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Benzylic Cyanation via Oxidation and Simultaneous Nucleophilic Substitution

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Use of dichlorodicyano benzoquinone and trimethylsilyl cyanide in suitable solvent permits the direct and ready transformation of benzylic C-H bonds to C-CN bonds with high yield and selectivity via oxidation and simultaneous nucleophilic substitution.

During the last few years a number of studies have shown that oxidation of benzylic carbon using dichlorodicyano benzoquinone (D.D.Q.) leads to chemo, regio and stereo-selective formation of C-O bonds.1) The reactivity and selectivity of this reagent is explained by the formation of an intermediate donor-acceptor complex between reagent and substrate, followed by abstraction of the hydride and simultaneous nucleophilic attack.2) Strictly speaking, this mechanism is an oxidative nucleophilic substitution, S_NOx. Recently we proposed using this same method and reagent (D.D.Q.) for the direct formation of C-N bonds.3) Application of such methodology to the formation of C-CN bonds is described in this paper.

Direct introduction of a nitrile group at the benzylic position of an aromatic substrate is of especial interest because such structures can easily be transformed into substituted aryl-acetic acids which are widely used as non-steroid antiinflammatory drugs (e.g. Naproxen®) or as starting material for drug synthesis. Introduction of a nitrile function on an aliphatic carbon is generally achieved by nucleophilic substitution4) or by reaction of a carbanion with p-toluenesulfonyl cyanide,5) phenylcyanate6) or diisopropylcyanamide.7) Reaction of TosMIC with carbonyl functions has equally been proposed.8) Nitrile introduction at the benzylic position of aromatic substrates has also been performed by anodic oxidation9) or oxidation by phenylselenic anhydride10) with simultaneous nucleophilic substitution. The methodology used in the latter two reactions, is analogous to that proposed in the present work.

The use of D.D.Q. as reagent presents several distinct advantages over methods previously described. Firstly, D.D.Q. is commercially available ; no activation of the substrate or specific equipment are required ; both the reaction

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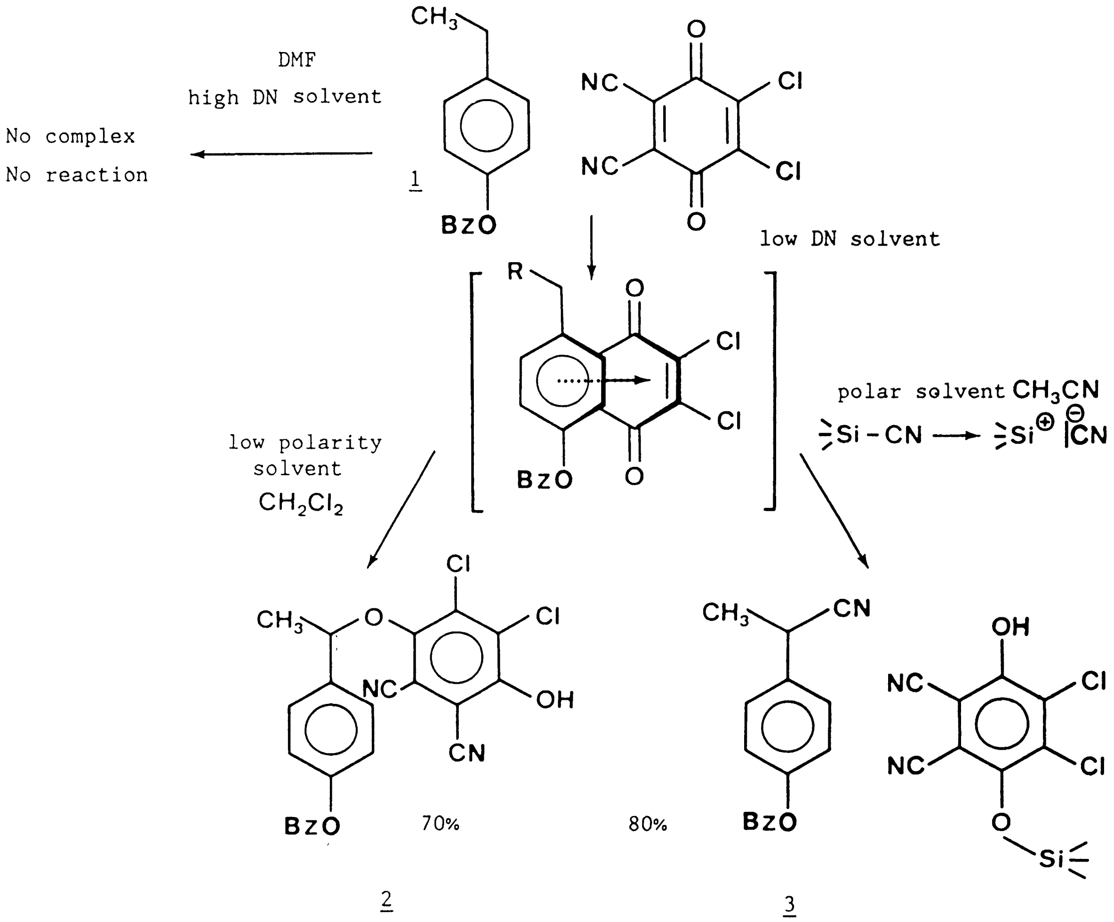
and work-up are particularly easy and the by-product, dichlorodicyano hydroquinone (D.D.H.Q.), can be recycled to the reagent by nitric oxidation.[11] Secondly and more importantly, when cyanide is used as nucleophile, high selectivity similar to that observed following the formation of ether and acetate functions by oxidation using D.D.Q. and in the presence of alcohol or acetic acid as nucleophile, may be expected.

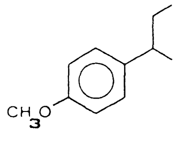
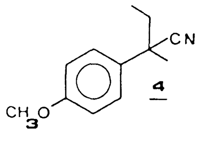
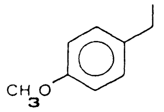
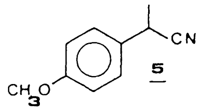
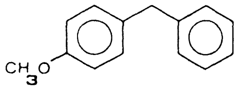
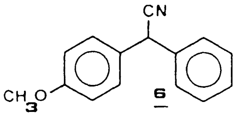
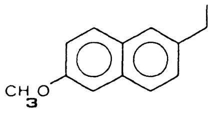
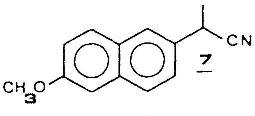
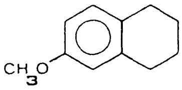
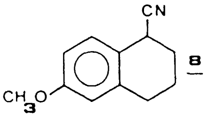
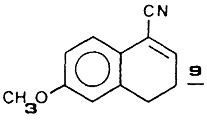
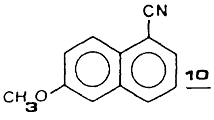
The general mechanism for the formation of acetate functions by oxidation using D.D.Q. involves three species in the limiting step : substrate acting as donor, D.D.Q. acting as acceptor and acetic acid acting as solvent, nucleophile and proton donor. Both a strong donor-acceptor interaction and a high concentration of nucleophile are necessary if high yield and selectivity are to be obtained.[1-2]



Scheme 1. Solvent effect on oxidation by D.D.Q. in the presence of TMS.CN.

Use of cyanhydric acid for the formation of nitrile functions is of little practical interest due to the very high toxicity of this gaseous reagent. Conversely, the easy to use liquid, trimethylsilyl cyanide (TMS.CN), can act as cyanide donor in polar solvents or with Lewis acids.[12] Introduction of a nitrile function using D.D.Q. as oxidative reagent and TMS.CN as nucleophilic donor therefore requires a solvent favouring formation of the intermediate donor-acceptor complex (low donating number : D.N.)[13] as well as dissociation of TMS.CN to nucleophilic cyanide (high polarity) (Scheme 1). A deep blue coloration which appeared in acetonitrile, methylene chloride or chloroform (but not in DMF) when reagent were first mixed and which disappeared as the reaction progressed was indicative of the charge transfer interaction.

Table 1. Cyanation using oxidative nucleophilic substitution

Substrate	Product	Solvent	DDQ/Substrate ratio	c.y. %	Entry
	 4	CH_2Cl_2	2	68	1
	 5	CH_3CN	1,5	69	2
	 6	CH_2Cl_2	1,2	94	3
	 7	CH_3CN	1,5	60	4
	 8	CH_2Cl_2	1,02	71	5
	 9	CH_2Cl_2	2	51	6
	 10	CH_2Cl_2	3	78	7

As shown by the results presented in Scheme 1, solvents of high donating number (D.N. of DMF = 26.6)[13] inhibit the formation of the donor-acceptor interaction and the oxidation reaction. Conversely, non-polar solvents prevent the dissociation of trimethylsilyl cyanide and dichloro-dicyano hydroquinone appears to be the more efficient nucleophile for this substrate when using dichloromethane (ν = 5.17) or chloroform (ν = 3.84) as solvent. Acetonitrile which exhibits intermediate D.N. and polarity (D.N. = 14.1) ; ν = 11.48) could be used as a general solvent for this reaction although in case of hindered substrates, the addition of DDHQ is prevented and only the nitrile is obtained in either CH_2Cl_2 or CH_3CN (Table 1, entries 1,3,5).

All these solvent and structural effects thus illustrate the importance of the donor-acceptor interaction during oxidation by DDQ. This reagent appears to be able to perform C-CN bond formation with high yields, chemo and regioselectivity. It should also be noted that introduction of a nitrile function and formation of double bonds[14] can be performed in a single step (Table 1, entries 6,7). Further studies of the application of S$_N$Ox to the selective or stereoselective introduction of other substituents are presently underway in our laboratory.

General procedure is a follows. Dichlorodicyanobenzoquinone was rapidly added to a solution of alkyl-aryl substrate (1 mmol. l^{-1}) and trimethylsilyl cyanide (5 mmol. l^{-1}) in acetonitrile or methylene chloride. Stirring was maintened for 24 h at 60 °C. The resultant solution was neutralized by washing with NaHCO$_3$ (10% in water) and water. The organic layer was dried and evaporated under vacuum and crude products were purified by flash chromatography. Physical data are reproted in Ref. 15.

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15) Analytical data

2 mp 260 °C decomp. : IR : (KBr) 3300 cm^{-1} ; 2600 cm^{-1}. NMR ^{1}H (CDCl$_3$) δ = 1.8 (d, 3H) ; 5.1 (s, 2H) ; 5.65 (q, 1H) ; 7.05 (d, 2H) ; 7,4 (m, 7H). 3 mp 60 °C ; IR (CHCl$_3$) 2250 cm^{-1} ; NMR ^{1}H (CDCl$_3$) δ = 1.63 (d, 3H) ; 3.85 (q, 1H) ; 5.1 (S, 2H) ; 7-7.3 (AA' BB' 4H) ; 7.40 (m, 5H). 4 liq. IR (CHCl$_3$) 2250 cm^{-1}. NMR ^{1}H (CDCl$_3$) δ = 0.95 (t, 3H) ; 1.67 (s, 3H) ; 1.91 (q, 2H) ; 3.80 (s, 3H) ; 6.9-7.34 (AA' BB', 4H). 5 liq. IR (CHCl$_3$) 2265 cm^{-1}. NRM ^{1}H (CDCl$_3$) δ = 1.57 (d, 3H) ; 3.77 (s, 3H) ; 3.78 (q, 1H) ; 6.9-7.25 (AA' BB', 4H) ; 6 mp 130. IR (CHCl$_3$) 2260 cm^{-1}. NMR ^{1H} (CDCl$_3$) δ = 3.80 (s, 3H) ; 5.11 (s, 1H) ; 6.90-7.26 (AA' BB', 4H) ; 7.36 (s, 5H). 7 mp 69 °C : IR (CHCl$_3$) 2250 cm^{-1} ; ^{1}H NMR (CDCl$_3$) = 1.72 (d, 3H) ; 3.93 (s, 3H) ; 4.02 (q, 1H) ; 7.5 (m, 6H). 8 liq. ; IR (CHCl$_3$) 2250 cm^{-1} ; NMR ^{1}H (CDCl$_3$) δ = 1.9 (m, 4H) ; 2.72 (m, 2H) ; 3.76 (s, 3H) ; 3.89 (t, 1H) ; 6.70 (m, 2H) ; 7.23 (d, 1H). 9 mp 50 ; IR (CHCl$_3$) 2240 cm^{-1}. NMR ^{1}H (CDCl$_3$) δ = 2.47 (m, 2H) ; 2.82 (m, 2H) ; 3.82 (s, 3H) ; 6.74 (m, 3H) ; 7.35 (d, 1H). 10 mp 77 °C ; IR (CHCl$_3$) 2230 cm^{-1}. NMR ^{1}H (CDCl$_3$) δ = 3.88 (s,3H) ; 7.1-8.0 (m, 6H).

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