

Quinoxalines. XXVII.¹⁾ The Cyanation of 2-Substituted Quinoxaline 4-Oxides with Trimethylsilyl Cyanide

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The deoxy-cyanation of 2-substituted quinoxaline 4-oxides (Ia-k) with trimethylsilyl cyanide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gave the corresponding 3-substituted 2-quinoxalinecarbonitriles (IIa-k). However, in the case of 2-(*p*-tolylsulfonyl)quinoxaline 4-oxide (II), the substitution with cyanide ion proceeded together with deoxy-cyanation to give 2,3-quinoxalinedicarbonitrile (III).

Keywords trimethylsilyl cyanide; quinoxaline N-oxide; quinoxalinecarbonitrile; 1,8-diazabicyclo[5.4.0]undec-7-ene; deoxy-cyanation

Recently, Vorbrüggen's²⁾ and Yamanaka's³⁾ groups have reported that some aromatic heterocyclic N-oxides, which do not undergo the Reissert-Henze reaction (the deoxy-cyanation of N-oxides with potassium cyanide and benzoyl chloride) smoothly, were treated with trimethylsilyl cyanide (TMSCN) in the presence of triethylamine (method A) in acetonitrile to give the corresponding α -cyano-N-heterocycles in satisfactory yields. On the other hand, we have previously reported⁴⁾ that the Reissert-Henze reaction with 2-phenylquinoxaline 4-oxide (Ia) gave only 8% of 3-phenyl-2-quinoxalinecarbonitrile (IIa) together with a considerable amount of by-products. Thus, in the expectation that a similar deoxy-cyanation would take place smoothly,

method A was applied to Ia.

When a solution of Ia, TMSCN, and triethylamine in acetonitrile was refluxed for 3 h, IIa was obtained in satisfactory yield (64%), as expected. In the same way, other 2-substituted quinoxaline 4-oxides such as 2-methoxy- (Ib), 2-ethoxy- (Ic), 2-isopropyl- (Id), and 2-*tert*-butylquinoxaline 4-oxide (Ie) were conveniently converted into the corresponding 3-methoxy- (IIb), 3-ethoxy- (IIc), 3-isopropyl- (IId), and 3-*tert*-butyl-2-quinoxalinecarbonitrile (Ie) (60-69%) (see Table I).

Further, to increase the yields of 2-quinoxalinecarbonitriles, reactions were carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in place of triethylamine.

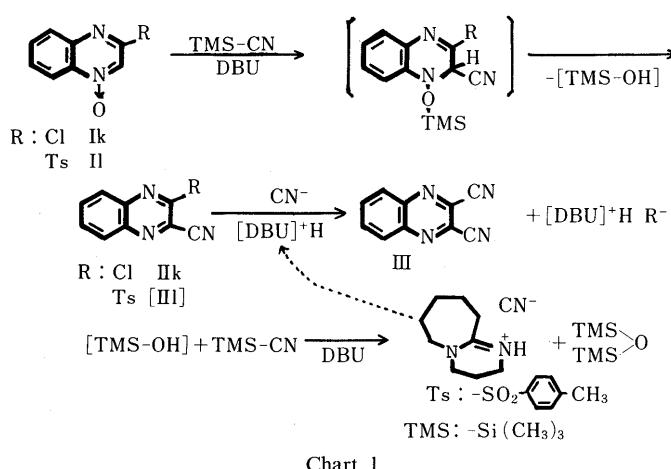
TABLE I. Reaction of Quinoxaline N-Oxides (Ia-I) with TMSCN

-R	N-Oxide		Product		Method ^{a)}	Yield (%) (Recovery)
		I	II	mp (°C) [lit.] Appearance		
-Ph		Ia	IIa	162-163 [163] ⁵⁾ Colorless needles	A ₁ A ₂ A B	4 (90) 32 (55) 64 95
-OCH ₃		Ib	IIb	150-151 [150] ⁶⁾ Colorless prisms	A B	60 76
-OC ₂ H ₅		Ic	IIc	109-110 [109] ⁷⁾ Colorless scales	A B	62 83
-CH(CH ₃) ₂		Id	IId	109-110 Colorless needles	A B	64 95
-C(CH ₃) ₃		Ie	IIe	118-119 Colorless needles	A B	69 78
-C ₂ H ₅		If	IIf	93-94 [93-94] ⁸⁾ Colorless needles	B	89
-CH ₃		Ig	IIg	151-152 [151-152] ⁸⁾ Colorless needles	B	87
1,2-Dihydro-1-methyl-2-oxo-		Ih	IIh	201-202 [211] ⁹⁾ Yellow needles	B	86
-COOC ₂ H ₅		Ii	IIi	126-127 [122-126] ⁷⁾ Colorless needles	B	72
-CN		Ij	III	217-218 [217-218] ¹⁰⁾ Colorless needles	B ₁ B ₂	44 21
-Cl		Ik	IIk	160-161 [159-160] ¹¹⁾ + III Colorless needles	B ₂	44+5
-SO ₂ --CH ₃		Il	III		B ₁	47

a) Using Et₃N: A, refluxing in MeCN for 3 h; A₁, refluxing in THF for 3 h; A₂, refluxing in MeCN for 30 min. Using DBU: B, stirring in THF for 30 min at room temperature; B₁, stirring in THF for 15 min at 0-5°C; B₂, stirring in THF for 30 min at 0-5°C.

TABLE II. Elemental Analysis, IR, $^1\text{H-NMR}$, and MS Data for II

Compd.	Formula	Analysis (%)			IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹	¹ H-NMR (CDCl ₃) ppm	MS <i>m/z</i>
		Calcd	Found	C			
IIb	C ₁₀ H ₇ N ₃ O	64.86 (64.76)	3.81 3.80	22.69 22.51)	2250 (CN)	4.20 (3H, s, CH ₃), 7.40—8.20 (4H, m, C ⁵⁻⁸ -H)	185 (M ⁺) 170 (M ⁺ —CH ₃) 155 (M ⁺ —CH ₂ O)
IIc	C ₁₁ H ₉ N ₃ O	66.32 (66.18)	4.55 4.55	21.10 20.82)	2250 (CN)	1.52 (3H, t, <i>J</i> =7 Hz, CH ₃), 4.62 (2H, q, <i>J</i> =7 Hz, CH ₂) 7.40—8.20 (4H, m, C ⁵⁻⁸ -H)	199 (M ⁺) 184 (M ⁺ —CH ₃) 171 (M ⁺ —C ₂ H ₄)
IId	C ₁₂ H ₁₁ N ₃	73.07 (73.04)	5.62 5.67	21.31 21.30)	2240 (CN)	1.46 (6H, d, <i>J</i> =7 Hz, CH ₃), 3.74 (1H, m, <i>J</i> =7 Hz, CH) 7.55—8.25 (4H, m, C ⁵⁻⁸ -H)	197 (M ⁺) 182 (M ⁺ —CH ₃) 169 (M ⁺ —C ₂ H ₄)
IIe	C ₁₃ H ₁₃ N ₃	73.90 (73.71)	6.20 6.28	19.89 19.67)	2240 (CN)	1.68 (9H, s, CH ₃), 7.50—8.30 (4H, m, C ⁵⁻⁸ -H)	211 (M ⁺) 196 (M ⁺ —CH ₃) 169 (M ⁺ —C ₃ H ₆)
IIh	C ₁₀ H ₇ N ₃ O	64.86 (64.78)	3.81 3.79	22.69 22.66)	1670 (CO) 2240 (CN)	3.74 (3H, s, CH ₃), 7.20—8.10 (4H, m, C ⁵⁻⁸ -H)	185 (M ⁺) 157 (M ⁺ —CO) 130 (157-HCN)
IIi	C ₁₂ H ₉ N ₃ O	63.43 (63.50)	3.99 3.95	18.50 18.47)	1730 (CO) 2240 (CN)	1.54 (3H, t, <i>J</i> =7 Hz, CH ₃), 4.62 (2H, q, <i>J</i> =7 Hz, CH ₂) 7.60—8.50 (4H, m, C ⁵⁻⁸ -H)	227 (M ⁺) 183 (M ⁺ —OC ₂ H ₄) 155 (183—CO) 128 (155—HCN) 191 (M ⁺ +2)
IIk	C ₉ H ₄ ClN ₃	57.01 (56.95)	2.13 2.19	22.16 22.05)	2220 (CN)	7.75—8.25 (4H, m, C ⁵⁻⁸ -H)	189 (M ⁺) 154 (M ⁺ —Cl) 137 (M ⁺ —(CN) ₂)



On reacting with TMSCN in the presence of DBU (method B) in tetrahydrofuran (THF) for 30 min at room temperature, Ia–e gave IIa–e in excellent yields (76–95%) (see Table I). Similarly, 2-ethyl- (If), 2-methyl- (Ig), 1,2-dihydro-1-methyl-2-oxoquinoxaline 4-oxide (Ih), and ethyl 2-quinoxalinecarboxylate 4-oxide (Ii) afforded the corresponding 2-quinoxalinecarbonitriles, 3-ethyl- (IIf), 3-methyl- (I Ig), 3,4-dihydro-4-methyl-3-oxo-2-quinoxalinecarbonitrile (IIf), and ethyl 3-cyano-2-quinoxalinecarboxylate (IIi), in good yields (72–86%) (see Table I). However, quinoxaline 4-oxides with an electron-withdrawing group, such as cyano, chloro, or *p*-tolylsulfonyl group, in the 2-position gave the quinoxalinecarbonitriles in low yields (44–47%) (see Table I); namely 2,3-quinoxalinedicarbonitrile (III) was obtained from 2-quinoxalinecarbonitrile 4-oxide (Ij), 3-chloro-2-quinoxalinecarbonitrile (IIk) together with 5% of III from 2-chloroquinoxaline 4-oxide (Ik), and III from 2-

(*p*-tolylsulfonyl)quinoxaline 4-oxide (II). The formation of III from I_k or II is illustrated in Chart 1. First, the deoxy-cyanation of I_k or II occurs to give II_k or 3-(*p*-tolylsulfonyl)-2-quinoxalinecarbonitrile (III), followed by further substitution with cyanide ion to afford III. In contrast to the other examples, no III could be isolated because II directly afforded III, not III, which was converted immediately into III. The rapid substitution of the *p*-tolylsulfonyl group by cyanide ion can be explained by its strongly electron-attractive character.

Structural determination of II_d, II_e, II_h, II_i, and II_k was accomplished on the basis of analytical and spectral data (in Table II). Products, II_a—c, II_f, II_g, and III, were characterized by comparison with authentic samples.

The deoxy-cyanation of quinoxaline N-oxides, except for Ij—l bearing an electron-withdrawing group, by method B occurs under milder conditions than by method A to give quinoxalinecarbonitriles in high yields. The stronger basic DBU promotes elimination of trimethylsilanol.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 diffraction grating IR spectrometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2 , Wakogel C-200 (100–200 mesh).

Starting 2-substituted quinoxaline 4-oxides (I) were synthesized according to the reported methods, except for 2-(*p*-tolylsulfonyl)quinoxaline 1-oxide (II): 2-phenyl- (Ia),⁴⁾ 2-methoxy- (Ib),⁶⁾ 2-ethoxy- (Ic),⁶⁾ 2-isopropyl- (Id),¹²⁾ 2-*tert*-butyl- (Ie),¹²⁾ 2-ethyl-(If),¹²⁾ 2-methyl- (Ig),⁶⁾ 1,2-dihydro-1-methyl-2-oxo- (Ih),¹³⁾ 2-chloroquinoxaline 4-oxide (Ik),⁶⁾ ethyl 2-quinoxalinecarboxylate 4-oxide (Ii),¹⁴⁾ and 2-quinoxalinecarbonitrile 4-oxide

(Ij).⁶⁾

2-(*p*-Tolylsulfonyl)quinoxaline 4-Oxide (II) A solution of 2-(*p*-tolylsulfonyl)quinoxaline¹⁵⁾ (500 mg, 1.8 mmol) and 70% *m*-chloroperbenzoic acid (455 mg, 1.9 mmol) in CHCl₃ (15 ml) was allowed to stand for 7 d in a refrigerator (at below 10 °C), made alkaline with 10% K₂CO₃, and extracted with CHCl₃. The crude product obtained from the CHCl₃ extract was recrystallized from CHCl₃-MeOH to give colorless needles, mp 179–180 °C. Yield 370 mg (70%). *Anal.* Calcd for C₁₅H₁₂N₂O₃S: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.17; H, 4.07; N, 9.39. IR (KBr) cm⁻¹: 1350, 1160 (SO₂). ¹H-NMR (CDCl₃): 2.45 (3H, s, CH₃), 7.38 (2H, d, *J*=9 Hz, C^{3',5'}-H), 8.02 (2H, d, *J*=9 Hz, C^{2',6'}-H), 7.75–8.75 (4H, m, C^{5–8}-H), 9.02 (1H, s, C²-H). MS *m/z*: 300 (M⁺), 236 (M⁺-SO₂), 219 (236–OH).

General Procedure for the Reaction of 2-Substituted Quinoxaline 4-Oxide (I) with TMSCN Method A Using Et₃N: A solution of I (300 mg, 1.4–1.7 mmol), TMSCN (2.8–3.4 mmol), and Et₃N (2.8–3.4 mmol) in dry MeCN (6 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was treated with 5% NaHCO₃ (20 ml) and extracted with CHCl₃. After purification of the CHCl₃ extract by SiO₂ column chromatography eluting with petr. benzene-C₆H₆, the product was recrystallized from petr. benzene.

Method B Using DBU: A solution of I (300 mg, 1.0–1.9 mmol), TMSCN (2.0–3.8 mmol), and DBU (1.3–2.5 mmol) in dry THF (6 ml) was stirred for 30 min at room temperature. The reaction mixture was worked up essentially as described for method A.

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References

- 1) Part XXVI: C. Iijima and T. Kyō, *Chem. Pharm. Bull.*, **37**, 618 (1989).
- 2) H. Vorbrüggen and K. Krolkiewicz, *Synthesis*, **1983**, 316.
- 3) H. Yamanaka, S. Nishimura, S. Kaneda, and T. Sakamoto, *Synthesis*, **1984**, 681; T. Sakamoto, S. Kaneda, S. Nishimura, and H. Yamanaka, *Chem. Pharm. Bull.*, **33**, 565 (1985).
- 4) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962).
- 5) F. Kröhnke, *Chem. Ber.*, **80**, 298 (1947).
- 6) E. Hayashi, C. Iijima, and Y. Nagasawa, *Yakugaku Zasshi*, **84**, 163 (1964).
- 7) K. Hermann and G. Simchen, *Justus Liebigs Ann. Chem.*, **1981**, 333.
- 8) E. Hayashi and T. Miyagishima, *Yakugaku Zasshi*, **87**, 1103 (1967).
- 9) G. Tennant, *J. Chem. Soc.*, **1964**, 1986.
- 10) E. Hayashi and A. Utsunomiya, *Yakugaku Zasshi*, **95**, 774 (1975).
- 11) K. Yoshida and H. Otomasu, *Chem. Pharm. Bull.*, **32**, 3361 (1984).
- 12) E. Hayashi and Y. Miura, *Yakugaku Zasshi*, **87**, 643 (1967).
- 13) G. Tennant, *J. Chem. Soc.*, **1963**, 2428.
- 14) A. S. Elina and O. Yu. Magidson, *Zh. Obshch. Khim.*, **25**, 161 (1955) [*Chem. Abstr.*, **50**, 1839 (1956)].
- 15) C. Iijima and E. Hayashi, *Yakugaku Zasshi*, **108**, 437 (1988).