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Regioselective Preparation of N-Substituted 3,5-Diamino-1,2,4-oxadiazoles

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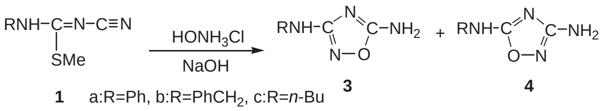
Regioselective preparation of 3,5-diamino-1,2,4-oxadiazoles which have a substituent on one or the other amino group has been developed. When 1-substituted 3-cyano-2-ethylisourea (**2**) was allowed to react with hydroxylamine under basic conditions, 5-amino-3-(substituted amino)-1,2,4-oxadiazole (**3**) was obtained in good yield. On the other hand, 3-amino-5-(substituted amino)-1,2,4-oxadiazoles (**4**), a regioisomer of **3**, could be synthesized by the reaction of *N*,*O*-bis(trimethylsilyl)hydroxylamine (**9**) with **2** or 1-substituted 3-cyano-2-methylisothiourea (**1**) and subsequent alcoholysis.

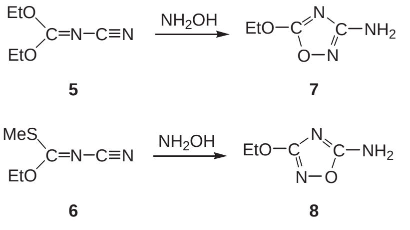
Many types of 1,2,4-oxadiazole derivatives are reported to exhibit pharmacological effects, such as acting as a sedative or analgesic, as well as herbicidal and insecticidal effects.[1] However, it is not necessarily easy to obtain them in high yield, so that new methodology for their regioselective preparation is still required.

Among them, preparation of 1,2,4-oxadiazoles bearing amino groups at both the 3- and 5-positions has been difficult. Tilley et al. have obtained 5-amino-3-(substituted amino)-1,2,4-oxadiazoles (**3**) by the reaction of 1-substituted 3-cyano-2-methylisothioureas (**1**) and hydroxylamine.[2] However, the reaction proceeds with difficulty, and regioselectivity and yields of **3** are very low. For example, **3c** (R = *n*-Bu) was merely isolated in 4% yield with 11% yield of **4c** (R = *n*-Bu) by the reaction of 1-butylisothiourea (**1c**) with hydroxylamine.

In a previous report, we showed selective preparation of amino-ethoxy-1,2,4-oxadiazoles.[3] Namely, the reaction of *N*-cyanocarbonimidate (**5**) or *N*-cyanocarbonimidothioate (**6**) with hydroxylamine proceeded to form 3-amino-5-ethoxy- (**7**) or 5-amino-3-ethoxy-1,2,4-oxadiazole (**8**) in high yield, respectively. In analogy with the above reaction, we expected that the reaction of 3-cyano-2-ethylisoureas (**2**), which were easily prepared from **6**, with hydroxylamine would selectively provide **3** or **4**.



Scheme 1.



Scheme 2.

Three types of **2**, namely, 1-phenyl- (**2a**), 1-benzyl- (**2b**), and 1-butylisourea (**2c**) were examined to compare with the results of Tilley's experiments.[2] In the initial experiment, to an aqueous solution of 3.0 equimolar amounts of hydroxylamine, which is prepared from hydroxylamine hydrochloride and an equimolar amount of sodium hydroxide, was added an alcoholic solution of **2a** at 30 °C. The starting material, **2a**, was consumed in 19 h; however, the yield of **4a** was only 14% and instead, compounds **7** and **8** were isolated as by-products in 52% and 13% yields, respectively (Table 1, Run 1). Compound **3** was not detected under these reaction conditions.

On the other hand, it was found that the use of excess alkali suppressed the formation of **7** and **8**, and increased the yield of **3a** (Runs 2 and 3). Benzyl (**2b**) and butyl (**2c**) derivatives gave the desired products **3b** and **3c** in substantial yields even under neutral conditions. In these cases, furthermore, reaction time was shortened significantly and yields of **3** also improved when alkali was used in excess.

A probable reaction process is outlined in Scheme 4. The amino group of hydroxylamine usually attacks the isourea moiety of **2**. Thus in the cases of **2b** and **2c** which are essentially neutral, **3** is formed via intermediate **B** even under the neutral conditions. However, the nucleophilicity of hydroxylamine is so weak that consumption of the starting material requires much time. The leaving ability of alkyl amine is less than that of ethanol, so compound **3** is given mainly. Whereas **2a** shows slightly acidic property: for example, it dissolves in aqueous sodium hydroxide, addition of hydroxylamine to the cyano group of **2a** may occur simultaneously, because acidic cyanoamino groups tend to be attacked by nucleophiles.[3,4] In addition, the leaving ability of aniline is superior to that of

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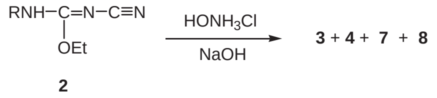
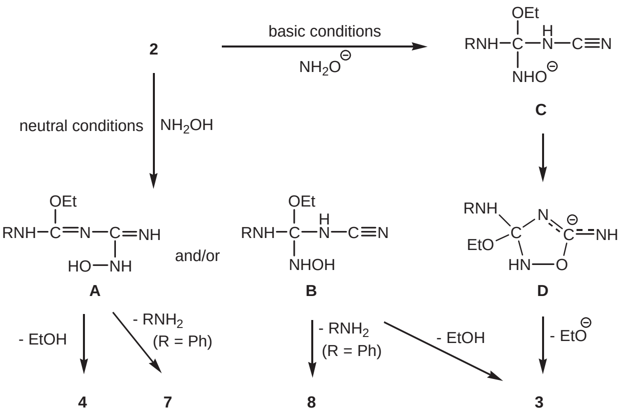
Table 1. Preparation of **3** from **2**

Run	Compound	R	Mole ratio[a]	Time/h	Product and yield/%	
1	**2a**	Ph	1:3:3	19	**3a**	0[b]
2			1:3:4	24		59[c]
3			1:3:5	24		67
4	**2b**	$PhCH_2$	1:3:3	20	**3b**	68
5			1:3:4	4		76
6			1:3:5	4		76
7	**2c**	Bu	1:3:3	36	**3c**	72
8			1:3:4	2		84
9			1:3:5	2		90

a) **2**:$HONH_3Cl$:NaOH. b) 14% of **4a**, 52% of **7**, and 13% of **8** were determined by HPLC analysis. c) 6% of **4a** and 11% of **7a** were also determined by HPLC analysis.



Scheme 3.



Scheme 4. Proposed reaction pathway.

ethanol, so that many 1,2,4-oxadiazoles, namely **4a**, **7a**, and **8a** are obtained via intermediates **A** and **B**.

On the other hand, a part of hydroxylamine will change to the corresponding alkoxide under basic conditions, and the relative nucleophilicity of the amino group increases; furthermore, the reactivity of the cyano group of **2a** diminishes. As a result, intermediate **C** should be formed, which gives exclusively **3** via intermediate **D** because the ethoxide anion is a better leaving group than the amide anion.

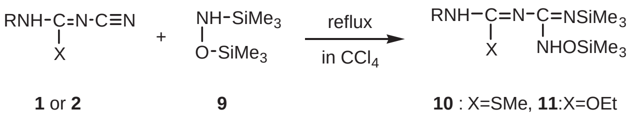
Incidentally, all cyanoisothioureas including **1b** and **1c** were found to show slightly acidic properties. The reason why the reaction products of Scheme 1 were **3** and **4** is apparently the same as that described for **2a** under neutral conditions.

The methodology described above was, however, unsuited to the preparation of 5-(substituted amino)oxadiazole (**4**), an isomer of **3**. From the above hypothesis for the present reaction process and results, if the nitrogen atom of hydroxylamine predominantly attacks the cyano group, the reaction can proceed regioselectively to produce **4** which is a regioisomer of **3**.

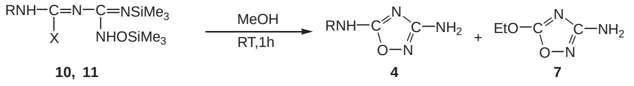
Earlier, we have reported that *N*-silylamines selectively add to the *N*-cyano group, affording the corresponding guanidine derivatives under mild conditions.[4] So the successful selective synthesis of **4** was thought to result from the reaction of **1** or **2** with *N*,*O*-bis(trimethylsilyl)hydroxylamine (**9**) instead of hydroxylamine. Actually, the addition reaction of **9** to **1a**, **1b**, and **2a** proceeded at the boiling point of carbon tetrachloride, giving 1-substituted 2-methyl-3-[*N*-trimethylsilyl-*N*′-(trimethylsilyloxy)amidino]isothiourea (**10a**, **b**) and the corresponding 2-ethylisourea (**11a**) in good yields, respectively (Table 2). Bis-silyl compounds (**10** and **11**) obtained were so stable as to recrystallize without hydrolyzing upon exposure to the atmosphere.

Table 2. Preparation of **10** and **11** by the Reaction of **1** or **2** with **9**

Compound	X	R	Time/h	Product and yield/%	
1a	SMe	Ph	3	**10a**	90
1b		$PhCH_2$	12	**10b**	85
2a	OEt	Ph	7	**11a**	75



Scheme 5.



Scheme 6.

Unfortunately, in the cases of **1c**, **2b**, and **2c** which have minimal acidic property, the reaction proceeded with difficulty to give a complex mixture of the starting materials and some by-products, and the corresponding **10** and **11** could not be isolated.

Methanolysis of **10** was completed at room temperature within about one hour, producing 5-(substituted amino)oxadiazole (**4**) in good yield. On the other hand, alcoholysis of **11a** yielded 5-ethoxy-1,2,4-oxadiazole (**7**) as a main product. This phenomenon shows again that aniline leaves in preference to ethanol. Therefore, in analogy with the reaction of **2a** with hydroxylamine, hydrolysis of **11a** was performed in the presence of alkali. As the result, the corresponding **4** was obtained in

Table 3. Preparation of **4**

Starting materials	X	R	Product and yield/%	
10a	SMe	Ph	**4a**	87
1a[a)]		Ph	**4a**	88
10b		$PhCH_2$	**4b**	91
1b[a)]		$PhCH_2$	**4b**	86
1c[a)]		Bu	**4c**	65
11a	OEt	Ph	**4a**	92[b)]

a) Bis-silyl compound (**10**) was not isolated before methanolysis. b) Methanolysis was performed in the presence of NaOH. When methanolysis was carried out in the absence of NaOH, 83% yield of **7** was isolated.

good yield as expected.

The one-pot conversion of **1** to **4** was also achieved without isolation of **10** or **11** (Table 3). In addition, even in the case of **1c** in which the bis-silyl compound (**10**) was not obtained, the corresponding oxadiazole **4c** could be obtained.

In conclusion, we have developed a method for regioselective preparation of 3,5-diamino-1,2,4-oxadiazole bearing a substituent on one or the other amino group by the reaction of **2** with hydroxylamine in the presence of alkali, or the reaction of **1** or **2** with **9** and subsequent methanolysis.

Experimental

General. Commercially available reagent-grade solvents were used after purification by distillation. The reactions using trimethylsilyl compounds are carried out under nitrogen atmosphere. The melting points were determined on a Yamato Mp Aparatus Model Mp-21. The ^1H and ^{13}C NMR was recorded on a JEOL JNM-LA300; tetramethylsilane (TMS) was used as an internal standard. The IR spectra were determined on a Hitachi 260-10 spectrophotometer. MS and high resolution MS spectra were measured on a Shimadzu GCMS-QP 1000A and a Hitachi M-80B, respectively. HPLC analysis was performed under the following conditions: column, shim-Pack CLC-SIL; eluent, dichloromethane/methanol (9/1, v/v); flow rate, 1 mL min^{-1}; detect, 230 nm.

Preparation of 1-Substituted 3-Cyano-2-methylisothioureas (1). Compounds **1** were readily prepared from cyanamide by improving the previous methods.[5,6] To a solution of 0.20 mol of cyanamide and 0.40 mol of aqueous sodium hydroxide in acetone (100 mL) was added dropwise 0.24 mol of carbon disulfide with vigorous stirring below 10 °C. After the mixture was stirred for 1.5 h, methyl iodide (0.40 mol) was added dropwise with stirring below 10 °C and the mixture was stirred for 2.5 h at rt. To the resulting solution of dimethyl *N*-cyanoimidodithiocarbonate was added 0.20 mol of amine, and then the mixture was allowed to stand overnight. A precipitate was collected by filtration and recrystallized. The second crop of crystals was obtained after concentration of the filtrate.

1a (R = Ph): 58%. Flakes (EtOH). Mp 191–192 °C (lit.[6] 191 °C). **1b** (R = $PhCH_2$): 75%. Needles (EtOH). Mp 156–157 °C (lit.[6] 157 °C). **1c** (R = *n*-Bu): 70%. Flakes (toluene). Mp 121–122 °C (lit.[6] 122 °C).

Preparation of 1-Substituted 3-Cyano-2-ethylisoureas (2). A methanolic solution of *O*-ethyl *S*-methyl *N*-cyanoimodothiocarbonate[5] and amine was refluxed for 1 h. After cooling, a precipitate was collected by filtration and recrystallized. The second crop of crystals was obtained after concentration of the filtrate.

3-Cyano-2-ethyl-1-phenylisourea (2a). Yield: 72%. Needles (EtOH). Mp 122–123 °C (lit.[7] 126–127 °C). IR (KBr) 3161, 2200, 1643, and 1037 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.37 (3H, t, $J = 7.1$ Hz, CH_3), 4.49 (2H, q, $J = 7.1$ Hz, CH_2), 7.22–7.40 (5H, m, Ph), 7.62 (1H, b, NH). MS (70 eV) m/z 189 (M).

1-Benzyl-3-cyano-2-ethylisourea (2b). Yield: 86%. Needles (H_2O). Mp 90–91 °C. IR (KBr) 3251, 2188, 1626, and 1045 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.32 (3H, t, $J = 7.1$ Hz, CH_3), 4.31 (2H, q, $J = 7.1$ Hz, CH_2), 6.14 (1H, b, NH), 7.25–7.37 (5H, m, Ph). HRMS (EI): calcd for $C_8H_{15}N_3O$ 169.1215, found 169.1220.

1-Butyl-3-cyano-2-ethylisourea (2c). Yield: 90%. granules (toluene). Mp 43–44 °C. IR (KBr) 3240, 2193, 1637, and 1041 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, $J = 7.3$ Hz, CH_3), 1.32 (3H, t, $J = 7.1$ Hz, CH_3), 1.36 (2H, tq, $J = 7.3$, 6.3 Hz, CH_2), 1.54 (2H, tt, $J = 6.3$, 6.3 Hz, CH_2), 3.24 (2H, q, $J = 6.3$ Hz, N-CH_2), 4.28 (2H, q, $J = 7.1$ Hz, O-CH_2), 6.14 (1H, s, NH). HRMS (EI): calcd for $C_{11}H_{13}N_3O$ 203.1059, found 203.1062.

General Procedure for Preparation of 3 in the Presence of Alkali. To a solution of hydroxylamine hydrochloride (2.15 g, 0.03 mol) in water (5 mL) was added a solution of 97% sodium hydroxide (0.03–0.05 mol) in ethanol (20 mL). After stirring for 15 min, the precipitated sodium chloride was filtered off. To the filtrate was added 0.01 mol of **2** and the mixture was allowed to stand for 2–24 h at 30 °C. After neutralization by adding acetic acid, the solvent was removed in vacuo and the residue was recrystallized to afford oxadiazole **3**. Yields are summarized in Table 1. The products were identified with regard to physical and spectral data (mp, IR, MS) by comparison with those reported.[2]

3a: Mp 182–183 °C (lit.[2] 183–184 °C). ^1H NMR (300 MHz, DMSO) δ 6.85 (2H, t, $J = 8.1$ Hz, Ph), 7.23 (2H, t, $J = 8.1$ Hz, Ph), 7.39 (2H, d, $J = 8.1$ Hz, Ph), 7.58 (2H, s, NH_2), 9.20 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO) δ 116.97, 120.40, 128.92, 140.85, 165.57, 169.83.

3b: Mp 177–178 °C (lit.[2] 179–181 °C). ^1H NMR (300 MHz, DMSO) δ 4.17 (2H, d, $J = 6.3$ Hz, Ph), 6.74 (1H, t, $J = 6.3$ Hz, NH), 7.17–7.33 (7H, m, Ph, NH_2). ^{13}C NMR (75 MHz, DMSO) δ 45.85, 126.82, 127.33, 128.32, 140.33, 168.91, 170.38.

3c: Mp 92–93 °C (lit.[2] 90–93 °C). ^1H NMR (300 MHz, DMSO) δ 0.85 (3H, t, $J = 7.3$ Hz, CH_3), 1.27 (2H, tq, $J = 7.3$ Hz, 7.3 Hz, CH_2), 1.43 (2H, tt, $J = 7.3$, 7.3 Hz, CH_2), 2.92 (2H, dt, $J = 5.9$–7.3, 7.3 Hz, CH_2), 6.07 (1H, t, $J = 5.9$ Hz, NH), 7.25 (2H, s, NH_2). ^{13}C NMR (75 MHz, DMSO) δ 13.95, 19.80, 31.39, 42.07, 168.94, 170.22.

The Reaction of 2a with Hydroxylamine under Neutral Conditions. A similar reaction procedure similar to that described above was carried out using 0.01 mol of **2a**, 0.03 mol of hydroxylamine hydrochloride, and 0.03 mol of sodium hydroxide. The solvent was removed in vacuo and the residue was extracted with 20 mL × 2 of ethyl acetate. This solution was found to contain 14% of **4a**, 52% of **7**, and 13% of **8** by HPLC analysis (see Table 1, Run 1).

Reaction of 1 or 2 with *N*,*O*-Bis(trimethylsilyl)hydroxylamine (9). To a solution of **1a**, **1b**, or **2a** (20 mmol) in carbon tetrachloride (30 mL) was added **9**[8] (30 mmol) and the mixture was refluxed for 3–12 h. The solvent was removed under reduced pressure and the residue was recrystallized from hexane to afford the corresponding **10** or **11** as needles. Reaction time and yields are summarized in Table 2.

2-Methyl-3-[*N*-trimethylsilyl-*N′*-(trimethylsilyloxy)amidino]-1-phenylisothiourea 10a. (R = Ph): Mp 111–112 °C. IR (KBr)

3386, 1604, 1573, 1287, 1249, and 845 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 0.20 (9H, s, SiMe$_3$), 0.28 (9H, s, SiMe$_3$), 2.40 (3H, s, *S*-Me), 5.26 (1H, s, NH), 7.26–7.38 (5H, m, Ph), 11.50 (1H, s, NH). MS (70 eV) *m/z* 368 (M). Found: C, 48.58; H, 7.56; N, 14.93%. Calcd for $C_{15}H_{28}N_4OSSi_2$: C, 48.87; H, 7.65; N, 15.20%.

1-Benzyl-2-methyl-3-[*N*-trimethylsilyl-*N'*-(trimethylsilyloxy)-amidino]isothiourea 10b. (R = PhCH$_2$): Mp 76–77 °C. IR (KBr) 3385, 1576, 1289, 1251, and 843 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 0.00 (9H, s, SiMe$_3$), 0.24 (9H, s, SiMe$_3$), 2.41 (3H, s, *S*-Me), 4.43 (2H, d, $J = 5.4$ Hz, CH$_2$), 5.16 (1H, s, NH), 7.33 (5H, s, Ph), 9.88 (1H, s, NH). MS (70 eV) *m/z* 382 (M). Found: C, 49.95; H, 8.08; N, 14.89%. Calcd for $C_{16}H_{30}N_4OSSi_2$: C, 50.22; H, 7.90; N, 14.64%.

2-Ethyl-3-[*N*-trimethylsilyl-*N'*-(trimethylsilyloxy)amidino]-1-phenylisourea 11a. (R = Ph): Mp 70–70.5 °C. IR (KBr) 3400, 1659, 1582, 1302, 1249, and 842 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 0.26 (18H, s, SiMe$_3$), 1.37 (3H, t, $J = 7.1$ Hz, CH$_3$), 4.36 (2H, q, $J = 7.1$ Hz, CH$_2$), 5.20 (1H, s, NH), 7.05 (1H, t, $J = 7.1$ Hz, 4-Ph), 7.21–7.31 (4H, m, 2- and 3-Ph), 10.84 (1H, s, NH). MS (70 eV) *m/z* 366 (M). Found: C, 52.18; H, 8.46; N, 15.42%. Calcd for $C_{16}H_{30}N_4O_2Si_2$: C, 52.42; H, 8.25; N, 15.28%.

Preparation of 4 by Alcoholysis of 10. Compound **10** (5 mmol) was stirred for 1 h in methanol (30 mL). The reaction mixture was dried up and recrystallized from an appropriate solvent giving pure **4**. The products were identified with regard to physical and spectral data (mp, IR, MS) by comparison with those reported[2] (Table 3).

4a: Mp 151–152 °C (lit.[2] 150–153 °C). ^{1}H NMR (300 MHz, DMSO) δ 5.99 (2H, s, NH$_2$), 7.00 (1H, t, $J = 7.8$ Hz, Ph), 7.31 (2H, t, $J = 7.8$ Hz, Ph), 7.52 (1H, d, $J = 7.8$ Hz, Ph), 10.47 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO) δ 117.71, 122.55, 129.18, 138.60, 166.31, 168.49.

4b: Mp 145–146 °C (lit.[2] 145–146 °C). ^{1}H NMR (300 MHz, DMSO) δ 4.35 (2H, d, $J = 6.1$ Hz, CH$_2$), 5.72 (2H, s, NH$_2$), 7.20–7.36 (5H, m, Ph), 8.36 (1H, t, $J = 6.1$ Hz, NH). ^{13}C NMR (75 MHz, DMSO) δ 46.17, 127.05, 127.11, 128.40, 138.92, 168.46, 169.73.

4c: Mp 73–74 °C (lit.[2] 74–75 °C). ^{1}H NMR (300 MHz, DMSO) δ 0.86 (3H, t, $J = 7.6$ Hz, CH$_3$), 1.28 (2H, tq, $J = 7.6$, 7.6 Hz, CH$_2$), 1.45 (2H, tt, $J = 7.6$, 7.6 Hz, CH$_2$), 3.11 (2H, dt, $J = 5.6$, 7.6 Hz, CH$_2$), 5.64 (2H, s, NH$_2$), 7.74 (1H, t, $J = 5.6$ Hz, NH). ^{13}C NMR (75 MHz, DMSO) δ 13.60, 19.34, 31.11, 42.40, 168.43, 169.59.

Methanolysis of 11a in the Absence of Alkali. 1.01 g (3 mmol) of **11a** in methanol (10 mL) was stirred for 3 h at rt. The reaction mixture was dried up and the residue was recrystallized from water to obtain 0.30 g (83%) of **7**, which was identified by direct comparison with an authentic sample[3] (mp 128–129 °C).

Methanolysis of 11a in the Presence of Alkali. Compound **11a** (2.20 g, 6 mmol) was stirred in methanol (30 mL) containing 8 mmol of NaOH and a small amount of water for 1 h at rt. After neutralization by bubbling carbon dioxide through the solution, the reaction mixture was dried up and recrystallized from water to obtain 0.96 g (92%) of **4a**.

One-Pot Procedure for the Preparation of 4c. To a suspension of 1.71 g (10 mmol) of **1c** in carbon tetrachloride (15 mL) was added 3.2 g (15 mmol) of **9**, and the mixture was refluxed for 20 h. The solvent was removed under reduced pressure, and the residue was dissolved to 20 mL of methanol and refluxed for 1 h. After cooling, slight amounts of insoluble impurities were filtered off and the filtrate was dried up. The organic materials were extracted with 50 mL of ether and dried up. The residue was recrystallized from benzene to afford 1.01 g (65%) of **4c**. Mp 73–74 °C (lit.[2] 74–75 °C).

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