PREPARATION OF HETEROARENECARBONITRILES BY REACTION OF HETEROARENE *N*-OXIDES WITH TRIMETHYLSILYL CYANIDE IN THE PRESENCE OF DBU

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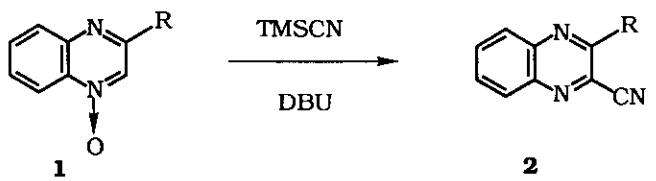
Abstract—— Several heteroarenecarbonitriles were prepared from the corresponding heteroarene *N*-oxides by treatment with trimethylsilyl cyanide (TMSCN) in the presence of a base in tetrahydrofuran (THF). 1,8-Diazabicyclo[5.4.0]-7-undecene (DBU) was found to be an effective base for the cyanation.

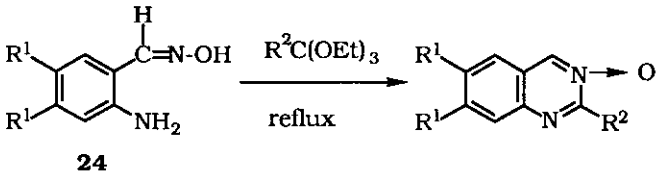
Recently, the preparation of heteroarenecarbonitriles by modified Reissert-Henze[1] reaction of corresponding heteroarene *N*-oxides with trimethylsilyl cyanide (TMSCN), which was carried out under anhydrous conditions, has been extensively investigated.[2-4] Namely, Vorbrüggen *et al.*[2] and Yamanaka *et al.*[3] reported a synthesis of the pyridinecarbonitriles by the reaction of the pyridine 1-oxides with TMSCN in the presence of triethylamine (TEA) in acetonitrile or in *N,N*-dimethylformamide (DMF). Additionally, Fife *et al.*[4] reported *N,N*-dimethylcarbamoyl chloride can be used as an acylating reagent for the cyanation of the pyridine 1-oxides with TMSCN in dichloromethane. Moreover, we reported[5] that 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) was an effective base for the reaction of the quinoxaline *N*-oxides (**1**) with TMSCN, resulting in the formation of the corresponding quinoxalinecarbonitriles (**2**). For instance, 3-methylquinoxaline 1-oxide (**1a**) reacted with TMSCN in the presence of DBU in acetonitrile or in tetrahydrofuran (THF) to give 3-methyl-2-quinoxalinecarbonitrile (**2a**) in good yield, as shown in Scheme 1.



1 (**1a**: R = Me) **2** (**2a**: R = Me)

Scheme 1

On the basis of the above results, we then applied the our method to preparation of various heteroarenecarbonitriles (**3**-**12**), and the effect of a base for the cyanation was examined. Following heteroarene *N*-oxides were used in this investigation: quinoline 1-oxide (**3**),[6] isoquinoline 2-oxide (**4**),[7] acridine 10-oxide (**5**),[8] phenanthridine 5-oxide (**6**),[9] quinazoline *N*-oxides (**7a**,[10] **7b-c**, **8a-b**, **9a-b**,[11] and **10**[11]), 1-phenylphthalazine 3-oxide (**11**),[12] and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (**12**).[13] The new starting quinazoline 3-oxides used in this paper were prepared by ring closure of the oximes (**24**) with orthoesters, as shown in Scheme 2.

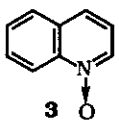
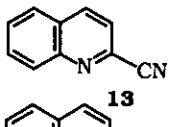
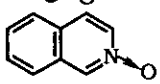
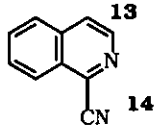
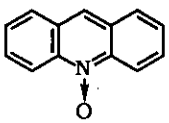
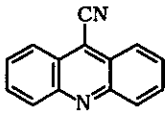
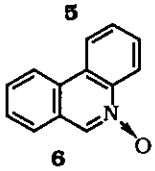
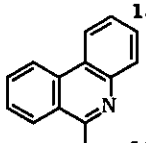
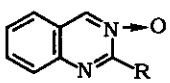
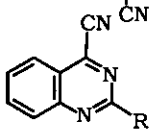
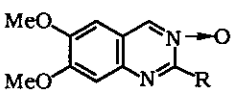
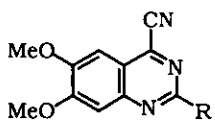
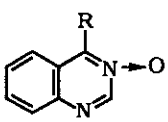
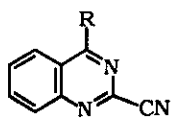


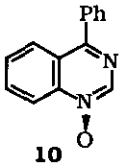
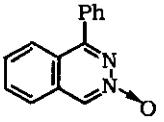
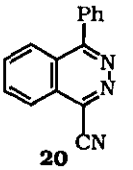
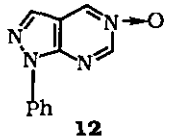
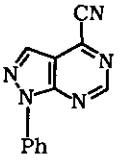
	R^1	R^2	Yield (%)
7b	H	Me	76
7c	H	Et	65
8a	OMe	H	79
8b	OMe	Me	60

Scheme 2

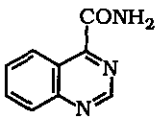
The reactions of **3** and **4** with TMSCN in the presence of DBU in refluxing THF gave 2-quinolinecarbonitrile (**13**)[14] and 1-isoquinolinecarbonitrile (**14**)[15] in 89% and 97% yields, respectively. The similar reaction of **5** in the presence of DBU gave the corresponding carbonitrile (**15**)[16] in 77% yield, but the use of TEA instead of DBU did not afford **15**. The same result was observed in the reactions of **6** and **9a**. Namely, the treatment of **6** with TMSCN in the presence of TEA in refluxing THF for 2 h gave 5-phenanthridinecarbonitrile (**16**)[9] in low yield (18%), but the same reaction in the presence of DBU instead of TEA for 1 h furnished **16** in 65% yield. Similarly, conversion of **9a** into 4-methyl-2-quinazolinecarbonitrile (**19a**) using TEA as a base in refluxing THF for 3 h failed, while the same reaction with DBU gave **19a** in 55% yield. The treatment of **7a** with TMSCN in the presence of DBU in refluxing THF gave 4-quinazolinecarbonitrile (**17a**)[17] together with 4-quinazolinecarboxamide (**22**).[18] A similar result was obtained in the reaction of **12**. Formation of the carboxamides (**22** and **23**[19]) may be considered through hydrolysis of the cyano groups of **17a** and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**21**).[19] Even if under milder conditions at room temperature for 10 min gave the carbonitriles (**17a** and **21**) in good yields. The C^4-ring carbon on the fused pyrimidine ring against nucleophiles has higher reactivity.[17] And therefore, both the reaction in the presence of DBU and in the presence of TEA underwent the cyanation to yield the carbonitriles. Moreover, the *N*-oxides (**7b-c**, **10**, and **11**) underwent the cyanation to give the corresponding carbonitriles (**17b-c**, **19b**, and **20**[20]) in good yields. The treatment of 6,7-dimethoxyquinazoline 3-oxide (**8a** and **8b**) with TMSCN in the presence of DBU at room temperature for 30 min resulted in the formation of the carbonitriles (**18a** and **18b**) in 86% and 76% yields, respectively. It seemes that use of DBU as a base for the cyanation reduced the reaction time and the cyanation was achieved by the lower reaction temperature compared with that of TEA. These results are shown in Table I.

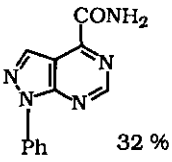
TABLE I. Preparation of Heteroarenecarbonitriles by Treatment of Heteroarene *N*-Oxides with TMSCN in the Presence of Base

Heteroarene *N*-Oxide	Base	Reaction Conditions: Time (min.)	Temp. (°C)	Product: Heteroarenecarbonitrile	Yield (%)	Recovery
 **3**	DBU	30	reflux	 **13**	89	
 **4**	DBU	30	reflux	 **14**	97	
 **5**	DBU	60	reflux	 **15**	77	
	TEA	60	reflux		—	65
 **6**	DBU	60	reflux	 **16**	65	
	TEA	120	reflux		18	45
 **7a** R = H	DBU	10	reflux	 **17a** R = H	32 [a]	
		10	r. t.[d]		82	
	TEA	60	reflux		86	
7b R = Me	DBU	30	reflux	**17b** R = Me	77	
	TEA	120	reflux		67	
7c R = Et	DBU	30	reflux	**17c** R = Et	74	
	TEA	150	reflux		64	
 **8a** R = H	DBU	30	r. t.[d]	 **18a** R = H	86	
8b R = Me	DBU	30	r. t.[d]	**18b** R = Me	76	
 **9a** R = Me	DBU	10	reflux	 **19a** R = Me	55	
	TEA	180	reflux		—	63
9b R = Ph	DBU	30	reflux	**19b** R = Ph	89	

 **10**	DBU	40	reflux	**19b**	87
	TEA	180	reflux		52
 **11**	DBU	40	reflux	 **20**	76
	TEA	180	reflux		37
 **12**	DBU	40	reflux	 **21**	35 [b]
		10	r. t.[c]		68
	TEA	180	reflux		71

22

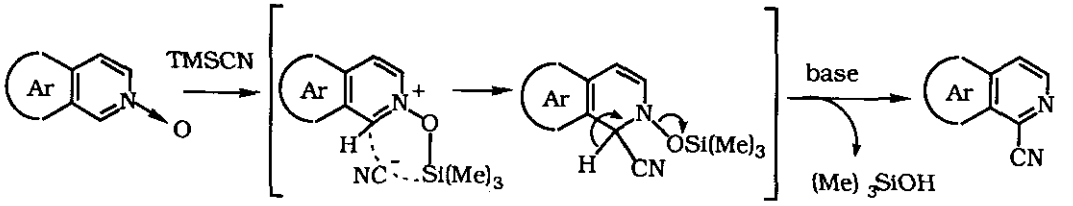
a)  22 % **22**

b)  32 % **23**

c) room temperature

As illustrated in Scheme 3, the heteroarenecarbonitriles are formed through the adduct between the *N*-oxides and TMSCN, followed by elimination of trimethylsilanol by the action of the base. In the above results, DBU is an effective base for the cyanation.

The structures of the heteroarenecarbonitriles (**13-16**, **17a**, **20**, and **21**) and the carboxamide (**22** and **23**) were identified by the comparison with the corresponding authentic specimens prepared by reported procedure. The structures of the other carbonitriles (**17b**, **c**, **18a**, **b**, **19a**, and **19b**) newly obtained in above reaction were supported by the elemental analyses and analyses of the spectral data, as described in the experimental section.



Scheme 3

In conclusion, the method using heteroarene *N*-oxide and TMSCN in the presence of DBU provides a simple and useful procedure for the preparation of the heteroarenecarbonitriles.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. Proton magnetic resonance (^{1}H-nmr) spectra were measured at 60 MHz on a HITACHI R-24B spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard, and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet. Column chromatography was carried out on SiO_2, Wakogel C-200 (200 mesh). Heteroarene *N*-oxides (**3**, **4**, **5**, **6**, **7a**, **10**, **11** and **12**) were prepared by reported procedure.[6-13]

2-Methylquinazoline 3-Oxide (7b)——A mixture of 2-aminobenzaldehyde oxime (**24a**, 10 g, 74 mmol) and triethyl orthoacetate (50 ml) was refluxed for 2 h. After cooling, the separated crystalline solid was collected and recrystallized from benzene-petroleum benzin to give **7b** (8.9 g, 76%) as pale yellow needles, mp 167 °C. *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.02; N, 17.46. Ms: m/z = 160 (M^+). ^{1}H-Nmr($CDCl_3$): 2.85 (3H, s, C^2-Me), 8.80 (1H, s, C^4-H), 7.45-8.00 (4H, m, aromatic H).

2-Ethylquinazoline 3-Oxide (7c)—— A mixture of **24a** (10 g, 74 mmol) and triethyl orthopropionate (50 ml) was refluxed for 2 h. After cooling, separated crystalline solid was collected by filtration, recrystallized from benzene-petroleum benzin to give **7c** (8.3 g, 65%) as pale yellow needles, mp 126-128 °C. *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.76; H, 5.76; N, 16.08. Ms: m/z = 174 (M^+). ^{1}H-Nmr ($CDCl_3$): 1.42 (3H, t, *J* = 8 Hz, $CH_2C\underline{H}_3$), 3.25 (2H, q, *J* = 8 Hz, $C\underline{H}_2CH_3$), 7.38-8.05 (4H, m, aromatic H).

2-Amino-4,5-dimethoxybenzaldehyde Oxime (24b)——A solution of 2-nitro-4,5-dimethoxybenzaldehyde (25 g, 118 mmol) in a mixture of 250ml of MeOH and 250 ml of benzene was reduced under an H_2 atmosphere over Raney Ni catalyst (prepared from 10 g of Ni-Al alloy). The reduction was continued until consumption of theoretical H_2. The Raney Ni was filtered off, and the filtrate was evaporated to dryness. The residue was disolved in 100 ml of MeOH, and hydroxylamine hydrochloride (16.4 g, 236 mmol) in 100 ml of H_2O was added to the solution. The mixture was heated at 80 °C for 1 h, and then allowed to

stand at room temperature overnight. The reaction mixture was concentrated to dryness, and the residue was passed through a short column of SiO_2 with $CHCl_3$. The obtained crystalline solid was recrystallized from MeOH to give **24b** (11 g, 47%) as colorless needles. mp 153-155 °C. *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.32; H, 6.04; N, 14.22.

6,7-Dimethoxyquinazoline 3-Oxide (8a)——A solution of 2-amino-4,5-dimethoxybenzaldehyde oxime (**24b**, 6.4 g, 33 mmol) in 30 ml of triethyl orthoformate was refluxed for 2 h. After cooling, the separated crystalline solid was collected by filtration, and recrystallized from MeOH to give **8a** as slightly yellow needles (5.3 g, 79%), mp 237-238 °C. *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89 ; N, 13.59. Found; C, 58.53; H, 4.85; N, 13.67. ^{1}H-Nmr ($CDCl_3$): 8.75 (1H, d, J = 2 Hz, C^4-H), 8.65 (1H, d, J = 2 Hz, C^2-H), 7.22 (1H, s, C^8-H), 6.85 (1H, s, C^5-H), 3.98 (6H, s, OMe x 2). ^{13}C-Nmr ($CDCl_3$): 154.5 (s), 152.7 (s), 146.1 (d), 139.0 (s), 138.9 (d), 120.2 (s), 107.4 (d), 101.8 (d), 56.6 (q, OMe), 56.5 (q, OMe).

6,7-Dimethoxy-2-methylquinazoline 3-Oxide (8b)——A solution of **24b** (8 g, 41 mmol) in 40 ml of triethyl orthopropionate was refluxed for 2 h. After cooling, the separated crystalline solid was collected by filtration, and recrystallized from MeOH to give **8b** (5.4 g, 60%) as slightly yellow needles, mp 180-182 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49, N, 12.72. Found: C, 59.19; H, 5.55, N, 12.54. ^{1}H-Nmr ($CDCl_3$): 8.65 (1H, s, C^4-H), 7.16 (1H, s, C^8-H), 6.80 (1H, s, C^5-H), 3.98 (6H, s, OMe x 2), 2.82 (3H, s, Me). ^{13}C-Nmr ($CDCl_3$): 155.9 (s), 154.5 (s), 151.8 (s), 139.3 (d), 138.9 (s), 119.7 (s), 106.6 (d), 101.4 (d), 56.5 (q, OMe), 56.4 (q, OMe).

General Procedure for the Reaction of Heteroarene *N*-oxide with TMSCN in the Presence of a Base—— To a mixture of an *N*-oxide (3 mmol) and TMSCN (3.6 mmol) in THF (20 ml) was slowly added a base (TEA 1 ml or DBU 1 ml). The resultant solution was stirred for an appropriate time (reaction conditions are shown in Table I), and then concentrated to dryness under reduced pressure. The residue was passed through a column of SiO_2 with benzene. The first fraction gave the heteroarenecarbonitriles (elemental analyses and spectral data for the carbonitriles newly obtained in this paper are shown below). In the reaction of **7a** or **12** using DBU in refluxing THF, the fraction eluted with $CHCl_3$ gave the carboxamides (**22** or **23**).

17b: Recrystallization from petroleum benzin gave colorless needles, mp 127-128 °C. *Anal.* Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.06; H, 4.17; N, 24.87. Ms: m/z = 169 (M^+). ^{1}H-Nmr ($CDCl_3$): 2.90 (3H, s, C^2-Me), 7.52-8.20 (4H, m, aromatic H).

17c: Recrystallization from petroleum benzin gave colorless needles, mp 86.5-88 °C. *Anal.* Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.04; H, 4.90; N, 22.87.

Ms: m/z = 183 (M^+). ^{1}H-Nmr ($CDCl_3$): 1.46 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$), 3.18 (2H, q, J = 8 Hz, $C\underline{H}_2CH_3$), 7.45-8.25 (4H, m, aromatic H).

18a: Recrystallization from MeOH gave slightly yellow needles, mp 221-223 °C. *Anal.* Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.42; H, 4.03, N, 19.66. ^{1}H-Nmr ($CDCl_3$): 9.01 (1H, s, C^2-H), 7.20 (1H, s, C^8-H), 7.17 (1H, s, C^5-H), 4.02 (6H, s, OMe x 2). ^{13}C-*Nmr* ($CDCl_3$): 157.8 (s), 153.5 (d, C^2), 153.0 (s), 149.5 (s), 138.3 (s), 121.7 (s), 114.8 (s), 106.9 (d), 103.1 (d), 56.85 (q, OMe), 56.75 (q, OMe).

18b: Recrystallization from benzene-petroleum benzin gave yellow needles, mp 193-194 °C. *Anal.* Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.79; H, 4.80; N, 18.32. ^{1}H-Nmr ($CDCl_3$): 7.10 (2H, s, C^5-H and C^8-H), 3.98 (6H, s, OMe x 2), 2.75 (3H, s, Me). ^{13}C-Nmr ($CDCl_3$); 163.0 (s), 157.7 (s), 152.1 (s), 149.8 (s), 138.9 (s), 119.3 (s), 114.9 (s), 106.3 (d), 101.1 (d), 56.75 (q, OMe), 56.65 (q, OMe), 25.9 (q, Me).

19a: Recrystallization from MeOH gave yellow needles, mp 148-150 °C. *Anal.* Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.88; H, 4.12; N, 24.82. IR (KBr): 2240 cm^{-1} (CN). ^{1}H-Nmr ($CDCl_3$): 3.01 (3H, s, C^4-H), 7.65-8.25 (4H, m, aromatic H).

19b: Recrystallization from petroleum benzin gave colorless needles, mp 127-129 °C. *Anal.* Calcd for $C_{15}H_9N_3$: C, 77.91; H, 3.92; N, 18.17. Found: C, 78.15; H, 3.86; N, 18.13. Ms: m/z = 231 (M^+). Ir (KBr): 2240 cm^{-1} (CN). ^{1}H-Nmr ($CDCl_3$): 7.45-8.20 (m, aromatic H).

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