A Simplified Procedure for Preparing 3,5-Disubstituted-1,2,4-Oxadiazoles by Reaction of Amidoximes with Acyl Chlorides in Pyridine Solution

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Received June 6, 1988

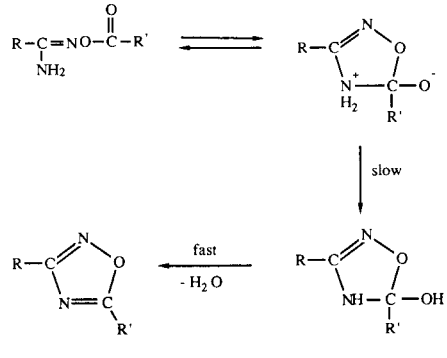
3-*R*-5-*R'*-1,2,4-Oxadiazoles are prepared in fair to good yield by short-time, one-pot reaction of an amidoxime, $RC(NH_2)NOH$, with an acyl chloride, R'COCl, in pyridine solution. Precipitation of the oxadiazole occurs on diluting the pyridine reaction solution with water. Ordinary acyl chlorides can be used; they do not have to be unusually reactive to succeed in the one-pot preparation. The procedure is simpler and more convenient than the conventional one, namely isolation and thermal rearrangement of an *O*-acylamidoxime.

J. Heterocyclic Chem., **26**, 125 (1989).

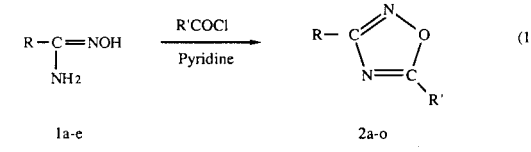
3,5-Disubstituted-1,2,4-oxadiazoles **2** can be prepared in a number of ways [1-3]. Clapp [3] has noted that the most widely used method of synthesizing oxadiazoles is the isolation and thermal cyclization of *O*-acylamidoximes. In some cases, reaction with very reactive acid chlorides (*e.g.* chloro- and dichloroacetyl chloride) can convert an amidoxime into a 1,2,4-oxadiazole at room temperature without isolating the *O*-acylamidoxime first. Eloy and Lenaers [1] and Eloy [2] have recorded also that cyclizing of *O*-acylamidoximes with dehydration is generally accomplished by heating, either in the dry state or in solution in glacial acetic acid, acetic anhydride, water, dilute sodium hydroxide or sulfuric acid. They note further that if acylation of amidoximes is carried out at 100° or above, spontaneous cyclization occurs. The conditions thus summarized have not changed much from those that were used when the reaction was first reported by Tiemann and Krüger in 1884 [4].

In 1980, Ooi and Wilson studied the kinetics of formation of 1,2,4-oxadiazoles from the cyclization of *O*-acylamidoximes in diphenyl ether and some other solvents over the temperature range of 100-145°, and proposed a mechanism as shown in Scheme I [5]. In accordance with the Scheme a small kinetic isotope effect (k_H/k_D) was found for cyclization of *N,N*-dideuterio-*O*-acetylbenzamidoxime. At the same time, it was found that cyclization could be effected at room temperature by treating an *O*-acylamidoxime in deuteriochloroform with sodium hydride. In that case, cyclization was attributed to the formation and attack of the amide ion on the carbonyl carbon of the acyl group.

Scheme I



These findings suggested to us that both acylation of an amidoxime and base-promoted dehydration of the *O*-acyl derivative might be achieved in a one-pot reaction if pyridine were used as a solvent (equation 1). This is, in fact, the case. Addition of an acyl chloride to a solution of an amidoxime in pyridine at room temperature is a very exothermic reaction. In some cases enough heat is generated to cause the mixture to boil, and the 1,2,4-oxadiazole is formed immediately. In other cases, formation of the oxadiazole is completed by further heating for 15-30 minutes, and can be followed by periodic thin layer chromatography (tlc). Thus, it is not necessary to isolate the *O*-acylamidoxime before bringing about its cyclization, and the acyl chloride does not have to be unusually reactive. Recovery of the product is very simple, by dilution of the pyridine solution with water. Yields of the 1,2,4-oxadiazoles **2a-o** were for the most part good, and are listed in Table I. For the most part also, the product had a satisfactory melting point without recrystallization. In one case,



(1)

the formation of 3-phenyl-5-ethyl-1,2,4-oxadiazole (**2b**), propionic anhydride was used in place of propionyl chloride. We made no attempt either to optimize yields or to find why some yields were low.

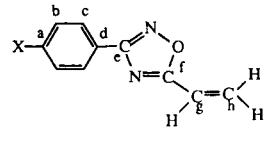
When acryloyl chloride was used, however, in the formation of **2h** and **2i**, a second product was formed in each

Table I

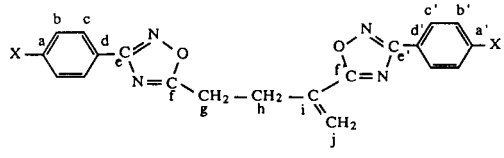
Preparation of 3-*R*-5-*R'*-1,2,4-Oxadiazoles by Reaction of Amidoximes with Acyl Chlorides in Pyridine Solution

Product	R	R'	Yield, %	mp, °C	lit mp, °C	Ref
2a	C_6H_5	CH_3	81.0	39-41	41	[7]
2b	C_6H_5	CH_3CH_2	85.6	oil	oil	[7]
2c	C_6H_5	C_6H_5	90.1	109-110	109-110	[2,8]
2d	C_6H_5	1-naphthyl	67.3	101-102	95-96	[8]
2e	C_6H_5	*p*-$MeOC_6H_4$	91.1	98-99	98	[9]
2f	*p*-MeC_6H_4	C_6H_5	73.8	105-106	107	[10]
2g	*p*-MeC_6H_4	*p*-MeC_6H_4	68.3	139-140	134-135	[11]
2h	*p*-MeC_6H_4	$CH_2=CH$	22.6	40-41		
2i	*p*-$MeOC_6H_4$	$CH_2=CH$	17.1	58-59		
2j	*p*-$Me_2NC_6H_4$	CH_3	81.4	127-128		
2k	*p*-$Me_2NC_6H_4$	C_6H_5	32.6	114-115		
2l	CH_3	C_6H_5	48.0	60-61	57-58	[12]
2m	CH_3	1-naphthyl	38.8	75-76		
2n	CH_3	*p*-MeC_6H_4	90.4	49-50		
2o	CH_3	*p*-ClC_6H_4	65.4	90-91	92-94	[13]

case, and is believed, on the basis of elemental analysis, ms, pmr and cmr spectroscopy, to be the dimer of the oxadiazole, *i.e.*, **3h** and **3i**. That **3h** and **3i** were dimers was shown by their mass spectra and by comparison of those spectra with those of their parent monomers, **2h** and **2i**. Thus, **3h** had a strong parent ion (M^+, 372) abundance (58%) and fragmentation ions characteristic of 3-substituted-oxadiazoles, *e.g.*, 241 (M -$CH_3C_6H_4N_2$, 72), 131 (M -241, 18), 133 ($CH_3C_6H_4CNO^+$, 51) and 117 ($CH_3C_6H_4CN^+$, 47). Similarly, **3i** had a strong parent ion (M^+, 404) abundance (35%) and characteristic fragments, such as 257 (M -$CH_3OC_6H_4N_2$, 100), 149 ($CH_3OC_6H_4CNO^+$, 17) and 133 ($CH_3OC_6H_4CN^+$, 30).



2h, X = CH_3 ; 2i, X = OCH_3

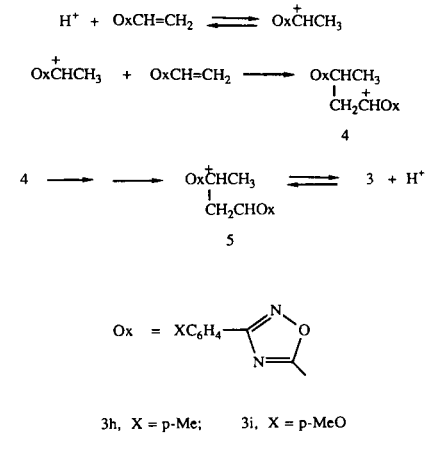


3h, X = CH_3 ; 3i, X = OCH_3

The structure of the dimers, particularly as to the central 1-butenyl unit, was deduced from 300 MHz pmr, proton-coupled and decoupled cmr, and COSY spectroscopy. That is, the triplet coupling patterns of the two CH_2 groups and the singlets of the vinylic methylene group were evident. The dimers **3h** and **3i** are unsymmetrical, and, in principle, should show the lack of symmetry in their nmr spectra. This feature was, in fact, seen in the cmr of the oxidiazole rings particularly, and to some extent in overlapping multiplets in the pmr spectra (*e.g.*, $H_{b,b'}$ of **3i**) of the oxadiazole rings.

The dimerization of **2h** and **2i** in the hot reaction solutions is undoubtedly acid catalyzed in spite of taking place in pyridine solvent. The first-formed dimer cation **4**, Scheme II, must, therefore, isomerize (in two steps) to the more stable **5** in order for **3h** and **3i** to be formed.

Scheme II



3h, X = p-Me; 3i, X = p-MeO

In the reaction of *p*-toluamidoxime with acryloyl chloride, furthermore, a small amount of 3,5-di-*p*-tolyl-1,2,4-oxadiazole (**2g**) was formed. We believe that cycloaddition must have involved *p*-tolunitrile, formed by loss of

hydroxylamine from the amidoxime. Formation of a 1,2,4-oxadiazole by heating an amidoxime with a nitrile was described recently [6]. Similar reactions have been observed in the thermal decomposition of amidoximes [1].

EXPERIMENTAL

Preparation of Amidoximes **1a-e**.

General Procedure.

Amidoximes, $RC(NH_2)NOH$, were prepared by heating under reflux for 2-4 days a solution of the appropriate nitrile with, in 10-20% excess, equimolar amounts of hydroxylamine hydrochloride and sodium hydroxide in aqueous ethanol. The mixture was then concentrated to small volume under vacuum, diluted with cold water, and placed in the refrigerator overnight. The precipitate that formed was recovered, washed with cold water and dried under vacuum.

Benzamidoxime (**1a**, R = C_6H_5, mp 76-78°), *p*-toluamidoxime (**1b**, R = *p*-MeC_6H_4, mp 148-149°), 4-methoxybenzamidoxime (**1c**, R = *p*-$MeOC_6H_4$, mp 127-128°), and acetamidoxime (**1d**, R = CH_3, mp 134-136°) have been reported elsewhere [1]. We were unable to find 4-dimethylaminobenzamidoxime (**1e**, R = *p*-$Me_2NC_6H_4$) listed elsewhere.

Preparation of 4-Dimethylaminobenzamidoxime (**1e**).

A solution of 1.96 g (13.4 mmoles) of *p*-dimethylaminobenzonitrile, 1.0 g (14.4 mmoles) of hydroxylamine hydrochloride, and 0.6 g (15 mmoles) of sodium hydroxide in 20 ml of ethanol and 5 ml of water was heated under reflux for 1.5 days. Most of the solvent was removed under reduced pressure at 60°. To the residue was added 50 ml of cold water, causing solid to precipitate. The precipitate was removed, washed with water, and dried under vacuum, giving 2.0 g (11.1 mmoles, 83%) of **1e**, mp 153-158°. Crystallization from methylene chloride gave 1.01 g (42%), mp 181-182°; pmr (perdeuterioacetone): δ 2.96 (s, 6 H, Me_2N), 5.33 (br s, 2 H, NH_2), 6.73 (d, 2 H, J = 12.4 Hz, aromatic), 7.58 (d, 2 H, J = 12.4 Hz, aromatic), 8.76 (br s, 1 H, NOH).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.3; H, 7.26; N, 23.4. Found: C, 60.3; H, 7.30; N, 23.5.

Preparation of 3-*R*-5-*R'*-1,2,4-Oxadiazoles **2a-o**.

General Procedure.

An acid chloride (R'COCl) was added dropwise to a stirred suspension of the amidoxime **1** in pyridine. An exothermic reaction occurred after which, in most cases, the solution was heated for a further 15-30 minutes. Thereafter, water was added and the solution was cooled to precipitate the oxadiazole. The precipitate was washed with water and dried under vacuum. In most cases the crude product was obtained in good yield and had a satisfactory melting point (Table I) and was not recrystallized. **2d** (R = phenyl, R' = 1-naphthyl) was crystallized from aqueous ethanol, **2l** (R = Me, R' = phenyl) was crystallized from hexane. In one case, **2b**, the acid anhydride was used in place of the acid chloride.

Preparation of 3-Phenyl-5-methyl-1,2,4-Oxadiazole (**2a**).

To a stirred suspension of 2.4 g (17.4 mmoles) of **1a** in 4 ml of pyridine was added dropwise 2.5 ml of acetyl chloride. Reaction caused the solution to boil. Heating under reflux was continued for 30 minutes, after which the presence of **1a** could no longer be detected by tlc. The solution was cooled, diluted with 30 ml of water and placed in the refrigerator overnight. The precipitate was removed, washed with water, and dried, giving 2.26 g (14.1 mmoles, 81%) of **2a**, mp 39-41°, and having a satisfactory pmr spectrum.

Preparation of 3-(4-Dimethylaminophenyl)-5-phenyl-1,2,4-oxadiazole (**2k**).

This new oxadiazole was prepared in the general way and had mp 114-115° (cyclohexane).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.4; H, 5.70; N, 15.7. Found: C, 72.4; H, 5.60; N, 15.7.

Preparation of 3-Methyl-5-(1-naphthyl)-1,2,4-oxadiazole (**2m**).

This new oxadiazole was prepared in the general way and had mp 75-76° (hexane).

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.3; H, 4.79; N, 13.3. Found: C, 74.3; H, 4.58; N, 13.4.

Preparation of 3-Methyl-5-(*p*-tolyl)-1,2,4-oxadiazole (**2n**).

This new oxadiazole was prepared in the general way and had mp 49-50° after purification by preparative-scale tlc.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.79; N, 16.1. Found: C, 69.1; H, 5.72; N, 16.2.

Preparation of 3-Phenyl-5-ethyl-1,2,4-oxadiazole (**2b**).

To a stirred suspension of 2.06 g (15.1 mmoles) of **1a** in 4 ml of pyridine was added dropwise 1.9 ml (15.1 mmoles) of propionic anhydride. After proceeding as described for **2a** and storage of the aqueous mixture in the refrigerator for 3 hours, an oil separated. The oil was extracted with methylene chloride and was recovered by evaporation of the dried (sodium sulfate) solution, giving 2.25 g (12.9 mmoles, 86%) of **2b** as an oil; pmr (neat): δ 1.30 (t, 3 H, J = 7.0 Hz), 2.80 (q, 2 H, J = 7.0 Hz), 7.24-7.55 (m, 3 H), 7.90-8.28 (m, 2 H).

Preparation of 3-(4-dimethylaminophenyl)-5-methyl-1,2,4-oxadiazole (**2j**).

To a stirred solution of 207 mg (1.16 mmoles) of **1e** in 5 ml of pyridine was added dropwise 0.5 ml of acetyl chloride. A very exothermic reaction occurred. The mixture solidified on being allowed to cool. Ten milliliters of water was added to dissolve the solid. The solution was made alkaline with 5% aqueous sodium hydroxide solution, which caused a white solid to precipitate. After overnight refrigeration the mixture was filtered to give 192 mg (0.944 mmole, 81%) of **2j**, mp 127-128° after purification by preparative-scale tlc; pmr (perdeuterioacetone): δ 2.61 (s, 3 H, 5-Me), 3.05 (s, 6 H, Me_2N), 6.75 (d, 2 H, J = 9.0 Hz), 7.82 (d, 2 H, J = 9.0 Hz).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.0; H, 6.45; N, 20.7. Found: C, 64.7; H, 6.39; N, 20.5.

Preparation of 3-(*p*-Tolyl)-5-vinyl-1,2,4-oxadiazole (**2h**) and Formation of 2,4-Di[3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl]-1-butene (**3h**).

To a solution of 2.55 g (17.0 mmoles) of **1b** in 6 ml of pyridine was added dropwise 1.4 ml (16.9 mmoles) of acryloyl chloride. The hot solution was heated for a further 30 minutes, cooled, and diluted with cold water. An oil separated, and was extracted with ether. The ether solution was washed with 5% aqueous sodium bicarbonate solution, dried and evaporated to give 1.57 g of a viscous oil. Preparative-scale tlc with cyclohexane/methylene chloride (2:1) gave 222 mg (0.888 mole, 10% based on **1b**) of **2g**, mp 138-140°, identified by pmr spectroscopy, 715 mg (3.54 mmoles, 23%) of **2h**, mp 40-41°, and 535 mg (1.32 mmoles, 17% based on **1b**) of **3h**, mp 91-92°.

Compound **2h**.

This compound had pmr (deuteriochloroform): δ 2.29 (s, 3 H, Me), 5.95 (dd, 1 H, J = 10.9 and 0.99 Hz, vinyl), 6.56 (dd, 1 H, J = 17.7 and 0.99 Hz, vinyl), 6.74 (dd, 1 H, J = 17.7 and 10.9 Hz, vinyl), 7.28 (d, 2 H, J = 7.53 Hz, aromatic), 7.98 (d, 2 H, J = 8.19 Hz, aromatic); cmr (deuteriochloroform): see drawing **2h** δ 21.53 (Me), 120.62 (h), 124.01 (d), 127.36 (b), 128.49 (g), 129.45 (c), 141.48 (a), 168.70 (e), 174.30 (f); ms: (m/e) 187 (M + 1, 77), 186 (M^+, 100), 133 ($CH_3C_6H_4CNO^+$, 100), 132 (99), 131 ($CH_3C_6H_4CN_2^+$, 31), 117 ($CH_3C_6H_4CN^+$, 43), 91 ($CH_3C_6H_4^+$, 100), 77, 65, 55, 53, 39.

Anal. Calcd. for $C_{11}H_{10}N_{20}$ (**2h**): C, 71.0; H, 5.41; N, 15.0. Found: C, 71.0; H, 5.33; N, 14.9.

Compound **3h** (see drawing).

This compound had pmr (deuteriochloroform): δ 2.42 (s, 6 H, 2 CH_3), 3.21 (t, 2 H, J = 7.5 Hz, CH_2), 3.57 (t, 2 H, J = 7.4 Hz, CH_2), 5.80 (s, 1 H, H_j), 6.40 (s, 1 H, H_j), 7.28 (d, 4 H, J = 7.86 Hz, $H_{b,b'}$), 7.96 (d, 2 H, J =

8.23 Hz, $H_{c(c')}$), 8.00 (d, 2 H, J = 8.22 Hz, $H_{c'(c)}$); cmr (deuteriochloroform): δ 21.58 (Me), 25.62 (g), 29.99 (h), 123.94, 123.99 (d, d'), 125.12 (j), 127.37, 127.44 (b,b'), 129.56 (c,c'), 131.58 (i), 141.49, 141.57 (a,a'), 168.38, 168.83 (e,e'), 174.84, 178.31 (f,f'). The exact assignment of atoms in pairs of C atoms, *e.g.*, a,a', cannot be made; ms: (m/e) 372 (M^+, 58), 241 (M^+ -$CH_3C_6H_4CN_2$, 72), 131 ($CH_3C_6H_4CN_2^+$, 18), 213 (M^+ -$CH_3C_6H_4C_2N_2O$, 26), 133 ($CH_3C_6H_4CNO^+$, 51), 117 ($CH_3C_6H_4CN^+$, 47), 109 ($CH_2=C(CO)CH_2CH=CO^+$, 100), 91 ($CH_3C_6H_4^+$, 50), 81 ($CH\equiv CCH_2CH_2CO^+$, 43), 77, 65, 55, 53, 39.

Anal. Calcd. for $C_{22}H_{20}N_4O_2$ (**3h**): C, 71.0; H, 5.41; N, 15.0. Found: C, 71.1; H, 5.40; N, 15.0.

Preparation of 3-(*p*-anisyl)-5-methyl-1,2,4-oxadiazole (**2i**) and Formation of 2,4-Di-[3-(*p*-anisyl)-1,2,4-oxadiazol-5-yl]-1-butene (**3i**).

To a solution of 1.06 g (7.06 mmoles) of **1c** in 2 ml of pyridine was added dropwise 1.0 ml (12.1 mmoles) of acryloyl chloride. The remaining procedure paralleled that for preparing **2h**, and gave 499 mg of a viscous oil. Preparative-scale tlc with methylene chloride gave 245 mg (1.21 mmoles, 17%) of **2i**, mp 58-59°, and 132 mg (0.326 mmole, 9.3 % based on **1c**) of **3i**, mp 93-94°; pmr (deuteriochloroform): δ 3.84 (s, 3 H, CH_3O), 5.95 (d, 1 H, J = 10.9 Hz, vinyl), 6.65 (d, 1 H, J = 17.6 Hz, vinyl), 6.74 (dd, 1 H, J = 17.6 and 10.9 Hz, vinyl), 6.98 (d, 2 H, J = 8.9 Hz, aromatic), 8.03 (d, 2 H, J = 8.9 Hz, aromatic); cmr (deuteriochloroform): see drawing **2i** δ 55.31 (MeO), 114.27 (b), 119.28 (d), 120.65 (h), 126.45. (g), 129.04 (c), 161.97 (a), 168.41 (e), 174.21 (f); ms: (m/e) 202 (M^+, 100), 149 ($CH_3OC_6H_4CNO^+$, 91), 133 ($CH_3OC_6H_4CN^+$, 13), 106 ($CH_3OC_6H_3^+$, 47), 78, 76, 64, 51, 39.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$ (**2i**): C, 65.3; H, 4.98; N, 13.9. Found: C, 65.2; H, 4.95; N, 13.6.

Compound **3i** (see drawing).

This compound had pmr (deuteriochloroform): δ 3.19 (t, 2 H, J = 7.4 Hz, CH_2), 3.34 (t, 2 H, J = 7.4 Hz, CH_2), 3.843 (s, 3 H, CH_3O), 3.847 (s, 3 H, CH_3O), 5.77 (s, 1 H, H_j), 6.38 (s, 1 H, H_j), 6.97 (overlapping d, 4 H, J = 8.83 and 9.12 Hz, $H_{b,b'}$), 8.00 (d, 2 H, J = 9.0 Hz, $H_{d(c')}$), 8.03 (d, 2 H, J = 8.73 Hz, $H_{c'(c)}$); cmr (deuteriochloroform): δ 25.61 (g), 29.96 (h), 55.35 (CH_3O), 114.25 (b,b'), 119.24, 119.30 (d,d'), 125.01 (j), 129.03, 129.11 (c,c'), 131.65 (i), 161.94, 161.99 (a,a'), 168.05, 168.09 (e,e'), 174.72, 178.20 (f,f'). The exact assignment of atoms in pairs of C atoms (*e.g.*, a,a') cannot be made; ms: (m/e) 404 (M^+, 35), 257 (M^+ -$CH_3OC_6H_4CN_2$, 100), 229 (M^+ -$CH_3OC_6H_4C_2N_2O$, 17), 149 ($CH_3OC_6H_4CNO^+$, 17), 133 ($CH_3OC_6H_4CN^+$, 30), 109 ($CH_2=C(CO)CH_2CH=CO^+$, 20), 106 ($CH_3C_6H_3^+$, 17), 81 ($CH\equiv CCH_2CH_2CO^+$, 13), 55, 53.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$ (**3i**): C, 65.3; H, 4.98; N, 13.9. Found: C, 65.5; H, 5.06; N, 13.5.

Acknowledgement.

We thank the Robert A. Welch Foundation, Grant No. D-028, for support of this work.

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