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ISONITRILES.[1] THE ISONITRILE - METAL EXCHANGE REACTION

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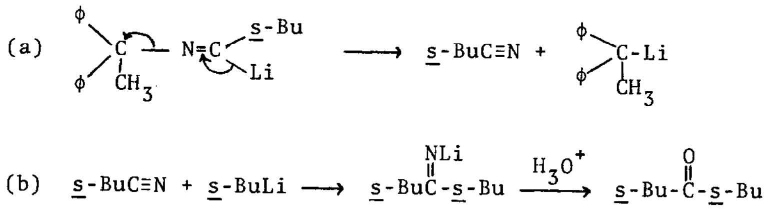
We have previously reported on the preparation of lithium aldimines by the addition of lithium reagents to isonitriles (eq. 1).[2] In addition, we have demonstrated that metallo aldimines are versatile intermediates for the preparation, *inter alia*, of aldehydes, ketones, α-keto acids, and α- and β-hydroxy ketones.[3]

$$R\text{-}N{=}C + R'Li \longrightarrow R\text{-}\ddot{N}{=}C\begin{matrix}\diagup R' \\ \diagdown Li\end{matrix} \qquad (1)$$

During the course of our investigation on the effect of the isonitrile structure on the course of the reaction (eq. 1) it was discovered that the reaction of 1,1-diphenylethylisonitrile with *s*-butyllithium yielded upon hydrolysis not only the expected 2-methylbutyraldehyde but 2-cyanobutane, *di*-*s*-butyl ketone and 1,1-diphenylethane as well. The formation of these latter products suggested that after the initial α-addition to yield the lithium aldimine (eq. 1) this intermediate dissociated to produce 1,1-diphenylethyllithium and 2-cyanobutane (eq. 2a). This unusual rearrangement is in effect a lithium-isonitrile exchange reaction.



$$\text{(b)}\quad \underline{s}\text{-BuC}{\equiv}\text{N} + \underline{s}\text{-BuLi} \longrightarrow \underline{s}\text{-Bu}\overset{\overset{\text{NLi}}{\|}}{\text{C}}\text{-}\underline{s}\text{-Bu} \xrightarrow{H_3O^+} \underline{s}\text{-Bu-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}\underline{s}\text{-Bu}$$

(2)

It appeared that the driving force for the exchange reaction was the propensity for the 1,1-diphenylethyl anion to behave as a leaving group. This then suggested that the trityl group would be even more effective.[4] Triphenylmethylisonitrile was prepared[5] and as expected it reacted much faster than 1,1-diphenylethylisonitrile in the metal-isonitrile exchange reaction. Moreover, the reaction mixture upon hydrolysis yielded nitrile and ketone exclusively (Table I) and no aldehyde could be detected.

Table I. Reaction of Triphenylmethylisonitrile (TPMI) With Organolithium Reagents.

RLi[a]	RLi/$(\phi)_3$CN=C	% Yield[b] Nitrile	Ketone
n-Butyl	1:1	8.5	48.5[c]
	2:1	9	59
s-Butyl	1:1	14	55[c]
	2:1	24	63
t-Butyl	1:1	88	-
	2:1	2	75
Cyclopropyl	1:1	1.5	20
Phenyl	1:1	-	93[c]
	2:1		94

(a) All lithium reagents were titrated before each experiment (R. L. Epplex and J. A. Dixon, J. Organometal. Chem., 8, 176 (1967). (b) Yields determined by glpc analysis based on recovered isonitrile. (c) Yield based on theoretical yield of ketone.

The exchange reaction also affords interesting synthetic possibilities. It provides a convenient method for the preparation of hindered nitriles such as t-butylnitrile which can be obtained in high yields since steric hindrance slows down reaction 2b.[6] In most cases reaction 2b competes favorably with reaction 2a and the product of the reaction is ketone, thus symmetrical ketones can best be obtained by using two equivalents of lithium reagent. Unsymmetrical ketones can be prepared by first using an equivalent of the more hindered lithium reagent, to permit reaction 2a to occur and then adding an equivalent of a less hindered lithium reagent. In this manner, t-butyl s-butyl ketone was prepared in 83% yield.[8] These syntheses are convenient since the intermediates are not isolated and all the reactions are performed in the same reaction flask.

Grignard reagents may also be used in place of lithium reagents. Moreover, in some cases they may not only be more convenient but more desirable. Preliminary investigation has shown that cyclopropylmagnesium bromide reacts with TPMI to give a 27% yield of cyclopropylnitrile whereas the lithium reagent gives only a 1.5% yield. Furthermore, cyclohexyl and mesityl Grignard reagent gave 78% and 39% yields of their respective nitriles. We are actively working to establish the scope and limitations of these reactions.

References

(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) H.M. Walborsky, W.H. Morrison, III and G.E. Niznik, J. Amer. Chem. Soc., 92, 6675 (1970).

(4) 2-Phenylbutylisonitrile does not undergo this exchange reaction. A detailed discussion of this effect will be made in our full paper. Also see, H.A. Smith and C.R. Hauser, J. Amer. Chem. Soc., 91, 7774 (1969).

(5) H.M. Walborsky and G.E. Niznik, J. Org. Chem., 36, 0000 (1971).

(6) Grignard reagents also give higher yields of nitriles due to the slow reaction of nitriles with these reagents. Whereas butyllithium yields mainly ketone, a 40% yield of n-valeronitrile is obtained when butylmagnesium bromide is used.

(7) It should be noted that careful hydrolysis will yield the precursor ketimine, i.e. di-t-butyl ketimine which can be isolated in 77% yield if desired. For difficulties in obtaining derivatives of di-t-butyl ketone see, H.D. Hartzler, J. Amer. Chem. Soc., 93, 4527 (1971).

(8) The scope and limitations of these reactions are under active investigation.