Selective Synthesis of 2-, 4-, and 5-Cyano Substituted Imidazoles from Imidazole *N*-Oxides and Trimethylsilyl Cyanide

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1-Substituted 2-, 4-, and 5-cyanoimidazoles were produced by reaction of 3-cyclohexyl or 3-*p*-tolylimidazole 1-oxide and trimethylsilyl cyanide in the presence of triethylamine. The product composition depended on reaction temperature and solvent polarity. By proper choice of these parameters each isomer could be obtained selectively in reasonable yield.

Introduction

Reaction of azine *N*-oxides with trimethylsilyl cyanide is a useful method for the preparation of α- and γ-cyanoazines. Thus pyridine *N*-oxides afford 2- and 4-cyanopyridines,[1−3] pyrazine *N*-oxides produce 2-cyanopyrazines[4,5] and pyrimidine *N*-oxides give 2-, 4-, and 6-cyanopyrimidines.[6]

The reaction is performed in the presence of triethylamine, and the mechanism proposed takes place via O-silylation, addition of cyanide, and elimination of trimethylsilanol (Scheme 1). This mechanism explains the observed regioselectivity since it is determined by the addition of cyanide anion to the activated α- and γ-positions of the intermediate quaternary azinium ion. Similar reactions take place between azines and other silylated nucleophiles.[3]

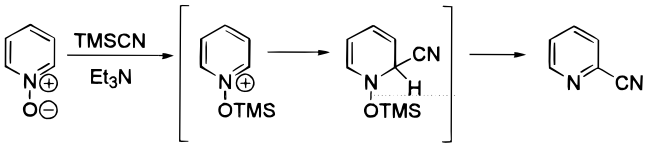
Although the reaction has been studied extensively in the azine series, no examples of the reaction between azole *N*-oxides and trimethylsilyl cyanide seem to have been reported.

Results

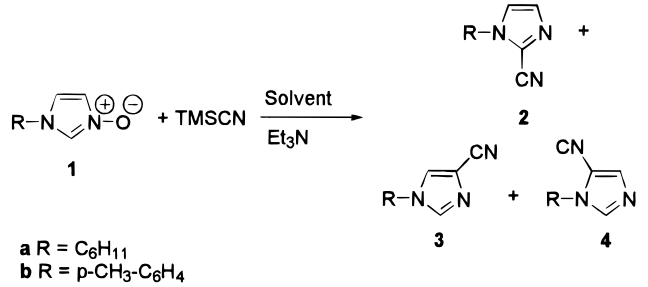
The reaction between imidazole *N*-oxides and trimethylsilyl cyanide has now been studied. Imidazole *N*-oxides devoid of substituents at the carbon atom are readily available by cyclization of 1,2-diimines and oximes.[7] Such compounds are well suited for a study of the regioselectivity and the mechanism of this reaction.

The reaction between imidazole *N*-oxides and trimethylsilyl cyanide is expected to give 2-cyanoimidazoles. According to the mechanism proposed for the reaction of azine *N*-oxides, after O-silylation, addition of cyanide to carbon-2, the activated α-position of the intermediate quaternary azolium ion, in favored. However, the reaction of 3-cyclohexylimidazole 1-oxide (**1a**) or 3-*p*-tolylimidazole 1-oxide (**1b**) afforded all three possible isomeric cyanoimidazoles **2**−**4**.

Scheme 1



Scheme 2



The product distribution was influenced by the N-substituent of the imidazole 1-oxide, temperature, and the nature of the solvent. Thus, in the reaction of 3-cyclohexylimidazole 1-oxide (**1a**) in chloroform the yield of 2-cyano-1-cyclohexylimidazole (**2a**) increased from 5% to 59% when the temperature was raised from 20 °C to 60 °C (Table 1) while the yield of 4-cyano-1-cyclohexylimidazole (**3a**) decreased from 68% to 19% and the yield of 5-cyano-1-cyclohexylimidazole (**4a**) remained almost constant at ca. 25%.

In contrast, the 3-*p*-tolylimidazole 1-oxide (**1b**) produced the regioisomers **2b**−**4b** in a ratio which was virtually independent of the temperature.

On the other hand, the selectivity was strongly influenced by the solvent polarity (Table 2). In the reaction of **1a** the yield of the 4-cyano-1-cyclohexylimidazole (**3a**) increased when solvents of higher polarity were used while the yield of 5-cyano-1-cyclohexylimidazole (**4a**) decreased. It was found that the ratio between **3a** and **4a** correlated linearly with the $E_T(30)$ values of solvent polarity.[8]

By the reaction of 3-*p*-tolylimidazole 1-oxide (**1b**) with trimethylsilyl cyanide the yield of 2-cyano-1-(*p*-tolyl)-imidazole (**2b**) increased and the yield of 5-cyano-1-(*p*-tolyl)imidazole (**4b**) decreased in solvents of high polarity while the yield of 4-cyano-1-(*p*-tolyl)imidazole **3b** reached a maximum at a solvent polarity $E_T(30)$ of ca. 39. In this reaction only the yield of **4b** correlated linearly with the $E_T(30)$ values of solvent polarity.[8]

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Table 1. Reaction of *N*-Oxides 1a and 1b with Trimethylsilyl Cyanide in Chloroform Solution at Different Temperatures

start. mat.	T (°C)	*t* (h)	**2** (%)	**3** (%)	**4** (%)	yield (%)[a]
1a	60	17	59	19	22	69
1a	40	24	15	50	35	77
1a	20	96	5	68	27	80
1b	20	24	31	36	33	80
1b	0	24	28	36	36	71
1b	−20	24	31	35	34	78

[a] Total yield of isolated products.

Table 2. Reaction of *N*-Oxides 1a at 40 °C and 1b at 20 °C with Trimethylsilyl Cyanide in Various Solvents

start. mat.	solvent	$E_T(30)$	**2** (%)	**3** (%)	**4** (%)	yield (%)[a]
1a	CCl_4	32.4	18	18	64	81
1a	THF	37.4	17	32	51	66
1a	$CHCl_3$	39.1	15	50	35	77
1a	CH_2Cl_2	40.7	15	54	31	76
1a	CH_3CN	45.6	15	57	28	80
1b	CCl_4	32.4	31	9	60	84
1b	THF	37.4	51	6	43	87
1b	$CHCl_3$	39.1	31	36	33	80
1b	CH_2C_{l2}	40.7	57	18	25	87
1b	CH_3CN	45.6	74	5	21	87

[a] Total yield of isolated products.

Table 3. Selected Conditions for the Selective Preparation of Cyanoimidazoles

entry	start. mat.	*T* (°C)	*t* (h)	solvent	**2** (%)	**3** (%)	**4** (%)	yield (%)[a]
1	**1a**	20	96	CH_3CN	16	**72**	12	87
2	**1a**	40	24	CCl_4	18	18	**64**	81
3	**1a**	60	72	$CHCl_3$	**59**	19	22	69
4	**1b**	20	24	$CHCl_3$	31	**36**	33	80
5	**1b**	20	24	CCl_4	31	9	**60**	84
6	**1b**	20	24	CH_3CN	**74**	5	21	87

[a] Total yield of isolated products.

Using this information it was possible to select reaction conditions which made possible the selective preparation of each of the three isomeric cyanoimidazoles in reasonable yields from 3-substituted imidazole 1-oxides **1** and trimethylsilyl cyanide (Table 3). Synthesis of the valuable[9] and unexpected 4-cyano- **3** and 5-cyanoimidazoles **4** must follow a different mechanism than the proposed for azine *N*-oxides. The mechanism of the reaction will be discussed in a subsequent paper.

Experimental Section

The imidazole *N*-oxides **1a** and **1b** were prepared as described previously.[7] Solvents and triethylamine were purified by standard methods. trimethylsilyl cyanide (Aldrich) was used without further purification. Silica gel Merck 60 and PF 60 F_{254} were used for column and preparative TLC, respectively. Mp's are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity 300 instrument at 299.94 MHz using tetramethylsilane as an internal standard.

Reaction with Trimethylsilyl Cyanide. General Procedure. To a solution of the imidazole *N*-oxide **1** (0.25 mmol) in the appropriate solvent (1 mL) were added triethylamine (0.105 mL, 0.75 mmol) and trimethylsilyl cyanide (0.135 mL, 1 mmol) at the temperature specified in Table 3.[10] The mixture was stirred under the conditions given in Table 3, and then the solvent was removed and the residue subjected to chromatography as described below.

2-Cyano-1-cyclohexylimidazole (2a). The reaction of 3-cyclohexylimidazole 1-oxide (**1a**) (Table 3, entry 3), followed by column chromatography on silica gel (4 g, ethyl acetate−light petroleum [1:2]) afforded 19.2 mg (41%) of 2-cyano-1-cyclohexylimidazole (**2a**), R_f 0.48, bp 190 °C/0.7 mbar (ball tube distillation). ^{1}H NMR ($CDCl_3$): δ_H 1.29 (1H, qt, J = 12.8 and 3.6 Hz), 1.49 (2H, qt, J = 13 and 3.2 Hz), 1.68 (2H, qd, J = 12.3 and 3.2 Hz), 1.8 (1H, dtt, J = 13, 3.2, and 1.6 Hz), 1.95 (2H, dt, J = 13.5 and 3.1), 2.12 (2H, dd, J = 12.7, 3.7 and 1.5, Hz), 4.25 (1H, tt, J = 11.7 and 3.7 Hz), 7.15 (1H, d, J = 1.2 Hz), 7.19 (1H, d, J = 1.2). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N: 23.98. Found: C, 68.54; H, 7.40; N, 23.62.

The second fraction contained 12.6 mg of a mixture of **3a** and **4a**, R_f 0.18.

4-Cyano-1-cyclohexylimidazole (3a). Similarly, 3-cyclohexylimidazole 1-oxide (**1a**) under the reaction conditions given in Table 3, entry 1, and subsequent column chromatography on silica gel (4 g) eluting with ethyl acetate−light petroleum (1:2) afforded 8.5 mg of **2a** and 31.7 mg of a mixture of **3a** and **4a**. The mixture of **3a** and **4a** was separated by preparative TLC (ethyl acetate−light petroleum [4:1]) to give 27.7 mg (63%) of **3a**, R_f 0.67, mp 89−91 °C (diethyl ether−light petroleum). ^{1}H-NMR ($CDCl_3$): δ_H 1.26 (1H, qt, J = 12.6 and 3.4 Hz), 1.44 (2H, qt, J = 12.8, and 3.2 Hz), 1.64 (2H, qd, J = 12.2 and 3.4 Hz), 1.77 (1H, dttt, J = 12.8, 3, and 1.5 Hz), 1.94 (2H, dt, J = 13.5 and 3.2 Hz), 2.14 (2H, dtd, J = 11.7, 3.7 and 1.4 Hz), 3.95 (1H, tt, J = 11.7 and 3.8 Hz), 7.50 (1H, d, J = 1.2 Hz), 7.55 (1H, d, J = 1.3 Hz). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N: 23.98. Found: C, 68.54; H, 7.46; N, 23.65.

5-Cyano-1-cyclohexylimidazole (4a). Similarly, 3-cyclohexylimidazole 1-oxide (**1a**) under the reaction conditions given in Table 3, entry 2, followed by column chromatography as above gave 7.2 mg of **2a** and 28.5 mg of a mixture of **3a** and **4a**. The mixture of **3a** and **4a** was separated by preparative TLC as described above to give 22.4 mg (51%) of **4a**, bp 110 °C/0.07 mbar (ball tube distillation), mp 45−46 °C. ^{1}H-NMR ($CDCl_3$): δ_H 1.28 (1H, qt, J = 12.8 and 3.4 Hz), 1.47 (2H, qt, J = 13 and 3.2 Hz), 1.75 (2H, qd, J = 12.4 and 3.3 Hz), 1.79 (1H, m), 1.96 (2H, dt, J = 13.6 and 2.3 Hz), 2.19 (2H, dd, J = 12.8 and 2.1 Hz), 4.11 (1H, tt, J = 12.1 and 3.8 Hz), 7.66 (1H, s), 7.69 (1H, s). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N: 23.98. Found: C, 68.32; H, 7.34; N, 23.66.

2-Cyano-(1-*p*-tolyl)imidazole (2b). 3-*p*-Tolylimidazole 1-oxide (**1b**) was reacted as given in Table 3, entry 6. Subsequent column chromatography on silica gel (4 g, ethyl acetate−light petroleum [1:1]) afforded 34.6 mg of a mixture of **2b** and **3b**, R_f 0.75 and 7.5 mg of **4b**, R_f 0.43. Compounds **2b** and **3b** were separated by preparative TLC (ethyl acetate−chloroform [1:9]) to give 32.6 mg (71%) **2b**, R_f 0.41, mp 131−133 °C (ethyl acetate−light petroleum). ^{1}H-NMR ($CDCl_3$): δ_H 2.45 (3H, s), 7.32 (2H, s), 7.35 (4H, s). Anal. Calcd for $C_{10}H_9N_3$: C, 72.11; H, 4.95; N: 22.94. Found: C, 72.05; H, 4.90; N, 23.30.

4-Cyano-(1-*p*-tolyl)imidazole (3b). Similarly, 3-*p*-tolylimidazole 1-oxide (**1b**) after reaction as given in Table 3, entry 4, and column chromatography on silica gel (4 g, ethyl acetate−light petroleum [1:1]) afforded 24.3 mg of a mixture of **2b** and **3b** and 11.4 mg of **4b**. Compounds **2b** and **3b** were separated by preparative TLC as described above to give 12.8 mg (28%) of **3b**, R_f 0.28, mp 115−116 °C (ethyl acetate−light petroleum). ^{1}H-NMR ($CDCl_3$): δ_H 2.43 (3H, s), 7.28−7.34 (4H, AA′BB′, J = 8.6 Hz), 7.78 (1H, d, J = 1.2 Hz), 7.82 (1H, d, J = 1.2 Hz). Anal. Calcd for $C_{10}H_9N_3$: C, 72.11; H, 4.95; N: 22.94. Found: C, 72.15; H, 5.08; N, 22.74.

5-Cyano-(1-*p*-tolyl)imidazole (4b). Similarly, 3-*p*-tolylimidazole 1-oxide (**1b**) after reaction as given in Table 3, entry 5, followed by column chromatography on silica gel (4 g, ethyl

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(9) 4- and 5-Cyanoimidazoles can be transformed, by reduction to aminometilimidazoles, analogs of midazolam or nizofenone with anticonvulsant or tranquilizer properties. See for instance Bhattacharyya, P. K.; Grant, A. *Anal. Chim. Acta.* **1982**, *142*, 249.

(10) Addition at the reaction temperature is crucial. If the addition was performed at 20 °C followed by heating to the reaction temperature, the product distribution corresponded to that obtained by keeping the temperature at 20 °C.

acetate−light petroleum [1:1]) afforded 17.3 mg of a mixture of **2b** and **3b** and 21.4 mg (47%) of **4b**, mp 137−139 °C (ethyl acetate−light petroleum). ^{1}H-NMR ($CDCl_3$): δ_H 2.45 (3H, s), 7.35 (4H, s), 7.8 (1H, d, J = 1 Hz), 7.81 (1H, d, J = 1 Hz). Anal. Calcd for $C_{10}H_9N_3$: C, 72.11; H, 4.95; N: 22.94. Found: C, 72.40; H, 4.86; N, 22.79.

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