALLIC REAGENTS

Recent work on the reaction of isocyanides with organometallic reagents has demonstrated the usefulness of these reactions in providing intermediates for the preparation of a variety of molecules. Isocyanides

may undergo two types of reactions depending on the structure. If the isocyanide possesses α-hydrogens then the organometallic reagent will react with the acidic hydrogen to produce α-metallated isocyanides. The chemistry of these intermediates is being explored actively by Schöllkopf and his collaborators.[20]

$$R\text{-}CH_2\text{-}N = C + R'M \longrightarrow R\text{-}\underset{\displaystyle M}{\underset{|}{CH}}\text{-}N = C + R'\text{-}H$$

If the isocyanide does not possess α-hydrogens then α-addition to the isocyanide moiety occurs.[21] Our discussion will focus on this latter reaction.

$$RN = C + R'M \longrightarrow R\text{-}N = C\begin{matrix}R' \\ \diagdown \\ \diagup \\ M\end{matrix}$$

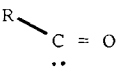
1. Formation of Metallo Aldimines

Metallo aldimines can conveniently be prepared by the α-addition of an organometallic reagent to an isocyanide that does not contain an α-hydrogen. In principle any aryl or tertiary isocyanide can be used, since aryl isocyanides have a tendency to oligomerize and need to be freshly prepared before use; tert-aliphatic isocyanides are thus more convenient for this purpose. Here, too, there is a structural limitation in that when there are two or more aryl groups attached to the α-carbon then the metallo aldimine formed is unstable and dissociates (see 2h below). The most convenient isocyanide to work with is 1,1,3,3-tetramethylbutyl isocyanide (TMBI) owing to the low cost of the starting material, ease of preparation and that it is not offensively malodorous.[21]

Organolithium, Grignard, organocopper and zinc reagents have been shown to react with isocyanides to yield the α-addition products, metallo aldimines. Primary, secondary and tertiary aliphatic organometallic

reagents react rapidly to produce excellent yields of the metallo aldimine. Aromatic organometallic reagents react to a varying degree depending both on the structure of the isocyanide and the nature of the aromatic reagent itself. Attempts to react anions generated from carbon acids, with pK_a<30 resulted in no α-addition. This was the case for allyl and benzyl lithium, sodium acetylide and sodium malonate. However, intramolecular ring closure reactions involving α-addition of anions of active methylene compounds or metal alkoxides to an isocyano group have been reported.[20]

2. Reaction of Metallo Aldimines (Masked acyl Carbanions)



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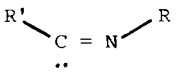
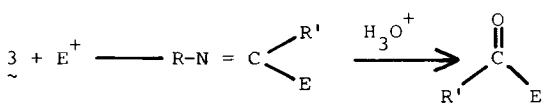


3

Metallo aldimines (3) may be viewed as masked acyl carbanions similar in principle to those derived by Corey and Seebach (lithiodithiane),[22] Stork (magnesium enamine)[23] and Meyers (dihydro-1,3-oxazine).[24] In contrast to the instability of the acyl carbanion (2), the derivative 3 is quite stable in solution. The reaction of 3 with electrophilic reagents followed by hydrolysis of the imine introduces the acyl moiety into the product.[21,25]



(a) Preparation of Aldehydes

Hydrolysis of metallo aldimine 3 provides a simple procedure for the preparation of various aldehydes as shown in Table 2. Although the yields of aldehyde from Grignard reagents are lower than those obtained with

lithium reagents, the use of Grignard reagents may be more expedient whenever the lithium reagent is not readily available.

Table 2. SYNTHESIS OF ALDEHYDES FROM R'M AND TMBI

No.	R'M	Yield, %
1	n-ButylLi	93
2	n-HeptylMgBr	62
3	sec-ButylLi	96
4	sec-ButylMgBr	67
5	t-ButylLi	92
6	t-ButylMgBr	48
7	PhenylLi	55
8	PhenylMgBr	2

Deuterolysis of 3 provides a simple and inexpensive synthesis of 1-deuterioaldehydes (Table 3). It should be noted that when 1-deuterioaldehydes are prepared using Grignard reagents, one does not obtain complete deuterium incorporation. This problem can be minimized by the addition of the metallo aldimine to the substrate.[25]

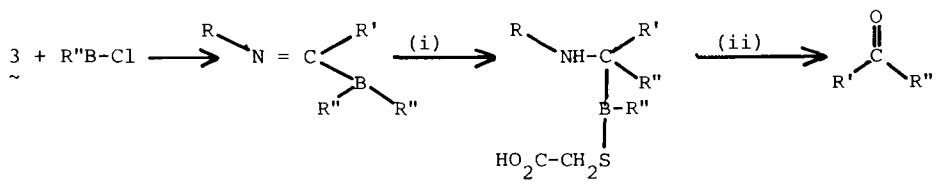
Table 3. SYNTHESIS OF 1-d-ALDEHYDES FROM RM AND TMBI

No.	RM	Yield, %	Deuterium, %
1	sec-ButylLi	92	98
2	t-ButylLi	92	98
3	sec-ButylMgBr	67	96
4	BenzylMgBr	63	80
5	c-PentylMgBr	66	89

Preparation of 1-d-2,2-Dimethylpropanal - To 0.2 mol of TMBI in 400 ml of ether under nitrogen was added, with mechanical stirring at -15°, 0.2 mol of tert-butyllithium (in pentane). D_2O (>99%, 0.4 mol) was injected into the reaction mixture with continued external cooling. Filtration of the mixture, followed by evaporation of the solvent, and steam distillation of the residue from 200 ml. of an oxalic acid solution (2M) gave 0.184 (92%) of deuterated product (98% isotopic purity), bp 75°.

(b) Preparation of Ketones

Alkylation of lithium aldimine 3 with ethyl and methyl iodide proceeds in good yield to give after hydrolysis the corresponding ketones. However, secondary halides yielded largely elimination products. This difficulty was overcome by utilizing dialkychloroboranes as the synthon for alkylhalides. In this manner Yamamoto, Konda and Moritani[26] reacted the lithium aldimine 3 with dialkylchloroborane, the iminoborane derivative was rearranged with thioglycolic acid and the new borane was oxidatively hydrolysed by H_2O_2/NaOH to yield the desired ketone.

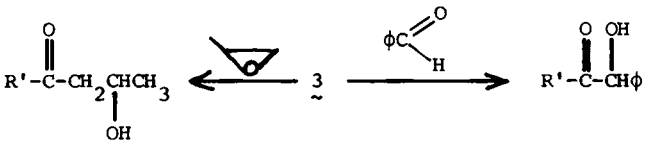


(i) $HSCH_2COOH$; (ii) H_2O_2/NaOH

Table 4. UNSYMMETRICAL KETONES FROM REACTION OF 3 with DIALKYLCHLOROBORANES

No.	R^2-BCI	R^1	Yield, %
1	Hexyl	Butyl	95
2	Hexyl	iso-Pentyl	92
3	Hexyl	Ethyl	86
4	Hexyl	Isopropyl	71
5	c-Pentyl	Butyl	63
6	c-Pentyl	Isopropyl	91

The lithium aldimines 3 were also shown to react with trimethylsilyl ketones.[25] Both α- and β-hydroxy ketones can be prepared as well. Reaction of 3 with benzaldehyde leads to an 81% yield of the α-hydroxy ketone and reaction with propylene oxide forms the β-hydroxy ketone in 90% yield. In the latter case very little, if any, dehydration occured.



This reaction shows promise in providing a convenient means for preparing mixed aldols. In the former case the reaction may be limited to non-enolizable carbonyls since reaction 3 with acetophenone resulted in the formation of aldimine rather than condensation product.

(c) Preparation of Keto Acids and Esters[25]

The carbonation of metallo aldimine 3 provides a simple synthesis of α-keto acids. The yields of various keto acids obtained from organolithium and Grignard reagents are given in Table 5. As noted earlier in the preparation of aldehydes, the yields of α-keto acids obtained from lithium reagents are superior to those prepared from Grignard reagents.

Table 5. SYNTHESIS OF α-KETO ACIDS FROM R'M AND TMBI FOLLOWED BY CARBONATION

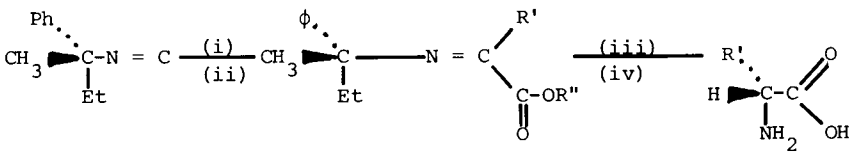
No.	R'M	Yield, %
1	ButylLi	56
2	ButylMgBr	34
3	PentylMgBr	26
4	sec-ButylLi	80
5	sec-ButylMgBr	47
6	PhenylLi	52

It was also shown[25] that the reaction of 3 with ethyl chloroformate produced α-keto esters in good yield.

(d) Asymmetric Synthesis of Amino Acids[27]

Carboxylation or carbethoxylation of the lithium aldimines formed

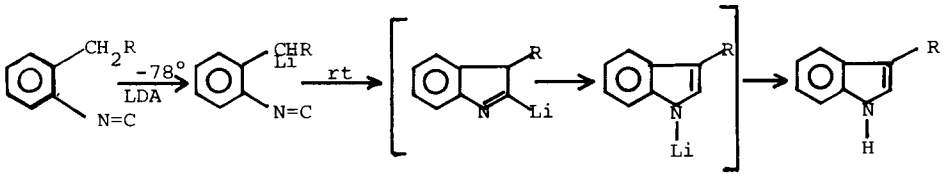
by the addition of ethyl, sec-butyl and isopropyllithium reagents to (R)-(+)-2-phenyl-2-butylisonitrile produced the corresponding α-imino acid or ester. Hydride reduction of the imino group followed by palladium catalyzed hydrogenolysis yield optically active amino acids in good yield and reasonable optical purity.



(i) R'Li; (ii) CO_2 or ClCOOEt; (iii) $LiBH_4$; (iv) $Pd(OH)_2/H_2$

(e) Preparation of Indoles

A unique and versatile synthesis of 3-substituted indoles has been developed by Saegusa and Ito[28] which involves the intramolecular α-addition of a lithium reagent to an isocyanide. Treatment of o-tolyl isocyanide with two equivalents of lithium diisopropyl amide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at -78° produced o-lithiomethylphenyl isocyanide, which upon warming to ambient temperature and hydrolysis yielded indole quantitatively.



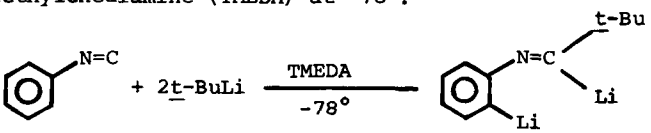
3-Substituted indoles may be prepared by reacting the o-lithiomethylphenyl isocyanide at -78° with electrophiles such as alkyl halides and epoxides, addition of more LDA and allowing reaction mixture to come to ambient temperature. The results are summarized in Table 6.

Table 6. PREPARATION OF 3-SUBSTITUTED INDOLES[28]

No.	R	Lithium amide	Yield, %
1	H	LDA	100
2	CH_3	LTMP	95
3	n-C_4H_9	LTMP	85
4	i-C_4H_9	LTMP	78
5	CH_2-CH(OH)-$(CH_3)_2$	LDA	68
6	CH_2CH(OH)-C_2H_5	LDA	61
7	CH_2-CH(OH)-CH_3	LDA	65

(f) α-Addition and Ortho Metallation of Phenyl Isocyanide

The conditions necessary to achieve α-addition followed by ortho lithiation is the use of t-butyllithium in the presence of N,N,N^1,N^1-tetramethylethylenediamine (TMEDA) at -78°.



Since phenyl isocyanide is made from aniline and because the aniline can be regenerated from the isocyanide, the isocyanide moiety may be used as a protecting group for aromatic amines. In this manner, aniline may be ortho alkylated or carboxylated via the ortho lithiated lithium aldimine of phenyl isocyanide.

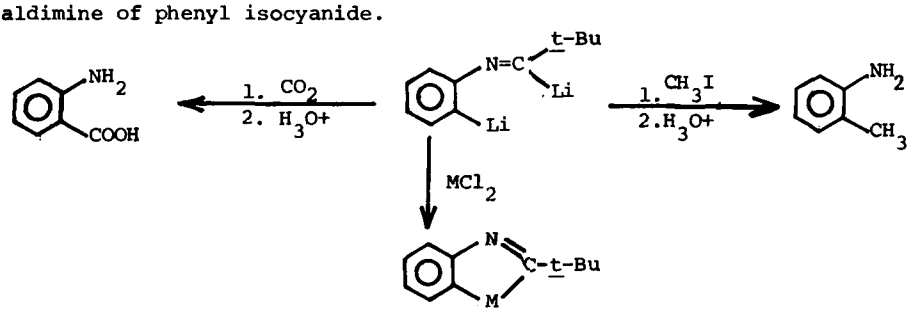


Table 7. PREPARATION OF 3-METALLO INDOLINES[29]

No.	MCl_2	Indoline (M)	Yield, %
1	SCl_2	S	65
2	$PhPbCl_2$	Ph.P	52
3	Ph_2SiCl_2	Ph_2Si	63
4	Me_2SiCl_2	Me_2Si	53
5	Me_2GeCl_2	Me_2Ge	68
6	Me_2SnCl_2	Me_2Sn	41

Preparation of 2-t-Butyl-3,3-diphenylbenzoazasilole[29] - To 21.6 mmol of t-butyllithium in 50 ml of anhydrous ether at -78° and under a nitrogen atmosphere was added dropwise a solution of 9.7 mmol of phenyl isocyanide in 15 ml of ether. The solution was allowed to warm to ambient temperature, 22 mmol of TMEDA was quickly added, and the solution was stirred for 6 h. The solution was cooled to ice-bath temperature and 19.5 mmol of diphenylsilyl dichloride was added and the reaction mixture was allowed to stir at ambient temperature for 6 h. before washing three times with water. The ethereal solution was dried over anhyd. sodium sulfate, and evaporated to yield 6.11 mmol (63%) of product, m.p. 128-129°.

(g) Deamination of Primary Amines Via Isocyanides

Aromatic and aliphatic primary amines can be converted to isonitriles conveniently and in high yields. Moreover, solutions of metals (Li, Na, K, Cu) in solvents like liquid ammonia, 1,2-dimethoxyethane and tetrahydrofuran have been shown to reduce isonitriles to the parent hydrocarbon.[30] This combination of reactions provides a method for deamination which is almost quantitative and relatively free of rearranged side products.

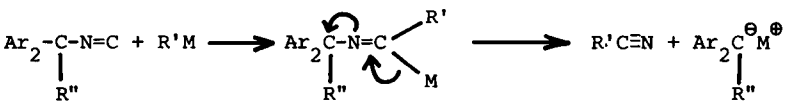
$$R\text{-}NH_2 \longrightarrow R\text{-}\overset{+}{N}\equiv C^{-} \longrightarrow R\text{-}H$$

The reducing medium of choice is sodium naphthalene in 1,2-dimethoxyethane.[31] A serious limitation to this reaction is that it is not stereospecific.[31]

Reduction of (-)-(S)-2-Phenyl-2-butyl Isocyanide - Under an argon atmosphere 0.03 g-atom of sodium and 0.03 mol of naphthalene in 50 ml of 1,2-dimethoxyethane were stirred for 1.5 h. The solution was cooled to -5° and 2 mmol of (-)-(S)-2-phenyl-2-butyl isocyanide was added and stirring was continued for 10 min. The reaction mixture was quenched with methanol, water and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, the solvent was removed and the residue distilled to give a quantitative yield of sec-butylbenzene, bp. 172-174°. The product was racemic.

(h) Dissociation of Metallo Aldimines

When the isocyanide moiety is attached to a carbon atom which contains two or more phenyl groups then the metallo aldimine, formed by addition of an organometallic to the isocyanide, is unstable, and decomposes to a cyanide and a stabilized carbanion. This amounts to an "isocyanide-metal exchange" reaction.[33] Thus, for example, trityl isocyanide can be viewed as a source of cyanide.



R"=CH_3, Ar.

This reaction is best suited for the preparation of secondary and tertiary cyanides. Grignard reagents give the best yields in the preparation of the secondary and lithium reagents for the preparation of tertiary cyanides. Table 8 lists a number of cyanides prepared in this manner. The significance of this reaction should be recognized from the

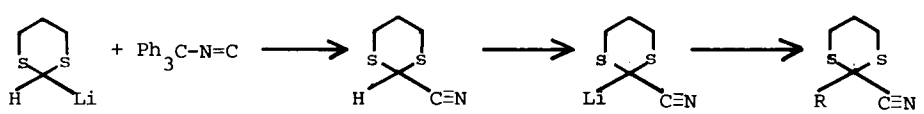
fact that secondary and tertiary halides ordinarily do not give satisfactory yields by the usual S_N2 displacement with cyanide ions.

Table 8. REACTIONS[33] OF TRIPHENYLMETHYL ISOCYANIDE WITH ORGANOMETALLIC REAGENTS

No.	R-M	Yield, %
1	sec-ButylMgBr	98
2	sec-HexylMgBr	79
3	c-HexylMgBr	94
4	c-HeptylMgBr	70
5	t-ButylLi	88

Cyclohexyl Cyanide - To 35 mmol of cyclohexylmagnesium bromide in ether at 0° under a nitrogen atmosphere was added 30 mmol of trityl isocyanide dissolved in 40 ml of dry tetrahydrofuran. The mixture was refluxed for 1.5 h., poured onto an ice-dilute hydrochloric acid mixture, and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a residue which was distilled to yield cyclohexylcyanide, (94%) bp. 44-45°/4mm.

Recently,[34] the "isocyanide-metal exchange" reaction was used for the preparation of a masked acyl cyanide as follows:



The 2-lithio-2-cyano-1,3-dithiane was reacted with a variety of halides (Table 9).

Table 9. ALKYLATION OF 2-LITHIO-2-CYANO-1,3-DITHIANE WITH RX

RX	CH_3I	i-PrI	$PhCH_2Br$	$PhC(=O)-CH_2Br$
Yield, %	81	91	94	97

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(Received March 26, 1979; in revised form July 9, 1979)