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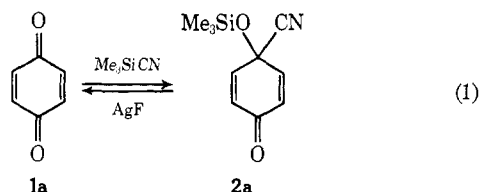
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A New Selective Carbonyl Blocking Group. The Regioselective Protection of p-Quinones

Sir:

The quinoid nucleus embodies the potential of being a highly useful structural building block in organic synthesis. To date, the applications of quinones in complex natural products synthesis have centered around the Diels–Alder reaction.[1] The major problems associated with executing carbon–carbon bond forming reactions on either quinones or hydroquinones lie with the generally high reactivity of these species with nucleophiles and electrophiles, respectively.[2] The purpose of this communication is to disclose the first general method of reversibly protecting quinone carbonyl groups under exceedingly mild conditions, the blocking operation being effected with trimethylsilyl cyanide (TMSCN)[3,4] (eq 1). This new carbonyl derivatization

(1)

1a   2a

process should amplify the utility of quinones as electrophilic substrates in organic synthesis.

We have found that the catalyzed addition of TMSCN to both aldehydes and ketones is both mild and efficient.[3] Catalysis by both zinc iodide and cyanide ion are equally effective. In the large number of systems studied to date the addition process has been devoid of side reactions such as silyl enol ether formation[5] and, in the case of α,β-unsaturated carbonyl derivatives, 1,4 addition.[6] In the present study, we have observed the first case of catalyst specificity for cyanide ion.

In order to demonstrate the generality of this new method of carbonyl protection, we have examined the scope of the TMSCN–carbonyl insertion process with a variety of substituted p-benzoquinones (1a–g) and p-naphthoquinones (1h–j). The results are summarized in Table I.[7] It is particularly noteworthy that, with

(2)

1   2   3
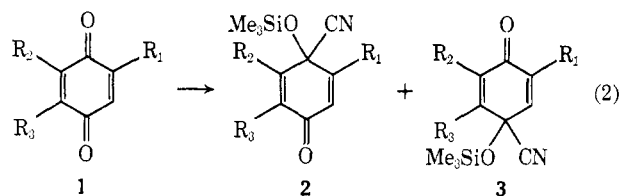
unsymmetrical quinones, the site of cyanosilylation is dictated by relative carbonyl electrophilicity (cf. 1b–e) and only in extreme cases (e.g., 1g) do steric effects become important. The position of cyanosilylation is evident from a comparison of the ^{1}H nmr chemical shifts of the starting quinones and the resulting adducts. The structural assignments of 2 and 3 are consistent with quinone reactivity patterns and their further transformation to p-quinols of known structure.[8]

The general procedure for quinone cyanosilylation involves the addition of a catalytic amount (0.01–0.02 equiv) of potassium cyanide–18-crown-6 complex[9] to a stirred mixture of quinone (1 equiv) and TMSCN (1.1 equiv) under anhydrous conditions. The reaction is exothermic and, in moderate scale reactions, cooling may be required. Solvents ($CHCl_3$, CCl_4, C_6H_6) may be used, although this was not done in the reported cases. The adducts may be purified by either molecular distillation or recrystallization; however, usually this is unnecessary.

Although the silyloxynitrile protective group is inherently unstable to both nucleophiles and aqueous media,[10] the competitive reactivity of the unprotected quinone carbonyl toward hydride reagents and both lithium and magnesium alkyls is quite high.[11] Thus, by coupling cyanosilylation with selective transforma-

(1) Notable examples include (a) M. Gates and M. Tschudi, *J. Amer. Chem. Soc.*, **78**, 1380 (1950); (b) L. H. Sarett, G. I. Poos, J. M. Robinson, R. E. Beyler, J. M. Vandergrift, and G. E. Arth, *ibid.*, **74**, 1393 (1952); (c) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952); (d) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(2) For representative reactions of quinones with organometallic reagents see W. Ried in "Newer Methods of Preparative Organic Chemistry," Vol. IV, W. Foerst, Ed., Academic Press, New York, N. Y., 1968, pp 97–110; E. Bamberger and L. Blangey, *Justus Liebigs Ann. Chem.*, **384**, 272 (1911); H. M. Crawford, *J. Amer. Chem. Soc.*, **57**, 2000 (1935); **70**, 1081 (1948); H. M. Crawford and M. McDonald, *ibid.*, **71**, 2681 (1949); D. E. Worrall and S. Cohen, *ibid.*, **58**, 533 (1936); L. S. Hegedus, E. L. Waterman, and J. Catlin, *ibid.*, **94**, 7155 (1972).

(3) The reaction of TMSCN with a variety of aldehydes and ketones has been shown by us and others to be a general, high yield transformation: D. A. Evans, L. K. Truesdale, and G. L. Carroll, *J. Chem. Soc., Chem. Commun.*, **55** (1973); W. Lidy and W. Sundermeyer, *Chem. Ber.*, **106**, 587 (1973).

(4) Prepared according to the procedure of E. C. Evers, W. O. Freitag, J. N. Keith, W. A. Kriner, A. G. MacDiarmid, and S. Sujishi, *J. Amer. Chem. Soc.*, **81**, 4493 (1959). A more convenient synthesis is being developed in our laboratory.

(5) TMSCN is an efficient silicon transfer reagent; thus, alcohols and enols are smoothly silylated at room temperature.

(6) The mild conditions for this carbonyl addition process suggest that α-silyloxynitriles should be ideal protective groups for acid-labile molecules.

(7) Consistent spectral data and combustion analysis have been obtained on all new compounds reported herein.

(8) M. Lovnasmaa, *Suom. Kemistilehti A*, **41**, 91 (1968). For example, the structure of 2f may be established by transformation to 5f (R = CH_3) whose structure is unequivocal.

(9) The KCN·crown complex was prepared by the dissolution of equimolar amounts of KCN and crown ether [R. N. Green, *Tetrahedron Lett.*, 1793 (1972)] in anhydrous methanol. Removal of solvent *in vacuo* afforded the active catalyst. Tetra-*n*-butylammonium cyanide is equally effective.

(10) Compound 1a appears to be stable in anhydrous methanol (37°); in aqueous methanol (37°) 1a has a half-life of *ca.* 30 min.

(11) The addition of other carbon nucleophiles to monoprotected quinones is currently under investigation.

Table I. Cyanosilylation of p-Quinones (eq 2)[7]

| p-Quinone[a]	Ratio 2:3[b]	% yield[c]	Mp (bp), °C [d]
1a ($R_1, R_2, R_3 = H$)		80	67–67.5
1b ($R_1 = CH_3$; $R_2, R_3 = H$)	89:11	92	(100–102 (0.8 mm))
1c ($R_1 = OCH_3$; $R_2, R_3 = H$)[e]	100:0	80	58–60
1d ($R_1 = OCH_3$; $R_2 = H$; $R_3 = CH_3$)[f]	100:0	90	63.5–64
1e ($R_1, R_2 = OCH_3$; $R_3 = H$)[g]	100:0	65 (100)	101.8–102
1f ($R_1, R_2 = CH_3$; $R_3 = H$)	94:6	(100)	...[h]
1g ($R_1, R_2 = t$-Bu; $R_3 = H$)	0:100	(98)	...[h]
1h ($R_1 = H$; $R_2R_3 = C_4H_4$)[i]		75	...[i]
1i ($R_1 = CH_3$; $R_2R_3 = C_4H_4$)[i]	91:9[h]	96	(110–120 (0.1 mm))
1j ($R_1 = OCH_3$; $R_2R_3 = C_4H_4$)[i]	100:0	82	72–73

[a] Unless specified, the starting quinone is commercially available. [b] Ratios determined by nmr. [c] Yields in parentheses determined by nmr; all others are of purified adduct. [d] Values in parentheses are boiling point of liquid products. [e] C. de Corral, *Chem. Abstr.*, **52**, 7257i (1958). [f] Reference 1c. [g] *Org. React.*, **4**, 343 (1948). [h] Adduct reverts to quinone upon attempted distillation. [i] Product always contaminated with 3–4% naphthoquinone. [j] Notation C_4H_4 refers to fused benzene ring.

Table II. p-Quinols from TMSCN-Quinone Adducts (eq 3)[7]

| Protected quinone	RM[a]	% yield[b] of 5	Mp, °C
2a ($R_1, R_2, R_3 = H$)	CH_3Li	89	76–78[c]
	C_6H_5MgBr	86	105–106.5[d]
	n-C_4H_9Li	75	48–50
	n-C_4H_9MgBr	65	48–50
2c ($R_1 = OCH_3$; $R_2, R_3 = H$)	CH_3Li	73	102–104
2d ($R_1 = OCH_3$; $R_2 = H$; $R_3 = CH_3$)	CH_3Li	87	114–115
2f ($R_1, R_2 = CH_3$; $R_3 = H$)	CH_3Li	77	37–43[e]
2h ($R_1 = H$; $R_2R_3 = C_4H_4$)	CH_3Li	89	103–104
2j ($R_1 = OCH_3$; $R_2R_3 = C_4H_4$)	CH_3Li	79	125–126

[a] One equivalent of RM was added to **2** in ether at $-70°$. [b] Values correspond to purified quinol. [c] F. Wessely and F. Sinwell, *Monatsch. Chem.*, **81**, 1055 (1950); see also ref 15a. [d] Reference 15b. [e] E. Adler, J. Dahlen, and G. Westin, *Acta Chem. Scand.*, **14**, 1580 (1960).

tions on the unprotected quinone carbonyl, a wide variety of otherwise relatively inaccessible compounds can be synthesized in good yield. A simple demonstration of the utility of TMSCN–quinone adducts as effective precursors to p-quinols is illustrated (eq 3). In

(3)

2　　　　**4**　　　　**5**
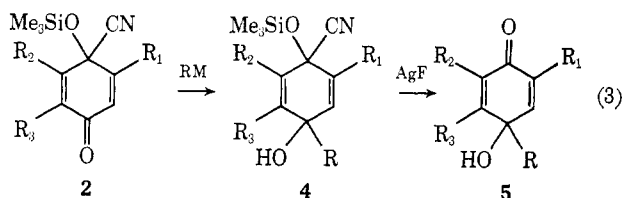
contrast to the behavior of unprotected p-quinones,[2] organometallic reagents have been found to undergo clean 1,2 addition to **2** at $-70°$[12] affording the adducts **4**. These intermediates can then be deblocked to the desired p-quinols in high yield with silver fluoride in aqueous tetrahydrofuran (25°). Removal of the TMS-CN blocking group under these conditions is virtually instantaneous. This general synthesis of p-quinols is far superior to existing methods.[13] As illustrated in Table II, the two-step conversion of the monoprotected quinones **2** into the p-quinols **5** proceeds in good yields.[7]

With a simple synthesis of p-quinols now available, further utilization of these intermediates should be encouraged. For example, TMSCN–quinone adducts **1c-e** and **1j** may serve as useful precursors to substituted o-quinones. This is suggested by the fact that quinol **5j** (R = CH_3) may be transformed (Cu(BF$_4$)$_2$, CH_3CN, 25°) in 85% yield to **7**.[14] On the other hand, p-quinols

5j　　　　**7**
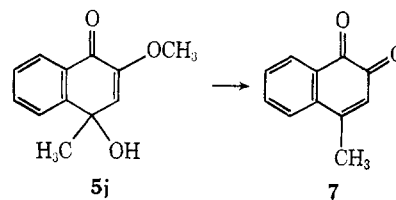
such as **5a** (R = CH_3 or C_6H_5)[15] undergo facile dienone-phenol rearrangement under standard conditions to substituted p-hydroquinones.

Applications of this new quinone blocking procedure[16] in the areas of alkaloid and quinone synthesis will be reported in the due course.

(12) Optimum yields of **4** are obtained with 1 equiv of RM in ether at $-70°$. At this temperature slightly better yields are obtained with the lithium as opposed to the magnesium alkyls.

(13) For an excellent review of methods of preparation of p-quinols as well as their reactions see A. J. Waring, *Advan. Alicycl. Chem.*, **1**, 129 (1966).

(14) Compound **7** has been synthesized independently: L. Fieser and C. Bradsher, *J. Amer. Chem. Soc.*, **61**, 417 (1939). This transformation correlates with the structural assignments for both **5j** (R = CH_3) and **2j**.

(15) (a) S. Woodwin and B. Witkop, *ibid.*, **79**, 179 (1957); (b) Y. Abe, *Bull. Chem. Soc. Jap.*, **18**, 93 (1943).

(16) Detailed experimental procedures will be provided upon request.

(17) Camille and Henry Dreyfus Teacher–Scholar Recipient (1971–1976); Alfred P. Sloan Fellow (1972–1974).

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Synthesis of a Tantalum Pentahydride Complex

Sir:

Phosphine-stabilized polyhydrides are known for transition metals of groups VI–VIII but not for metals