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CROWN ETHER CATALYSIS II CYANIDE AND NITRITE AS "NAKED" ANIONS

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During the past few years, the concept of phase transfer reactions has been explored extensively by synthetic chemists The pioneering work of Starks,(1) Weber,(2) and Markoza(3) on the liquid/liquid phase transfer process has led to an explosion in the synthetic usefulness of this class of reactions (4) The extension into solid/liquid phase transfer by Liotta(5) and others(6) have extended the usefulness of this reaction further. We wish to report on our study with two solid/liquid phase transfer processes moderated by crown ethers, specifically 18-Crown-6 (7)

In the classic work by Starks(1) on cyanide nucleophilicities in the liquid/liquid phase transfer process, he reports very good yields with primary and secondary alkyl halides being converted to their corresponding alkyl nitriles However, he reports that when benzyl halides were the substrate, hydrolysis to the alcohol, not displacement by cyanide, was the principle product We have also observed this same behavior with activated halides (allylic and benzylic) Since the conversion of activated halides to their corresponding nitriles is especially important in introducing ^{14}C, ^{13}C, and ^{15}N into biologically active compounds we have developed a solid/liquid phase transfer method which employs 18-Crown-6 to overcome this disadvantage For instance, reaction of benzyl chloride (or bromide) with dry KCN in the presence of 18-Crown-6 gives 90-95% yields of the corresponding nitrile The 18-Crown-6 is used in a catalytic amount and is quite easy to remove after the reaction is over (8) The same reaction was observed in the conversion p-nitrobenzyl chloride, p-chlorobenzyl chloride, and 3,4-dimethoxybenzyl chloride to their corresponding nitriles We also found that small amounts of water did not substantially effect the course of the reaction. When benzyl chloride was reacted with KCN in 1-2% H_2O/CH_3CN, only phenylacetonitrile was observed. All yields were isolated yields and ranged from 85-95%.

A more important application of this technique is the ability to do S_N2 displacements on substrates which can tolerate no nucleophilic solvents (H_2O, alcohols, or DMSO). Evans, *et al.*(9) have recently shown the usefulness of trimethylsilyl cyanide as a synthetic intermediate.

The synthesis of this intermediate is tedious and expensive, however. By the simple modification of doing a cyanide displacement on trimethylsilyl chloride in the presence of 18-Crown-6, 40-50% distilled yields of pure trimethylsilyl cyanide may be obtained. This reaction is much easier to perform, although yields are slightly lower, than reported by Evans.

We have also observed that nitrite is solid/liquid phase transferred under 18-Crown-6 catalysis to form nitro compounds as the major product, the major by-product being nitrite esters. The yields and product distribution are similar, although slightly lower, to nitrite displacements in DMSO.(10) The simplicity of reaction and ease of workup makes this difference in yields inconsequential. The nitrite displacement in the Starks(1) system is not an efficient process, although this problem has recently been circumvented by Weber.(11) Table One gives a representative sample of the nitro compounds formed by this procedure.

Table One

Nitrite Displacements in Acetonitrile using
1:20 Molar Ratio of 18-Crown-6[a]

Starting Halide	Product	Isolated Yield
1-bromo octane	1-nitro octane	65-70%
1-iodo octane	1-nitro octane	50-55%
cyclohexylbromide	1-nitrocyclohexane	0-3%
2-bromoethylbenzene	2-nitroethylbenzene	32%
3-bromo-1-phenylpropane	3-nitro-1-phenylpropane	51%
benzyl chloride	α-nitrotoluene	34%

[a] All reactions run at a temperature range of 25-40°C, molar ratio of halide nitrite catalyst = 20:22 1.

A representative experimental procedure is given for the synthesis of trimethylsilyl cyanide. A dry 250 ml round-bottom flask was charged with dry KCN (6 6 g, 0 1 mol), 20 ml methylene chloride, trimethylsilyl chloride (14.0 ml, 12 g, 0.11 mol, distilled from CaH_2 before use), 18-Crown-6 (0.1 g, 0.4 mmol) and the mixture was refluxed, protected from the atmospheric moisture with a $CaCl_2$ drying tube, with stirring, for 24 hours At the end of the reflux the salts had acquired a light brown color. The reflux condenser was then replaced with a 12.5 cm Vigreaux column and the mixture distilled directly from the pot The fraction boiling at 114-117°C yielded pure water-white trimethylsilyl cyanide (3.3 g, 0.036mol) which was identical in all respects with the properties reported by Evans(8). Gc analysis showed impure trimethylsilyl cyanide in the lower fractions from which another 5-10% could be obtained upon redistillation. Overall yield ∿ 45%.

We think the above solid/liquid phase transfer procedures offer substantial advantages over the more classical procedures, especially in small-scale reactions to introduce isotopes into biological molecules. From these and other(5,6) reactions, crown ethers, specifically 18-Crown-6, have been demonstrated to be of proven utility in the arsenal of the synthetic chemist.

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REFERENCES

1. C M. Starks, *J. Amer. Chem. Soc.*, *93*, 191 (1970); C M Starks and R.M. Owens, *J. Amer. Chem. Soc.*, *95*, 3613 (1973), C.M. Starks, First Fall Organic Conference, Cape Cod, Mass., Oct 1, 1973.

2. W.P. Weber, K.V Scherer, D.T. Sepp, *Tetrahedron Lett.*, 2983 (1974); W.P. Weber and J.P. Shepherd, *Tetrahedron Lett.*, 4907 (1972); W.P Weber, G W Gokel, and I.K. Ugi, *Angew. Chem. internat. Ed.*, *11*, 520 (1972).

3. M. Mzkosza and M Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969), M. Makosza, A. Jonczyk, B Serafin, *Tetrahedron Lett.*, 1351 (1971).

4. E V Dehmlow, *Angew. Chem. internat. Ed.*, *13*, 170 (1974), J. Dockx, *Synthesis*, 441 (1973).

5. C.L. Liotta and H P. Harris, *J. Amer. Chem. Soc.*, *96*, 2252 (1974), C.L. Liotta, H.P. Harris, M McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974)

6 H D. Durst, *Tetrahedron Lett.*, 2421 (1974); H.D. Durst, J.W. Zubrick, and J.R. Kieczykowski, *Tetrahedron Lett.*, 1777 (1974), D.J. Sam and H.E. Simmons, *J. Amer. Chem. Soc.*, *96*, 2252 (1974), D.J Sam and H E. Simmons, *J. Amer. Chem. Soc.*, *94*, 4024 (1972), D.J. Cram, *Science*, *183*, 801 (1974), C.J. Pederson and H.K. Frensdorff, *Angew. Chem. internat. Ed.*, *11*, 16 (1972); J.J. Christensen, J.O. Hill, and R.M. Izatt, *Science*, *174*, 459 (1971), C J Pederson, *J. Amer. Chem. Soc.*, *89*, 7017 (1967), *92*, 391 (1970)

7. Pederson's Nomenclature 18-Crown-6 is 1,4,7,10,13,16-hexaoxacyclooctadecane and can be synthesized according to the procedure of R N. Green, *Tetrahedron Lett.*, 1793 (1972) or by that of G.W. Gokel, D.J Cram, C.L. Liotta, H.P. Harris, and F.L Cook, *J. Org. Chem.*, *39*, 2445 (1974) This material is supplied commercially by P C.R., Inc , P.O. Box 1466, Gainesville, Florida, 32602.

8 The usual procedure was either to filter the reaction through a small column (3-4 g) of dry column silica gel or high vacuum distillation of the crude reaction product The silica gel absorbs the 18-Crown-6, along with residual salts, allowing the reaction product to pass through. See Ref. 6 for experimental detail.

9 David A. Evans, Gary L Carroll, and L K Truesdale, *J. Org. Chem.*, *39*, 914 (1974), D.A. Evans, L.K. Truesdale, and G L. Carroll, *Chem. Commun.*, 55 (1973), D.A Evans, J M Hoffman, and L K Truesdale, *J. Amer. Chem. Soc.*, *95*, 5822 (1973), D.A. Evans and L.K. Truesdale, *Tetrahedron Lett.*, 4929 (1973), also see W.E Parham and L.J. Ceuba, *J. Amer. Chem. Soc.*, *90*, 4030 (1968), W.E. Parham and C.S. Roosevelt, *J. Org. Chem.*, *37*, 1975 (1972), *Tetrahedron Lett.*, 923 (1971).

10. N Kornblum, N N Lichtin, J.T. Patton, and J.C Iffland, *J. Amer. Chem. Soc.*, *69*, 307 (1947); N. Kornblum, J T Patton, and J.B. Nordmann, *J. Amer. Chem. Soc.*, *70*, 746 (1948), N Kornblum and C.Tietlebaum, *J. Amer. Chem. Soc.*, *74*, 3076 (1952); N Kornblum, B. Taube, and H.E Ungnade, *J. Amer. Chem. Soc.*, *76*, 3209 (1954), N. Kornblum, R.K Blackwood, and D.D. Mooberry, *J. Amer. Chem. Soc.*, *78*, 1501 (1956), N Kornblum and P A. Wade, *J. Org Chem*, *38*, 1418 (1973), N. Kornblum in "Organic Reactions, Vol 12," A.C Cope, Ed in Chief, J Wiley & Sons, New York, N.Y., 1962, p 142.

11. W.P Weber, personal communication, April, 1974