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ADDITION OF TRIMETHYLSILYL CYANIDE TO α-SUBSTITUTED KETONES: CATALYST EFFICIENCY

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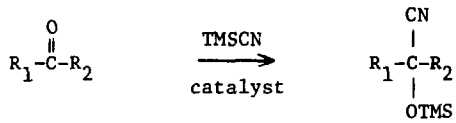
Abstract: Addition of trimethylsilyl cyanide to α-substituted ketones is often slow and incomplete when catalyzed by zinc iodide. Use of potassium cyanide/18-crown-6 complex as catalyst is a superior method, providing high yields of adducts.

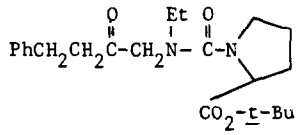
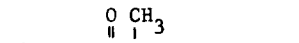
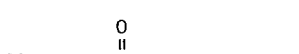
The addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds is a convenient route for preparation of the corresponding cyanohydrin trimethylsilyl ethers.[1] These serve not only as protected analogs of aldehydes and ketones but also as intermediates for synthesis of cyanohydrins,[2] α-hydroxyamides,[3] α,β-unsaturated nitriles,[4] and β-aminoalcohols.[5] The addition of TMSCN to ketones has been shown to be accelerated by addition of a catalytic amount of a Lewis acid, most notably zinc iodide.[6] Nucleophilic catalysis, particularly with potassium cyanide/18-crown-6 complex has also been demonstrated to be effective, especially for acid-sensitive ketones.[1a,6] However, the utility of the KCN/18-crown-6 catalyst system has not been generally recognized, as evidenced by the frequent use of ZnI_2, even where elevated temperatures and extended reaction times are required.



Recently we had occasion to attempt the addition of TMSCN to α-acylamino-substituted ketones 1 and 2 using ZnI_2 catalysis. Neither ketone underwent addition under these conditions; in fact ketone 1 was heated at 60°C in neat TMSCN for 20 hrs in the presence of ZnI_2 with no change. In contrast, use of KCN/18-crown-6 complex gave rapid and complete formation of adducts. Heretofore p-quinones have provided the only example of substrates for which use of KCN/18-crown-6 was required.[7]

Additional examples in the table illustrate the frequent ineffectiveness of ZnI_2 catalysis for ketones bearing electron-withdrawing substituents at the adjacent carbon atoms.[8] For these ketones, catalysis with KCN/18-crown-6 proved the method of choice, affording the cyanosilylation products in high yields.

Table: Addition of Trimethylsilylcyanide to Ketones Catalyzed by KCN/18-crown-6 or ZnI_2 [a]

	Ketone	KCN/18-crown-6 Time	KCN/18-crown-6 Yield	ZnI_2 Time	ZnI_2 Yield
1.		2.5 hr	88%	24 hr	none [c]
2.		10 min	81%	24 hr	none [c]
3.		1.5 hr	88%	24 hr	none [c]
4.		2 hr	96%	24 hr	none [c]
5.		2.5 hr	95%	24 hr	83%
6.		10 min	94%	24 hr	(85%) [b]
7.		10 min	83%	24 hr	d)
8.		10 min	77%	3.5 hr	71%

[a] The ketone (1 mmol) was combined with TMSCN (1.2 mmol), CH_2Cl_2 (2 ml) and either KCN (10 mg) and 18-crown-6 (10 mg) or ZnI_2 (10 mg) were added. All reactions were run under a nitrogen atmosphere. Yields are for products purified by silica gel chromatography. All adducts gave spectral data (^1H NMR, IR, and MS) in accord with the assigned structures.

[b] Yield in parentheses refers to conversion as determined by ^1H nmr spectrum (product not isolated).

[c] No reaction observed.

[d] Slow conversion to several spots on tlc (silica gel).

References

1. (a) D. A. Evans, L. K. Truesdale, G. L. Carroll, Chem. Commun., 55 (1973); J. Org. Chem., 39, 914 (1974). (b) W. Lidy, W. Sundermeyer, Chem. Ber., 106, 587 (1973).
2. P. G. Gassman, J. J. Talley, Tetrahedron Lett., 3773 (1978).
3. G. L. Grunewald, W. J. Brouillette, J. A. Finney, ibid., 21, 1219 (1980).
4. M. Oda, A. Yamamuro, T. Watabe, Chem. Lett., 1427 (1979).
5. D. A. Evans, L. K. Truesdale, G. L. Carroll, J. Org. Chem., 39, 914 (1974); R. Amouroux, G. P. Axiotis, Synthesis, 270 (1981); W. E. Parham, C. S. Roosevelt, Tetrahedron Lett., 923 (1971).
6. D. A. Evans, L. K. Truesdale, Tetrahedron Lett., 4929 (1973).
7. D. A. Evans, J. M. Hoffman, L. K. Truesdale, J. Amer. Chem. Soc., 95, 5822 (1973).
8. Complexation of ZnI_2 at sites other than the carbonyl oxygen in these substrates may contribute to its ineffectiveness as a catalyst.

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