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# NON-AQUEOUS CYANATION OF HALIDES USING LITHIUM CYANIDE

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**Summary** : Efficient conversion of various halides into the corresponding nitriles with lithium cyanide in tetrahydrofuran is described.

Recently we reported that reaction of various carbonyl compounds with diethyl phosphorocyanidate1), chlorotrimethylsilane2) and acyl chlorides in the presence of lithium cyanide gave the corresponding protected cyanohydrins. Lithium cyanide3), which is inexpensive and easily available, has received little attention4) as a reagent for organic synthesis in contrast to potassium and sodium cyanides widely employed. The high reactivity of lithium cyanide may be ascribed to an affinity of the oxygenophilic lithium ion for the carbonyl oxygen and a good solubility in tetrahydrofuran (THF). We wish to report that a general non-aqueous cyanation has been achieved by reaction of lithium cyanide with various halides in THF.

Cyanation of alkyl halides5) can be generally accomplished by sodium and potassium cyanides in an aqueous alcohol solvent or dimethyl sulfoxide. Another approach is to use a phase-transfer catalyst5). These procedures require either aqueous or high-boiling polar solvents. Reaction of lithium cyanide with 1-bromo and 1-iodooctane in refluxing THF for 1 h gave 1-cyanooctane in 90% yield (entries 1 and 4). On the contrary, potassium and sodium cyanides did not generate any trace of 1-cyanooctane6) even with 15 h refluxing (entries 2, 3, 5 and 6). These results indicate the superiority of this procedure under non-aqueous condition. Other examples are listed in the Table, which include the conversion of benzyl and allyl halides into the corresponding cyanides (entries 9, 10 and 11).

Tributyltin cyanide7), which is the new source of cyanide ion, has been prepared by 18-crown-6 catalyzed reaction of potassium cyanide with tributyltin chloride. The current procedure quantitatively gave tributyltin cyanide without any catalysts (entry 14).

Another intriguing examples were realized in the preparation of benzeneselenyl cyanide8) and _p_-tolyl thiocyanate9)(entries 15 and 16). The existing procedures8)9) have required the use of cyanotrimethylsilane for the conversion of corresponding chlorides into cyanides.

In addition, simple conjugate hydrocyanation10) of 4-cholesten-3-one was achieved with lithium cyanide to give 5-cyanocholestan-3-one (80%, $5\alpha/5\beta$-cyano=3/1)11). This procedure can avoid the use of diethylaluminum cyanide or hydrogen cyanide in the Nagata method$^{12)}$.

Thus, the non-aqueous cyanation using lithium cyanide may have a wide applicability in organic synthesis.

**Table.** $\mathrm{RX} + \mathrm{MCN}^{a)}(3eq) \xrightarrow{\mathrm{THF}} \mathrm{RCN}$

| Entry | Substrate | M | Conditions (h) | Yield (%)$^{b)}$ |
|---|---|---|---|---|
| 1 | n-$C_8H_{17}I$ | Li | 1 , reflux | 90 |
| 2 | | Na | 15 , reflux | No reaction |
| 3 | | K | 15 , reflux | No reaction |
| 4 | n-$C_8H_{17}Br$ | Li | 1 , reflux | 90 |
| 5 | | Na | 15 , reflux | No reaction |
| 6 | | K | 15 , reflux | No reaction |
| 7 | n-$C_8H_{17}Cl$ | Li | 18 , reflux | 50$^{c)}$ |
| 8 | n-$C_8H_{17}OTs$ | Li | 1 , reflux | quant. |
| 9 | $C_6H_5CH_2Br$ | Li | 2 , reflux | 92 |
| 10 | $C_6H_5CH_2Cl$ | Li | 6 , reflux | quant. |
| 11 | 3-Bromocyclohexene | Li | 1 , reflux | 93 |
| 12 | $C_6H_5CH_2CH_2Br$ | Li | 1 , reflux | quant. |
| 13 | $BrCH_2CH_2CO_2C_2H_5$ | Li | 1 , reflux | 66 |
| 14 | $(C_4H_9)_3SnCl$ | Li | 1 , r.t. | quant. |
| 15 | p-$CH_3C_6H_4SCl$ | Li | 0.5, r.t.$^{d)}$ | 83 |
| 16 | $C_6H_5SeCl$ | Li | 0.5, r.t.$^{d)}$ | 87 |

a) See reference 3. b) Unless otherwise stated, yields were based on isolation. c) Based on n.m.r.. d) The reaction was carried out in the coexistence of 0.1 (entry 15) and 0.2 eq. (entry 16) of iodine, respectively.

## References and Notes

1) S. Harusawa, R. Yoneda, T. Kurihara, Y. Hamada and T. Shioiri, Tetrahedron Lett., **25**, 427 (1984). 2) R. Yoneda, K. Santo, S. Harusawa and T. Kurihara, Synthesis, **1986**, 1054. 3) LiCN was prepared according to the Livinghouse procedure( Org. Synth. **60**, 126, (1981)) and generally used without further purification. LiCN (0.5M in DMF) is also available from Aldrich Chemical Company. 4) For nucleophilic cyanation, see : a) I. B. Johns and H. R. DiPietro, J. Org. Chem., **29**, 1970 (1964). b) D. A. Evans, G. L. Carroll and L. K. Truesdale, ibid., **39**, 914 (1974). c) K. Mai and G. Patil, ibid., **51**, 3545 (1986). 5) J. March, "Advanced Organic Chemistry", 3rd ed. Wiley-Interscience, 1984 , p429 and references cited therein. 6) H. Fujihara, K. Imaoka, N. Fukukawa and S. Oae, J. Chem. Soc. Perkin Trans. I, **1986**, 333. 7) M. Tanaka, Tetrahedron Lett., **21**, 2959 (1980). 8) S. Tomoda, Y. Takeuchi and Y. Nomura, Chem. Lett., **1981**, 1069. 9) D. N. Harpp, B. T. Friedlander, R. A. Smith, Synthesis, **1979**, 181. 10) For a review, see W. Nagata and M. Yoshioka, Org. React., **25**, 255 (1977). 11) To a LiCN, which was freshly prepared from acetone cyanohydrin (213mg) and lithium hydride (20mg) according to reference 3, was added a solution of 4-cholesten-3-one (193mg) in anhydrous THF (12ml). The mixture was refluxed overnight under nitrogen. After addition of 2N NaOH, the ordinary work-up gave 5-cyanocholestan-3-one (80%, 5α/5β=3/1). 12) W. Nagata and M. Yoshioka, Org. Synth. **52**, 90 (1972).

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