A Facile Synthesis of 3-Substituted 5-Oxo-1,2,4-thiadiazoles from Amidoximes [1]

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The reaction of amidoximes **1** with 1,1'-thiocarbonyldiimidazole (TCDI) followed by treatment with silica gel or boron trifluoride diethyl etherate (BF_3·OEt_2) provided 3-substituted 4,5-dihydro-5-oxo-1,2,4-thiadiazoles **2** in moderate yields. The Lewis acids are considered to promote the rearrangement of the thioxocarbamate intermediates **5** to the thiolcarbamate intermediates **7**, which cyclize to afford 4,5-dihydro-5-oxo-1,2,4-thiadiazoles **2**.

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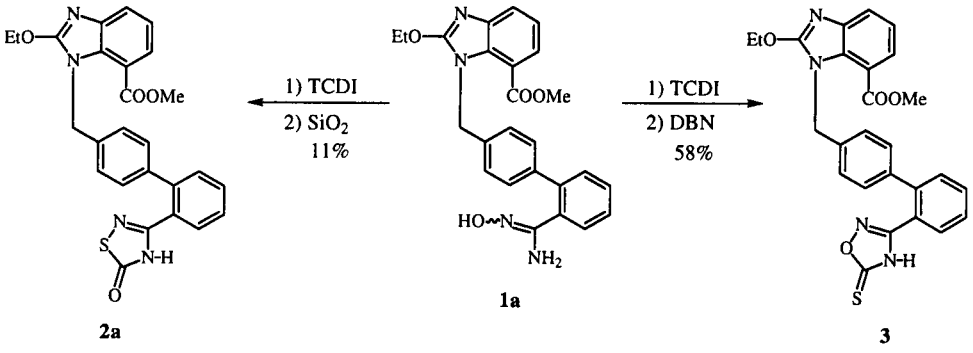
In our efforts to discover new nonpeptide angiotensin II (AII) receptor antagonists, the 4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl and 4,5-dihydro-5-thioxo-1,2,4-oxadiazol-3-yl moieties were proved to work as bioisosteres of the acidic tetrazol-5-yl moiety [2].

In this report, we describe a new and convenient method for the synthesis of 3-substituted 4,5-dihydro-5-oxo-1,2,4-thiadiazoles **2** by the reaction of amidoximes **1** with TCDI in the presence of silica gel or BF_3·OEt_2. A few reports are available on the preparation of 3-substituted 4,5-dihydro-5-oxo-1,2,4-thiadiazoles, including the reaction of amidines or benzamidoximes with chlorocarbonylsulfenyl chloride in the presence of base [3, 4] and the condensation of amidines with perchloromethanethiol followed by acidic hydrolysis [5]. However, these methods require highly toxic reagents, such as chlorocarbonylsulfenyl chloride or perchloromethanethiol, and lead to a mixture of 4,5-dihydro-5-oxo-1,2,4-thiadiazoles and 4,5-dihydro-5-oxo-1,2,4-oxadiazoles in low yields [4].

In the course of our search for AII receptor antagonists with improved bioavailability, we tried to prepare the 4,5-dihydro-5-thioxo-1,2,4-oxadiazole derivative **3** by the reaction of the amidoxime **1a** and TCDI without base. Purification of the reaction mixture by silica gel chromatography afforded an unexpected product, the 4,5-dihydro-5-oxo-1,2,4-thiadiazole derivative **2a**, in 11% yield, and the expected 4,5-dihydro-5-thioxo-1,2,4-oxadiazole derivative **3** was not isolated. On the other hand, the reaction of **1a** with TCDI followed by the addition of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) afforded the expected oxadiazole **3** in 58% yield [2], and the thiadiazole **2a** was not detected in the reaction mixture (Scheme 1).

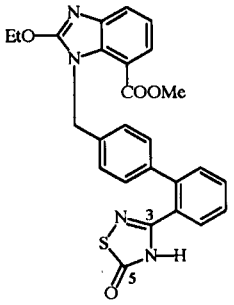
The structural assignment of the thiadiazole **2a** and the oxadiazole **3** was carried out as follows: Combustion analyses for C, H and N of **2a** and **3** supported their molecular formulae. The infrared and ^{13}C nmr spectra of **2a** and **3** were compared with those of 4,5-dihydro-5-oxo-3-phenyl-1,2,4-thiadiazole **2b** [3] and 4,5-dihydro-3-phenyl-5-thioxo-1,2,4-oxadiazole **4** [6,7] (Table 1). The infrared spectrum for **2a** displayed a strong carbonyl absorption at 1660 cm^{-1}, which is similar to that of the thiadiazole **2b** at 1650 cm^{-1}. However, no carbonyl absorption was observed in the cases of the oxadiazoles, **3** and **4**. The ^{13}C nmr spectra of the thiadiazoles, **2a** and **2b**, exhibited the characteristic sp^2 carbon signals at δ 178.95 and 179.57, respectively, corresponding to the carbonyl carbons (C5), and the additional sp^2 carbon signals for C3 appeared at δ 156.16 and 154.71, respectively. In the case of the oxadiazoles, **3** and **4**, the signals assigned to the thiocarbonyl carbons (C5) were observed at δ 186.96 and 187.53, respectively, and the signals of the C3 carbon appeared at δ 159.81 and 159.11, respectively. In addition, the formation of the 4,5-dihydro-5-oxo-1,2,4-thiadiazole skeleton was verified from the fact that the reaction of the

Scheme 1

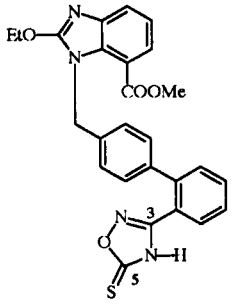


2a **1a** **3**

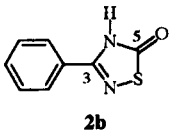
Table 1
Representative ^{13}C NMR and IR Data of Compounds **2a**, **2b**, **3** and **4**



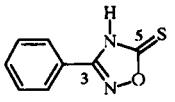
2a



3



2b

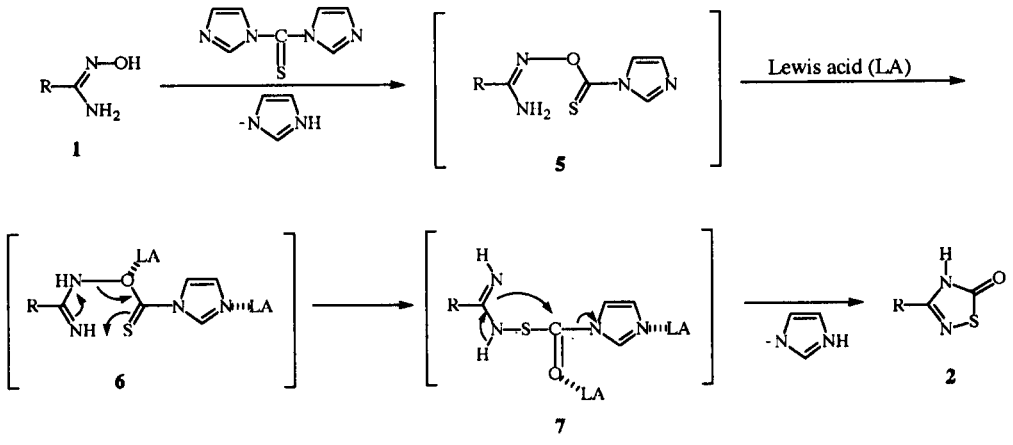


4

Compound	^{13}C-NMR, δ (ppm) [a] C3	C5	IR, ν (cm^{-1}) [b] C=O
2a	156.16	178.95	1660
2b	154.71	179.57	1650
3	159.81	186.96	no absorption
4	159.11	187.53	no absorption

[a] The spectra were recorded in dimethyl sulfoxide-d_6. [b] Potassium bromide pellets.

Scheme 2

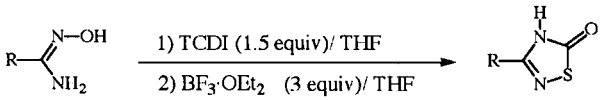


benzamidoxime **1b** with TCDI in the presence of silica gel afforded the thiadiazole **2b** in 35% yield, which was identical with an authentic sample [3].

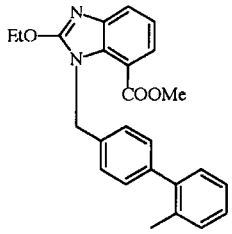
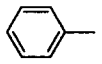
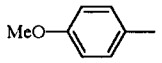
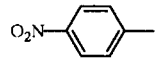
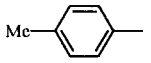
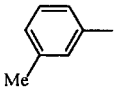
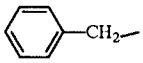
This rearrangement reaction requires a long reaction time (*ca.*48 hours) as well as 25 times excess weight of silica gel based on the amidoxime, and still the yield is low. Therefore, we started to optimize the reaction employing **1b** as a substrate. It was assumed that silica gel works as a Lewis acid to induce the rearrangement, because **2b** was not detected in the reaction mixture without the use of silica gel. Therefore we applied Lewis acids such as $BF_3{\cdot}OEt_2$, zinc chloride, tin (II) chloride, tin (IV) chloride and triisopropyl borate to this rearrangement. To a solution of **1b** in tetrahydrofuran, one molar equivalent of TCDI and then an excess amount of a Lewis acid (more than 3 molar equivalents) were added. The mixture was stirred at room temperature and then worked up. Among the Lewis acids examined, only $BF_3{\cdot}OEt_2$ gave the desired product **2b**. Zinc chloride and tin (II) chloride failed to promote the reaction, and tin (IV) chloride and triisopropyl borate resulted in decomposition of the intermediate **5** (R=Ph) (Scheme 2).

Table 2

Reaction of Amidoximes with 1,1'-Thiocarbonyldiimidazole in the Presence of Boron Trifluoride Diethyl Etherate



1a-i **2a-i**

Entry	Product	R	Yield (%) [a]
1	**2a**		35
2	**2b**		63 25 [b] 55 [c]
3	**2c**		18
4	**2d**		67
5	**2e**		51
6	**2f**		55
7	**2g**		10
8	**2h**		58
9	**2i**	Bu	56

[a] Isolated yield. [b] yield of the one-pot reaction (1 equiv. of TCDI, 5 equiv. of BF_3•OEt_2). [c] yield of the two-step reaction (equiv. of TCDI, 2 equiv. of BF_3•OEt_2).

We subsequently investigated the solvent effect on the reaction using tetrahydrofuran, dichloromethane, 1,2-dichloroethane, acetonitrile and nitromethane in the presence of 5 molar equivalents of BF_3·OEt_2. Reaction in tetrahydrofuran only gave **2b**, whereas dichloromethane and 1,2-dichloroethane caused the intermediate **5** to be precipitated from the reaction mixture. Acetonitrile gave a complex mixture, and the reaction did not proceed in nitromethane.

It is worth noting that when the reaction of **1b** and TCDI was carried out without the use of BF_3·OEt_2 and the isolated intermediate **5** was subsequently treated with BF_3·OEt_2, 2~3 molar equivalents of BF_3·OEt_2 were sufficient to promote the rearrangement. This two-step reaction gave a better yield of the thiadiazole **2b** than the corresponding one-pot reaction (Table 2).

Although the detailed mechanism of the reaction remains unclear at this stage, the pathway illustrated in Scheme 2 seems plausible. The thiocarbonylation of the amidoximes **1** with TCDI forms the thioxocarbamate intermediates **5**. The coordination of BF_3·OEt_2 to the thioxocarbamate oxygen and the imidazole nitrogen leads to the

rearranged thiolcarbamate intermediates **7**. Subsequent intramolecular cyclization would then provide the 4,5-dihydro-5-oxo-1,2,4-thiadiazoles **2**.

Our new method was applied to aromatic and aliphatic amidoximes bearing a variety of substituents, and the results are summarized in Table 2. The optimized reaction conditions to prepare the thiadiazole derivatives (the two-step reaction using tetrahydrofuran as solvent in the presence of 3 molar equivalents of $BF_3 \cdot OEt_2$ as a catalyst) provided the desired products, 3-aryl (entries 1, 2 and 4-6) and 3-alkyl-4,5-dihydro-5-oxo-1,2,4-thiadiazoles (entries 8 and 9), in moderate yields. However, in the cases of 4-methoxy (entry 3) and 2-methylbenzamidoxime (entry 7), the yields of the corresponding 4,5-dihydro-5-oxo-1,2,4-thiadiazoles (**2c,g**) were poor (<18%). The methoxy group might form a complex with $BF_3 \cdot OEt_2$ to lead to decomposition of intermediate **5**, in the case of entry 3. The methyl group at the 2-position presumably prevents the reaction, by its steric hindrance, in the case of entry 7.

In conclusion, we have discovered a facile method for the synthesis of 3-substituted 4,5-dihydro-5-oxo-1,2,4-thiadiazoles **2** from amidoximes **1** by a Lewis acid-mediated rearrangement reaction.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (ir) spectra were recorded on a Hitachi 215 or a HORIBA FT-200 grating infrared spectrophotometer. The proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Varian Gemini-200 (200 MHz). The carbon nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a JEOL JNM-GX270 (67.8 MHz) or Gemini-200 (50.3 MHz). Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard, and coupling constants (J) are given in Hz. Column chromatography was performed using silica gel (Wakogel C-300, Merck Art 7734 or Merck Art 9385).

The benzamidoxime **1b** was purchased from Tokyo Kasei Organic Chemicals. **1c** [8], **1d** [9], **1e** [8], **1f** [10], **1g** [11], **1h** [12], **1i** [13] were prepared from the corresponding nitriles by the methods described in the literature.

Procedure for the Preparation of the 3-Phenyl-1,2,4-thiadiazole-5-one (**2b**) Using Silica Gel.

A mixture of **1b** (0.28 g, 2.1 mmol) and 1,1'-thiocarbonyldiimidazole (90%, 0.41 g, 2.1 mmol) in tetrahydrofuran (15 ml) was stirred at room temperature for 30 minutes. A suspension of silica gel (Merck Art.7734) (7.0 g) in chloroform-methanol (5:1) (150 ml) was added to the reaction mixture, and the resulting mixture was stirred at room temperature for further 48 hours. Silica gel was filtered off and washed with chloroform-methanol. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography. The product was recrystallized from ethyl acetate to give **2b** (0.13 g, 35%) as colorless needles, mp 200-201 °C (lit. 202 °C [5]); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.48-7.58 (3H, m), 7.91-7.97 (2H, m); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 126.55, 128.57, 129.02, 131.44, 154.71, 179.57; ir (potassium bromide): 1650, 1585, 1540, 1460, 1435, 1175 cm-1.

General Procedure for the Preparation of the 5-Oxo-1,2,4-thiadiazoles **2** Using Boron Trifluoride Diethyl Etherate.

A mixture of **1** (5 mmol) and TCDI (90%; 1.5 g, 7.5 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 30 minutes. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo*, and the residue was dissolved in tetrahydrofuran (20 ml). Boron trifluoride diethyl etherate (2.13 g, 15 mmol) was added to the solution, and the resulting mixture was stirred at room temperature for a further 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried (magnesium sulfate). The solvent was evaporated *in vacuo*, and the residue was purified by flash column chromatography and recrystallization.

Methyl 1-[[2'-(4,5-Dihydro-5-oxo-1,2,4-thiadiazole-3-yl)-biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (**2a**).

The synthesis of **2a** was already reported in the literature [2]. ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.58, 46.61, 52.40, 66.77, 115.66, 120.97, 121.81, 123.15, 126.39, 127.70, 128.83, 129.96, 130.50, 131.09, 131.16, 136.62, 138.48, 140.51, 141.86, 156.16, 158.53, 166.32, 178.95.

Anal. Calcd. for $C_{26}H_{22}N_4O_4S \cdot 0.2H_2O$: C, 63.71; H, 4.60; N, 11.43. Found: C, 63.63; H, 4.59; N, 11.24.

3-Phenyl-1,2,4-thiadiazole-5-one (**2b**).

This compound was obtained as colorless needles in 63% yield.

3-(4-Methyoxyphenyl)-1,2,4-thiadiazole-5-one (**2c**).

This compound was obtained as pale yellow needles in 18% yield (acetone), mp 226-228 °C (lit. 226 °C [4]).

3-(4-Nitrophenyl)-1,2,4-thiadiazole-5-one (**2d**).

This compound was obtained as pale yellow needles in 67% yield (*N,N*-dimethylformamide-water), mp 289-292 °C dec (lit. 253 °C [4]); ^1H nmr (dimethyl sulfoxide-d_6): δ 8.19 (2H, d, J = 8.8), 8.38 (2H, d, J = 8.8); ir (potassium bromide): 1645, 1520, 1456, 1348 cm^{-1}.

Anal. Calcd. for $C_8H_5N_3O_3S$: C, 43.05; H, 2.26; N, 18.83. Found: C, 43.04; H, 2.26; N, 18.94.

3-(4-Methylphenyl)-1,2,4-thiadiazole-5-one (**2e**).

This compound was obtained as pale yellow needles in 51% yield (acetone), mp 214-216 °C (lit. 218 °C [4]); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.37 (3H, s), 7.34 (2H, d, J = 8.5), 7.84 (2H, d, J = 8.4); ir (potassium bromide): 1663, 1647, 1638, 1456 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.03; H, 4.15; N, 14.50.

3-(3-Methylphenyl)-1,2,4-thiadiazole-5-one (**2f**).

This compound was obtained as colorless needles in 55% yield (ethyl acetate), mp 172-174 °C; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.38 (3H, s), 7.36-7.46 (2H, m), 7.71-7.79 (2H, m); ir (potassium bromide): 1665, 1647, 1541, 1449 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.08; H, 4.22; N, 14.84.

3-(2-Methylphenyl)-1,2,4-thiadiazole-5-one (**2g**).

This compound was obtained as colorless needles in 10% yield (ethyl acetate), mp 166-167 °C; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.42 (3H, s), 7.29-7.52 (4H, m); ir (potassium bromide): 1711 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.26; H, 3.93; N, 14.71.

3-Benzyl-1,2,4-thiadiazole-5-one (**2h**).

This compound was obtained as pale yellow needles in 58% yield (ethyl acetate-hexane), mp 106-108 °C (lit. 106-107 °C [5]); ^{1}H nmr (deuteriochloroform): δ 3.90 (2H, s), 7.26-7.42 (5H, m); ir (potassium bromide): 1654, 1570, 1472 cm^{-1}.

Anal. Calcd. for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.29; H, 4.22; N, 14.59.

3-Butyl-1,2,4-thiadiazole-5-one (**2i**).

This compound was obtained as colorless prisms in 56% yield (ethyl acetate-hexane), mp 46-47 °C; ^{1}H nmr (deuteriochloroform): δ 0.96 (3H, t, J = 7.3), 1.35-1.50 (2H, m), 1.67-1.79 (2H, m), 2.62 (2H, t, J = 7.6); ir (potassium bromide): 1686, 1580, 1464 cm^{-1}.

Anal. Calcd. for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.70. Found: C, 45.60; H, 6.45; N, 17.67.

Methyl 1-[[2'-(4,5-Dihydro-5-thioxo-1,2,4-oxadiazole-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (**3**).

The synthesis of **3** was already reported in the literature [2], ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.59, 46.62, 52.48, 66.82, 115.62, 120.57, 121.01, 121.81, 123.20, 126.47, 128.07, 129.09, 130.76, 130.91, 132.33, 137.10, 137.83, 141.28, 141.87, 158.54, 159.81, 166.33, 186.96.

3-Phenyl-1,2,4-oxadiazole-5-thione (**4**).

This compound was obtained by the method described in the literature [6,7] as colorless needles, mp 159-161 °C (lit. 160 °C [7]); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 126.92, 128.53, 129.44, 132.66, 159.11, 187.53; ir (potassium bromide): 1600, 1560, 1500, 1470, 1440, 1390, 1265, 1180, 1160, 980, 780, 700 cm^{-1}.

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