HETEROCYCLES, Vol. 63, No. 12, 2004, pp. 2859 - 2862
Received, 13th September, 2004, Accepted, 28th October, 2004, Published online, 29th October, 2004

PALLADIUM(II)-MEDIATED NUCLEOPHILIC CYANATION OF 4-SUBSTITUTED QUINOLINE 1-OXIDE IN THE PRESENCE OF TRIMETHYLSILYL CYANIDE AND AN OXIDANT

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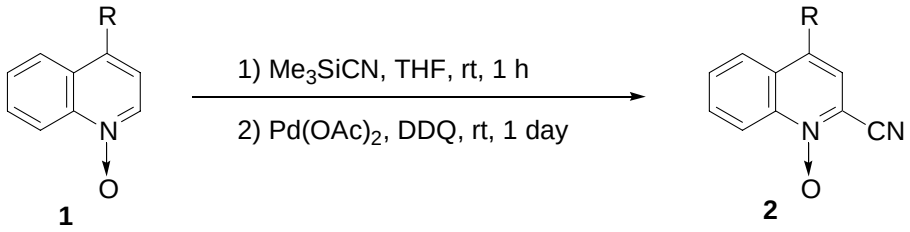
Abstract- Reaction of 4-substituted (electron-releasing group) quinoline 1-oxides (**1**) with trimethylsilyl cyanide in the presence of palladium(II) acetate and DDQ gave 2-cyano-4-substituted quinoline 1-oxides (**2**) in THF in moderate yields. It was reasoned that this reaction proceeds through palladium-catalyzed dehydrosilylation.

Cyanation is one of the most useful synthetic methods for the formation of a carbon-carbon bond. Two convenient procedures for introducing a cyano group into a heteroaromatic ring involve the reaction of the cyanide ion with an *N*-oxide in the presence of an acylating agent (Reissert-type reaction), or with an *N*-oxide quaternary salt, and the cyanation usually occurs in an α-position, accompanied by deoxygenation of the *N*-oxide group.[1] If it is possible for the *N*-oxide group to be left intact after cyanation, the resulted α- or γ-cyanoheteroaromatic *N*-oxides will become much more versatile for further chemical transformation than the corresponding deoxygenated products due to the various reactivities of the *N*-oxide function. However, *N*-reoxygenation by peracids incurs some difficulties in that hydrolysis, oxidation or rearrangement[1b] may possibly occur if the compounds have substituents vulnerable to peracids. Therefore, exploring the reaction of heteroaromatic *N*-oxides with nucleophile, not accompanied by deoxygenation of the *N*-oxide group, is desirable and theoretically interesting. However, reports on such cyanation not accompanied by deoxygenation of heteroaromatic *N*-oxides are almost unavailable with the exception of the reaction of bi- and tricyclic aromatic *N*-oxides with KCN in the presence of $K_3Fe(CN)_6$ to afford the corresponding α-cyanoaromatic *N*-oxide in moderate yields.[2] It has been recently reported that palladium(II) acetate catalyzes dehydrosilylation of silyl enol ether in the presence of *p*-benzoquinone to give α,β-unsaturated carbonyl compounds,[3] which reaction led us to embark upon the reaction of the

trimethylsilyloxy adduct of heteroaromatic *N*-oxide with palladium(II) acetate in the presence of an oxidant.

In this report, we would like to present the reaction of 4-substituted quinoline 1-oxide (**1**) with trimethylsilyl cyanide in the presence of palladium(II) acetate and 2,3-dichloro-5,6-dicyano- 1,4-benzoquinone (DDQ) as an oxidant in THF to give 2-cyano-4-substituted quinoline 1-oxides (**2**). The general procedure of the present reaction is as follows: **1** (1.5 mmol) was stirred with trimethylsilyl cyanide (3 mmol) in THF at room temperature for 1 h under N_2, followed by the addition of palladium(II) acetate (0.15 mmol) and stirring for 1 h and successively the addition of DDQ (0.75 mmol) and then the mixture was further stirred at room temperature for 1 day. Usual work-up of chloroform extraction and SiO_2-purification gave **2** in the yields shown in Table 1.

Table 1 Reaction of 4-substituted quinoline 1-oxides (1) with Me_3SiCN in the presence of $Pd(OAc)_2$ and DDQ



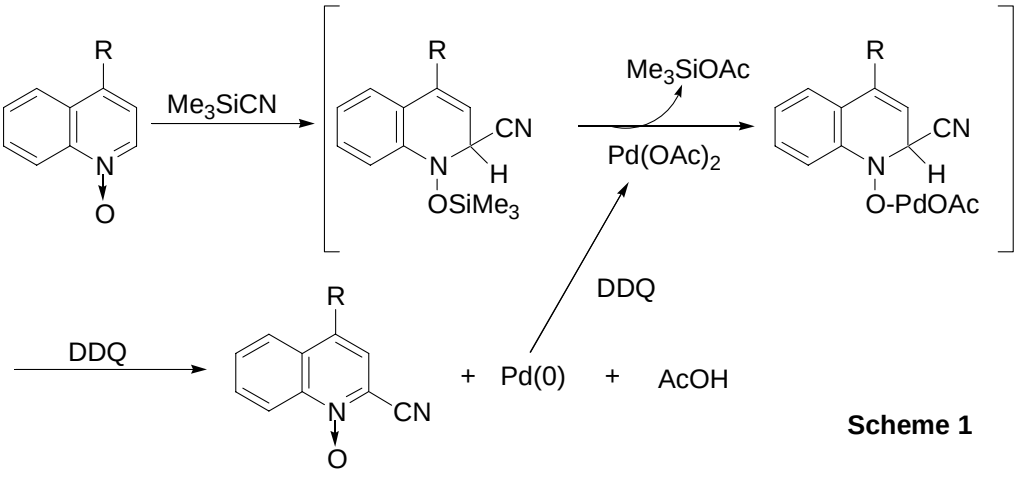
1 **2**

Product No.	R	Temp. (℃)	Time (h)	Equiv. of $Pd(OAc)_2$	Yield (%)
2a	H	rt	24	0	8
		rt	24	0.1	35[4]
2b	Me	rt	24	0	9
		rt	24	0.1	45[5]
2c	OMe[6]	rt	24	0	40
		rt	24	0.1	66
2d	NMe_2[7]	rt	24	0	46[b)]
		rt	24	0.1	51[b)]
2e	EWG[a)]	rt	24	0	0[c)]
		rt	24	0.1	0[c)]

a) EWG = electron-withdrawing group, NO_2[8] and CHO[9] groups
b) The yields include also that of the deoxygenated product (2f) in this case. Formation ratio, *N*-oxide : deoxygenated product = 1 : 4 ~ 1 : 5
c) starting material recovery

As can be seen from Table 1, the reaction of **1** having an electron-releasing group at the 4-position of the quinoline nuclei in the presence of a catalytic amount of palladium(II) acetate (0.1 eq.) provided the corresponding 2-cyanoquinoline 1-oxides in better yields than the reaction in the absence of palladium(II) acetate, however, the reaction of **1** having electron-withdrawing groups at the 4-position and that of pyridine 1-oxide did not proceed at all. It is conceivable as a reaction mechanism that in the reaction without palladium(II) acetate, the cyano anion attacks the carbon atom at the 2-position which is activated by both the electron-releasing group at the 4-position and the trimethylsilyloxy group, and then dehydrosilylation takes place by oxidant (DDQ) to give the products. On the other hand, in the reaction using palladium(II) acetate more efficient dehydrosilylation would proceed through metal exchange reaction between the trimethylsilyloxy group and palladium(II) acetate and

finally the resulted Pd(0) is reoxidized by DDQ to regenerate the active palladium(II) species (Scheme 1).[3]



Scheme 1

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded in the following spectrometers: IR spectra, JASCO FT/IR-470Plus; ^{1}H-NMR spectra, JEOL GX-400 (400MHz) and JEOL A-500 (500MHz); ^{13}C-NMR spectra, JEOL GX-400 (100MHz) and JEOL A-500 (125MHz); MS spectra, Shimadzu GC-MS QP5050 for EI-MS and JMS-HX100 for FAB-MS. The H-COSY, DEPT and HMQC experiments were also used for the assignments of the structures. The chemical shifts are given in the δ scale. Elemental analyses were performed on a Yanaco CHN CORDER MT-6 instrument. Medium-pressure liquid chromatography (MPLC) was carried out with Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40 μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck). High-performance thin layer chromatography (HPTLC) for the yields shown Table 1 was conducted on Shimadzu high speed thin layer chromatoscanner (CS-9300PC) with the detector set at uv 254nm.

General procedure for reaction 4-substituted quinoline 1-oxides (1) with Me_3SiCN in the presence of $Pd(OAc)_2$ and DDQ----- 1 (1.5 mmol) was stirred with trimethylsilyl cyanide (3 mmol) in THF at rt for 1 h under N_2, followed by the addition of palladium(II) acetate (0.15 mmol) and stirring for 1 h and successively the addition of DDQ (0.75 mmol) and then the mixture was further stirred at rt for 1 day. The catalyst was removed by filtration and the solvent was evaporated off. The residue was extracted with $CHCl_3$ and after removal of the solvent the residue was respectively post-treated in the manner as shown below.

2-Cyano-4-methoxyquinoline 1-oxide (2c)

The residue was purified by medium-pressure liquid chromatography (AcOEt) to afford 2c (0.2 g, 66% yield). mp 236-238 ℃(from benzene), *Anal*. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.98; H, 4.07; N, 13.85. ^{1}H-NMR($CDCl_3$): δ 4.09(3H, s, CH_3), 6.81(1H, s, H-3), 7.76(1H, dd, J=7.9 and 7.9Hz, H-6), 7.86(1H, dd, J=7.6 and 7.6Hz, H-7), 8.24(1H, d, J= 8.2Hz, H-5), 8.70(1H, d, J= 9.2Hz, H-8). ^{13}C-NMR($CDCl_3$): δ 56.7(q, CH_3), 101.5(d, C-3), 113.0(s, Ar), 120.3(d,

C-8), 123.1(d, C-5), 123.8(s, Ar), 130.3(d, C-6), 131.9(d, C-7), 141.6(s, Ar), 152.7(s, Ar). MS(FAB$^+$): 201(M^++H).

2-Cyano-4-dimethylaminoquinoline 1-oxide (2d) and 2-Cyano-4-dimethylaminoquinoline (2f)

The residue was purified by medium-pressure liquid chromatography to afford 2d (*n*-hexane:AcOEt = 5:1) and 2f (*n*-hexane:AcOEt = 10:1), 0.03g (10% yield) and 0.12g (41% yield), respectively. Compound (**2d**): mp 145-146 ℃(from Et_2O, yellow-green prisms). *Anal*. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.57; H, 5.29; N, 19.67. ^{1}H-NMR($CDCl_3$): δ 3.03(6H, s, CH_3 ×2), 6.88(1H, s, H-3), 7.71(1H, dd, J=7.8 and 7.6Hz, H-6), 7.80(1H, dd, J=7.9 and 7.6Hz, H-7), 8.13(1H, d, J= 9.2Hz, H-5), 8.74(1H, d, J= 8.9Hz, H-8). ^{13}C-NMR($CDCl_3$): δ44.2(q, CH_3×2), 109.5(d, C-3), 113.2(s, Ar), 121.0(d, C-8), 125.3(d, C-5), 125.7(s, Ar), 129.4(d, C-6), 131.1(d, C-7), 142.0(s, Ar), 148.4(s, Ar). MS(FAB$^+$): 214(M^++H).

Compound (**2f**): mp 88-89 ℃(from petr.ether-Et_2O, pale yellow prisms). *Anal*. Calcd for $C_{12}H_{11}N_3$: C, 73.02; H, 5.62; N, 21.30. Found: C, 73.16; H, 5.71; N, 21.30. ^{1}H-NMR($CDCl_3$): δ 3.13(6H, s, CH_3 ×2), 6.98(1H, s, H-3), 7.54(1H, dd, J=7.8 and 7.6Hz, H-6), 7.71(1H, dd, J=7.9 and 7.5Hz, H-7), 8.04-8.07(2H, m, H-5 and H-8). ^{13}C-NMR($CDCl_3$): δ43.7(q, CH_3×2), 109.2(d, C-3), 118.1(s, Ar), 122.8(s, Ar), 124.6(d, C-8), 126.7(d, C-6), 130.2(d, C-7), 130.5(d, C-5), 149.8(s, Ar), 158.1(s, Ar). MS(FAB$^+$): 198(M^++H).

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