A Two-Step Synthesis of Diaminofurazan and Synthesis of *N*-Monoarylmethyl and *N,N'*-Diarylmethyl Derivatives

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Received February 10, 1997

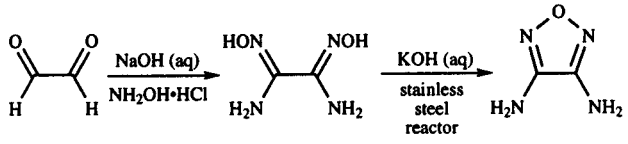
Diaminofurazan (**1**) was synthesized from glyoxal (**2**) by an improved two-step procedure. The *N*-monoarylmethyl derivatives **4a-e** and *N,N'*-diarylmethyl derivatives **5a-e** of **1** were prepared in good yields by reductive alkylation with the corresponding aryl aldehydes.

J. Heterocyclic Chem., **34**, 1057 (1997).

Diaminofurazan (**1**, 3,4-diamino-1,2,5-oxadiazole) has been shown to be a useful intermediate for the preparation of energetic compounds [1–4]. In addition, **1** has been identified as an urea equivalent for histamine H_2-receptor antagonists [5–7]. Moreover, **1** has recently been employed as a subunit for the construction of crown ethers and macrocycles [8,9]. The increased chemical and medicinal applications of **1** and its derivatives have led to a renewed interest in the synthesis and chemistry of this versatile heterocycle [10]. As part of a program aimed at the development of synthetic methods for the construction of new furazan derivatives, herein we report a short and reliable synthesis of diaminofurazan (**1**). We also wish to describe the synthesis of *N*-monoarylmethyl derivatives and *N,N'*-diarylmethyl derivatives of **1** which can be obtained in good yields.

As illustrated in Scheme 1, the synthesis of **1** was achieved in two steps from commercially available glyoxal (**2**). Treatment of **2** with hydroxylamine hydrochloride (4 equivalents) in the presence of sodium hydroxide (4 equivalents) in water at 90° afforded the diaminoglyoxime (**3**) in 52% yield. This single step conversion of **2** into **3** greatly improved the efficiency of the overall synthesis of **1** relative to previous reports [1,4,11].

Scheme 1

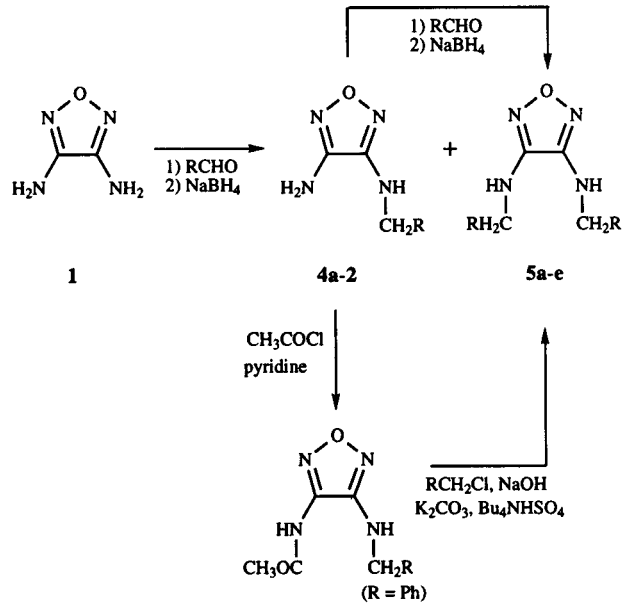


2 **3** **1**

The conversion of **3** into **1** was achieved in similar fashion to that previously reported [4]. The reaction was performed in a sealed stainless steel reactor heated by an oil bath at 170°. The cyclization reaction was also performed in a stainless steel reactor in which the internal reaction temperature was monitored and maintained at 170°. Either method afforded **1** consistently in 50% yield as a pure white crystalline material. Variation in reaction temperature led to reduced yields due to incomplete conversion of **3** or decomposition of **1**.

It follows from the literature, that aminofurazans are weak nucleophiles and do not react with such typical alkylating agents as methyl iodide, dimethyl sulfate, bromoacetophenone and trityl chloride [12]. However, it was recently reported that *N,N'*-dibenzylaminofurazan derivatives could be obtained by reductive alkylation of **1** with derivatives of benzaldehyde [13]. As an extension of this work, we have found that both the monoarylmethyl derivatives **4a–e** and the diarylmethyl derivatives **5a–e** could be easily prepared by reductive alkylation with the corresponding aryl aldehydes. Because of the weak nucleophilicity of the amino groups of **1**, the initial condensation reaction required fairly vigorous conditions (*p*-toluenesulfonic acid, benzene, reflux). No reaction was observed at lower reaction temperatures or without an acid catalyst. Unfortunately, these conditions were found to be unsuitable for the reaction of **1** with alkyl aldehydes which lead to intractable mixtures.

Scheme 2



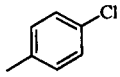
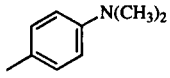
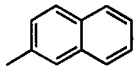
1 **4a-2** **5a-e**

6

As summarized in Table 1, the monoarylmethyl derivatives **4a–e** could be prepared in good isolated yields (40–58%) by limiting the reaction times to less than 20 hours. However, a minimum of 1.5 to 2 equivalents of aldehyde was necessary to consume all of **1** present in the reaction mixture and force the reactions to completion. As a result, a small amount of the *N,N'*-diarylmethyl derivatives **5a–e** were also formed. However, **4a–e** and **5a–e** could be easily separated by column chromatography. Alternatively, the *N,N'*-diarylmethyl derivatives **5a–e** were obtained in high yields (50–82%) with two equivalents of aldehyde when longer reaction times (35–55 hours) were employed.

Table 1

Synthesis of *N*-Monoarylmethyl Derivatives and *N,N'*-Diarylmethyl Derivatives of **1**

Entry	R	RCHO/1 equivalent	Re action Time (hours)	Yields (%) [a] **4**	**5**
a		2	20	58	13
		2	35	8	77
b		1.5	15	53	45
		2	45	27	70
c		2	19	45	5
		2	55	17	82
d		1.5	18	50	41
		2	45	20	70
e		1.5	17	40	26
		2	35	11	50

[a] Isolated yields after column chromatography.

Further derivatization of the diaminofurazan nucleus was investigated with the *N*-benzyl derivative **4a**. Conversion of **4a** into **5a** proceeded regiospecifically in 60% yield under the conditions employed for monoalkylation. Acylation of **4a** was also achieved regiospecifically with acetyl chloride/pyridine to provide **6** in 57% yield. As an alternative approach for the synthesis of diaryl derivatives, the *N,N'*-dibenzyl derivative **5a** was prepared from **6** by a one-pot alkylation/hydrolysis reaction with benzyl bromide. This afforded **5a** in 35% yield (Scheme 2).

EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Company, Milwaukee, WI. The ^1H and ^{13}C nmr spectra were obtained on a Varian–Gemini Multiprobe 300 MHz nmr spectrometer. Melting points were determined on a Mel–Temp II and are reported uncorrected. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA. Reactions were performed in a Parr 4561 Mini reactor (300 ml) or in an inexpensive stainless steel reactor made in the Machine Shop at the University of New Orleans [14].

Diaminoglyoxime (**3**).

To a cooled solution (ice-cooling) of sodium hydroxide (140 g, 3.5 moles) in water (400 ml), hydroxylamine hydrochloride (222 g, 3.2 moles) was added in portions with stirring over a period of 10 minutes. To this mixture, glyoxal (40%, 92 ml, 0.8 mole) was added in one portion with stirring and cooling (ice-bath). The mixture was stirred at 0–5° for 10 minutes and at 90–100° (bath temperature) for 5 hours. The yellow solution was left at 0–5° for 24 hours which afforded yellow crystals. The yellow crystals were collected by filtration and dried under reduced pressure to yield 49.7 g (52%), mp 200–203° (lit mp 203°) [4].

Diaminofurazan (**1**).

A suspension of **3** (23.6 g, 0.2 mole) in aqueous potassium hydroxide (2 *M*, 80 ml) was placed in a stainless steel reactor, which was heated at 170° (bath temperature) for 2 hours. The reactor was then cooled at 0–5° for 2 hours. White crystals were collected by filtration and dried under reduced pressure to yield 10 g (50%), mp 178–180° (lit mp 179–180°) [4].

General Procedure for the Reaction of Diaminofurazan (**1**) with Aryl Aldehydes.

All the reactions were performed under a nitrogen atmosphere. A mixture of **1** (0.5 g, 5 mmoles), the corresponding aldehyde (1.5–10 mmoles), *p*-toluenesulfonic acid (10–15 mg) and benzene (60 ml) was refluxed with a Dean–Stark apparatus for the time specified in Table 1. The resulting solution was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of methanol (10 ml) and tetrahydrofuran (25 ml). Sodium borohydride (1.5 g) was added in portions to the stirred solution at room temperature. Once the addition was complete, the resulting mixture was stirred for 20 hours, then neutralized with 1 *M* hydrogen chloride. Any inorganic material which precipitated was filtered off as necessary and the filtrate was extracted with ethyl acetate (4 x 50 ml). The combined organic fractions were dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane/ethyl acetate, 3:1) to give **4a–e** and **5a–e** as white or yellow crystals.

3-Amino-4-benzylamino-1,2,5-oxadiazole (**4a**).

This compound was obtained as white crystals (ethyl acetate/hexane), mp 97–99°; ^1H nmr (deuteriochloroform): δ 7.30 (s, 5H), 6.38 (t, 1H, J = 5 Hz), 5.10 (s, 2H), 4.36 (d, 2H, J = 5 Hz); ^{13}C nmr (deuteriochloroform): δ 150.0, 148.4, 137.8, 128.0, 127.7, 127.0, 48.0.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.82; H, 5.30; N, 29.47. Found: C, 56.84; H, 5.27; N, 29.52.

3,4-Dibenzylamino-1,2,5-oxadiazole (**5a**).

This compound was obtained as white crystals (ethyl acetate/hexane), mp 110–112° (lit mp 109–111°) [13].

3-Amino-4-(*p*-chlorobenzylamino)-1,2,5-oxadiazole (**4b**).

This compound was obtained as white crystals (ethyl acetate/-hexane), mp 114–116°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 7.42 (s, 4H), 6.54 (t, 1H, J = 6 Hz), 5.90 (s, 2H), 4.35 (d, 2H, J = 6 Hz); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 150.2, 149.1, 137.7, 131.8, 129.5, 128.3, 46.8.

Anal. Calcd. for $C_9H_9ClN_4O$: C, 48.20; H, 4.05; N, 25.00. Found: C, 48.22; H, 4.07; N, 24.95.

3,4-Di-(*p*-chlorobenzylamino)-1,2,5-oxadiazole (**5b**).

This compound was obtained as white crystals (benzene/hexane), mp 123–125°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 7.41 (s, 8H), 6.53 (t, 2H, J = 5 Hz), 4.35 (d, 4H, J = 5 Hz); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 149.4, 137.5, 131.8, 129.6, 128.3, 46.8.

Anal. Calcd. for $C_{16}H_{14}Cl_2N_4O$: C, 55.16; H, 4.05; N, 16.09. Found: C, 55.19; H, 4.08; N, 16.08.

3-Amino-4-(*p*-dimethylaminobenzylamino)-1,2,5-oxadiazole (**4c**).

This compound was obtained as yellow crystals (benzene/-hexane), mp 122–124°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 7.22–7.19 (m, 2H), 6.72–6.70 (m, 2H), 6.24 (t, 1H, J = 5 Hz), 5.87 (s, 2H), 4.18 (d, 2H, J = 5 Hz), 2.86 (s, 6H); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 150.2, 149.5, 149.0, 128.9, 125.9, 112.3, 47.4, 40.2.

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.62; H, 6.48; N, 30.03. Found: C, 56.73; H, 6.44; N, 29.89.

3,4-Bis-(*p*-dimethylaminobenzylamino)-1,2,5-oxadiazole (**5c**).

This compound was obtained as yellow crystals (benzene/-hexane), mp 147–149°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 7.20–7.17 (m, 4H), 6.71–6.70 (m, 4H), 6.27 (t, 2H, J = 5 Hz), 4.18 (d, 4H, J = 5 Hz), 2.87 (s, 12H); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 149.9, 149.5, 129.0, 125.8, 112.3, 47.4, 40.2.

Anal. Calcd. for $C_{20}H_{26}N_6O$: C, 65.53; H, 7.16; N, 22.94. Found: C, 65.80; H, 7.13; N, 22.68.

3-Amino-4-(2-naphthylmethylamino)-1,2,5-oxadiazole (**4d**).

This compound was obtained as white crystals (ethyl acetate/-hexane), mp 125–127°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 7.93–7.90 (m, 4H), 7.56–7.50 (m, 3H), 6.61 (t, 1H, J = 6 Hz), 6.00 (s, 2H), 4.54 (d, 2H, J = 6 Hz); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 150.3, 149.1, 136.2, 132.9, 132.3, 128.0, 127.6, 126.3, 126.2, 126.0, 125.8, 47.8.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.97; H, 5.04; N, 23.33. Found: C, 65.04; H, 5.11; N, 23.31.

3,4-Di-(2-naphthylmethylamino)-1,2,5-oxadiazole (**5d**).

This compound was obtained as white crystals (ethyl acetate/-hexane), mp 197–198°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 8.14–8.10 (m, 8H), 7.76–7.70 (m, 6H), 6.84 (t, 2H, J = 6 Hz), 4.73 (d, 4H, J = 6 Hz); ^{13}C nmr (dimethyl sulfoxde–d_6): δ 149.6, 136.0, 132.8, 132.3, 128.0, 127.6, 127.5, 126.2, 126.1, 125.8, 47.8.

Anal. Calcd. for $C_{24}H_{20}N_4O$: C, 75.76; H, 5.30; N, 14.73. Found: C, 75.75; H, 5.40; N, 14.83.

3-Amino-4-(3-furylmethylamino)-1,2,5-oxadiazole (**4e**).

This compound was obtained as white crystals (ethyl acetate/-hexane), mp 113–115°; ^{1}H nmr (deuteriochloroform): δ 7.47–7.45 (m, 1H), 7.40–7.39 (m, 1H), 6.45–6.44 (m, 1H), 5.17 (t, 1H, J = 5 Hz), 4.82 (s, 2H), 4.30 (d, 2H, J = 5 Hz); ^{13}C nmr (deuteriochloroform): δ 149.7, 148.1, 142.5, 139.7, 121.5, 109.8, 38.7.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.65; H, 4.48; N, 31.11. Found: C, 46.87; H, 4.53; N, 30.90.

3,4-Di-(3-furylmethylamino)-1,2,5-oxadiazole (**5e**).

This compound was obtained as white crystals (ethyl acetate/-hexane), mp 88–90°; ^{1}H nmr (deuteriochloroform): δ 7.43–7.42 (m, 2H), 7.40–7.39 (m, 2H), 6.41–6.40 (m, 2H), 4.28 (t, 2H, J = 5 Hz), 4.24 (d, 4H, J = 5 Hz); ^{13}C nmr (deuteriochloroform): δ 149.9, 143.6, 140.7, 121.8, 110.5, 39.7.

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.37; H, 4.65; N, 21.54. Found: C, 55.36; H, 4.64; N, 21.43.

3-Acetylamino-4-benzylamino-1,2,5-oxadiazole (**6**).

A mixture of **4a** (1.65, 8.7 mmoles), acetyl chloride (0.76 g, 9.7 mmoles), pyridine (2 ml) and dioxane (45 ml) was stirred at room temperature for 2 hours. To this mixture, water (20 ml) and ethyl acetate (50 ml) were added, the organic layer was separated and the water layer was extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with water (20 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from benzene to yield white needles, 1.15 g (57%), mp 100–112°; ^{1}H nmr (dimethyl sulfoxide–d_6): δ 10.80 (s, 1H), 7.49–7.47 (m, 5H), 6.80 (t, 1H, J = 5 Hz), 4.50 (d, 2H, J = 5 Hz), 2.25 (s, 3H); ^{13}C nmr (dimethyl sulfoxide–d_6): δ 169.7, 152.5, 143.7, 138.7, 128.6, 128.0, 127.5, 47.6, 23.1.

Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.87; H, 5.21; N, 24.13. Found: C, 56.68; H, 5.26; N, 24.41.

3,4-Dibenzylamino-1,2,5-oxadiazole (**5a**) from **4a**.

A mixture of **4a** (0.5 g, 2.6 mmoles), benzaldehyde (0.3 g, 2.8 mmoles), *p*-toluenesulfonic acid (10 mg) and benzene (50 ml) was refluxed under nitrogen in a Dean–Stark apparatus for 20 hours. The solution was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of methanol (10 ml) and tetrahydrofuran (25 ml). Sodium borohydride (1.5 g) was added in portions to the stirred solution at room temperature. Once the addition was complete, the resulting mixture was stirred for 20 hours, then evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, pentane/ethyl acetate, 3:1) to yield 0.44 g (60%).

3,4-Dibenzylamino-1,2,5-oxadiazole (**5a**) from **6**.

A mixture of **6** (0.9 g, 4 mmoles), sodium hydroxide (1.125 g), potassium carbonate (0.675 g), tetrabutylammonium hydrogen sulfate (0.27 g) and benzene (50 ml) was stirred at 60° for 30 minutes. To this mixture a solution of benzyl bromide (0.81 g, 4.7 mmoles) in benzene (10 ml) was added dropwise with stirring at 60°. The resulting mixture was refluxed for 4 hours. After cooling the inorganic material was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, pentane/ethyl acetate, 4:1) to yield 0.38 g (35%).

Acknowledgements.

We greatly appreciate the financial support provided by the Ballistic Missile Defense Organization and the Office of Naval

Research through contract N00014–95–1339; Program Officers: Dr. Leonard H. Caveny (BMDO) and Dr. Richard S. Miller (ONR).

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