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New Cyclization of *N*-Hydroxyiminoyl Chlorides with *N*-Alkyl Ethynesulfonamides: Synthesis of 4-Alkyl-3-aryl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-diones

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ABSTRACT: *N-Hydroxyiminoyl chlorides reacted with N-alkyl ethynesulfonamides in the presence of triethylamine in CH_2Cl_2 to afford the 4-alkyl-3-aryl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-diones (3) as the major products together with N-alkyl-3-aryl-5-isoxazolesulfonamides (4).* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 461–464, 1999

INTRODUCTION

It is well known that *N*-hydroxyiminoyl chlorides are the precursors of nitrile oxides which are short-lived reactive species [1]. Nitrile oxides are important substrates in the preparation of heterocycles via 1,3-dipolar cycloadditions and react with alkenes and alkynes to give isoxazoline and isoxazole derivatives. Because the reactive nitrile oxides are used mainly in the synthesis of heterocycles, there have been a number of [3 + 2] cyclizations using *N*-hydroxyiminoyl chlorides [2]. However, the cyclization of *N*-hydroxyiminoyl chlorides to 7-membered ring compounds has never been reported.

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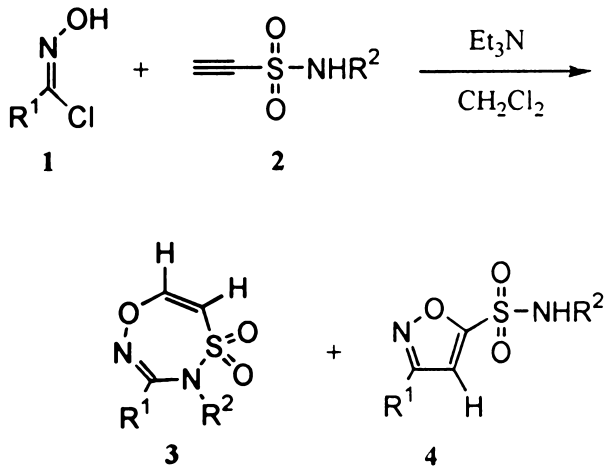
RESULTS AND DISCUSSIONS

During the course of studies on the preparation of heterocycles with nitrile oxides, we found that *N*-hydroxyiminoyl chlorides (**1**) [3] can react with *N*-alkyl ethynesulfonamides (**2**) [4] in the presence of triethylamine to give new 7-membered heterocyclic products, 4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-diones (**3**), as the major products together with 5-membered isoxazolesulfonamides (**4**), as shown in Scheme 1. It is not clear whether the reaction mech-

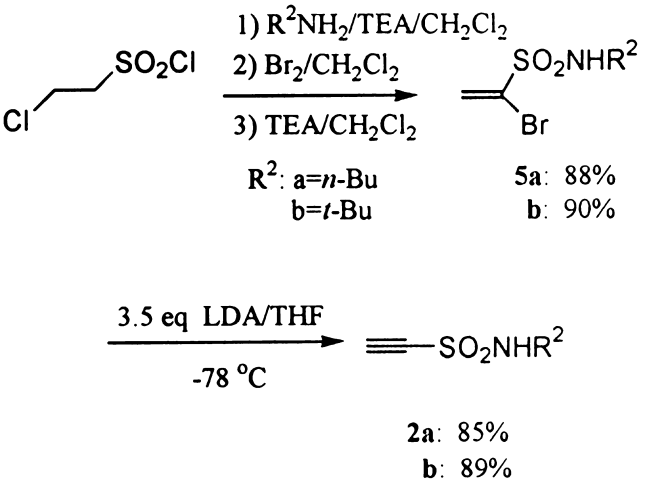


SCHEME 1

anism proceeds via a concerted or stepwise cyclization.

Ethynesulfonamides (2) were prepared from 2-chloroethanesufonyl chloride by a known method (see Scheme 2). Results obtained are shown in Table 1. It is noteworthy that 7-membered ring compounds (**3**) are obtained in higher yields than 5-membered ring compounds (**4**), which are expected to be formed by [3 + 2] cycloaddition. In spite of the introduction of a bulky *t*-butyl substituent as R^2 instead of an *n*-butyl substituent, the ratio of yields was not greatly changed (entry in Table 1). The structure of **4** was identified by comparison with the structures of methyl 3-phenyl-5-isoxazolecarboxylate and methyl 3-phenyl-4-isoxazolecarboxylate [2b], and Nuclear Overhouser Effect (NOE) experiments as shown in Figure 1.

The proton peak of the sulfonamide group (SO_2NH) was not detected in **3** and the coupling constants of the vinylic protons in **3** were identical to each other (J_{cis} = 7.1 Hz for **3a**). The structures of 4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-diones (**3**) were determined by ^1H, ^{13}C NMR, and IR spectroscopy, and by high resolution mass spectroscopy (MS).



SCHEME 2

TABLE 1 The Cyclization Reactions of *N*-Hydroxyiminoyl Chlorides with *N*-Alkyl Ethylnesulfonamides

Entry	R^1	R^2	*Products*	*Yield*[a] (%)	*Products*	*Yield*[a] (%)
a	4-$CH_3OC_6H_5$	*n*-Bu	**3a**	43	**4a**	19
b	3-$NO_2C_6H_4$	*n*-Bu	**3b**	44	**4b**	23
c	C_6H_5	*n*-Bu	**3c**	48	**4c**	22
d	C_6H_5	*t*-Bu	**3d**	49	**4d**	24
e	3-ClC_6H_4	*n*-Bu	**3e**	38	**4e**	28
f		*n*-Bu	**3f**	37	**4f**	28

[a]Isolated yields.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are not corrected. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. Mass (MS) and high resolution mass (HRMS) spectra were recorded on a Micromass Autospec.

Preparation of N-Butyl-1-bromoethenesulfomamide (**5a**)

To a stirred solution of 2-chloroethanesulfonyl chloride (8.15 g, 50 mmol) in CH_2Cl_2 (50 mL), a solution of butylamine (3.5 g, 55 mmol) and triethylamine (14.0 g, 150 mmol) in CH_2Cl_2 (50 mL) was added dropwise at 0°C over a period of 30 minutes. After the reaction mixture was stirred for 3 hours at 20°C, the precipitated solid was filtered off. The filtrate was washed three times with distilled water (50 mL) and dried over $MgSO_4$. To this solution, bromine (8 g, 50 mmol) was added dropwise over 20 minutes and the reaction mixture was stirred for 18 hours at room temperature. After the reaction mixture had been washed three times with saturated sodium thiosulfate solution (50 mL), triethylamine (5.2 g, 55 mmol) was added over 30 minutes and the reaction mixture was then stirred for 15 hours at 25°C. The precipitated solid was filtered off. The filtrate was washed three times with distilled water (50 mL and dried over $MgSO_4$. After concentration, chromatography was performed on the residue on a silica gel column (30 mm × 30 cm, hexane:ethyl acetate = 5:1) to give *N*-butyl-1-bromoethenesulfomamide as an oil (10.6 g, 88%). ^1H NMR δ 0.93 (t, 3H, J = 7.3 Hz), 1.33–1.45 (m, 2H), 1.52–1.62 (m, 2H), 3.05 (q, 2H, J = 6.3 Hz), 4.94 (br, 1H), 6.22 (d, 1H, J = 2.9 Hz), 6.85 (d,

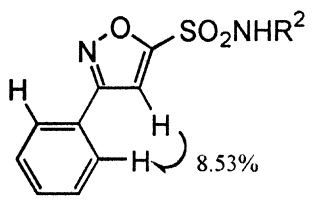


FIGURE 1 Nuclear Overhouser Effect (NOE) experiment of **4c**

1H, J = 2.9 Hz). ^{13}C NMR δ 13.49, 19.65, 31.49, 43.31, 127.27, 128.31.

Preparation of N-t-Butyl-1-bromoethenesulfomamide (**5b**)

N-t-Butyl-1-bromoethenesulfomamide was prepared from 2-chloroethanesulfonyl chloride (8.15 g, 50 mmol) and *t*-butylamine (3.5 g, 55 mmol) and obtained as a solid (10.8 g, 90%), m.p. 96–97°C. ^{1}H NMR δ 1.34 (s, 9H), 5.04 (br, 1H), 6.09 (d, 1H, J = 2.5 Hz), 6.82 (d, 1H, J = 2.5 Hz). ^{13}C NMR δ 29.55, 55.21, 126.75, 131.20.

Preparation of N-Butylethynesulfomamide (**2a**)

To a stirred solution of *N*-butyl-1-bromoethenesulfomamide (7.23 g, 30 mmol) in dry tetrahydrofuran (THF) (100 mL), lithium diisopropylamide (LDA) (53 mL, 2M solution in THF) was added at −78°C over 2 hours. After the reaction mixture had been stirred for 3 hours, hydrochloric acid (30 mL, 5 M solution) was added dropwise at −78°C. To the reaction mixture, ethyl acetate (200 mL) and distilled water (100 mL) were added. After separation, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was Kugelrohr distilled (170–175°C/1 mmHg) to give **2a** as an oil (4.1 g, 85%). ^{1}H NMR δ 0.92 (t, 3H, J = 7.2 Hz), 1.33–1.45 (m, 2H), 1.52–1.62 (m, 2H), 3.18 (q, 2H, J = 6.9 Hz), 3.32 (s, 1H), 4.94 (br, 1H). ^{13}C NMR δ 13.46, 19.55, 30.90, 43.29, 76.97, 78.16. MS (EI): m/z = 161 (M^+, 5%), 118 (100%). HRMS (EI): m/z (M^+): Calcd. for $C_6H_{11}NO_2S$; 161.0510. Found; 161.0486.

Preparation of N-t-Butylethynesulfomamide (**2b**)

The reaction of *N-t*-butyl-1-bromoethenesulfomamide with LDA afforded **2b** as a solid (4.3 g, 89%). M.p. 48–49°C. ^{1}H NMR δ 1.42 (s, 9H), 3.27 (s, 1H), 5.23 (br, 1H). ^{13}C NMR δ 29.69, 55.98, 75.58, 81.23. MS (E1): m/z = 161 (M^+, 7%), 118 (100%). HRMS (EI): m/z (M^+): Calcd. for $C_6H_{11}NO_2S$; 161.0510. Found 161.0505.

Typical Procedure for the Cyclization of N-Hydroxyiminoyl Chloride with N-Alkyl Ethynesulfonamide

To a stirred solution of each *N*-alkyl ethynesulfonamide (2 mmol) in dry CH_2Cl_2 (10 mL), a solution of *N*-hydroxyiminoyl chloride (4 mmol) in CH_2Cl_2 (10 mL) and a solution of triethylamine (4 mmol) in CH_2Cl_2 (10 mL) were added dropwise at 0°C simultaneously over 2 hours. The reaction mixture was stirred at 0°C for 5 hours. Ethyl acetate (30 mL) and water (30 mL) were then added to the reaction mixture. The separated organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue was performed on a silica gel column (10 mm × 20 cm, hexane:ethyl acetate = 6:1) to give **3** as an oil and **4** as a solid.

4-Butyl-3-(4-methoxyphenyl)-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3a**)

^{1}H NMR δ 0.87 (t, 3H, J = 7.3 Hz), 1.24–1.42 (m, 2H), 1.47–1.73 (m, 2H), 3.62 (t, 2H, J = 7.7 Hz), 3.85 (s, 3H), 6.00 (d, 1H, J = 7.1 Hz), 6.96 (d, 2H, J = 9.8 Hz), 7.02 (d, 1H, J = 7.1 Hz), 7.92 (d, 2H, J = 9.8 Hz). ^{13}C NMR δ 13.53, 19.65, 31.10, 49.19, 55.33, 110.75, 114.39, 120.73, 131.47, 151.87, 160.92, 163.40. MS (EI): m/z = 310 (M^+, 27%), 204 (100%). HRMS (EI): m/z (M^+): Calcd. for $C_{14}H_{18}N_2O_4S$; 310.0988, Found, 310.0981.

N-Butyl-3-(4-methoxyephenyl)-5-isoxazolesulfonamide (**4a**)

M.p. 97–98°C. ^{1}H NMR δ 0.90 (t, 3H, J = 7.3 Hz), 1.29–1.35 (m, 2H), 1.43–1.56 (m, 2H), 3.20 (q, 2H, J = 6.5 Hz), 3.86 (s, 3H), 5.27 (br, 1H), 6.99 (d, 2H, J = 8.7 Hz), 7.08 (s, 1H), 7.74 (d, 2H, J = 8.7 Hz). ^{13}C NMR δ 13.44, 13.52, 31.57, 43.32, 55.38, 105.48, 114.53, 119.71, 128.39, 161.63, 162.15, 166.27. IR (KBr) ν 3287 (s), 2961 (m), 2875 (w), 1561 (w), 1451 (m), 1428 (m), 1337 (s), 1164 (s), 1085 (m). MS (EI): m/z = 310 (M^+, 87%), 174 (100%). HRMS (EI): m/z (M^+): Calcd. for $C_{14}H_{18}N_2O_4S$: 310.0988, Found: 310.0980. Anal. Calcd. For $C_{14}H_{18}N_2O_4S$: C 54.19, H 5.81, N 9.03; Found: C 54.17, H 6.13, N 9.10.

4-Butyl-3-(3-nitrophenyl)-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3b**)

^{1}H NMR δ 0.88 (t, 3H, J = 7.3 Hz), 1.28–1.43 (m, 2H), 1.50–1.62 (m, 2H), 3.65 (t, 2H, J = 7.7 Hz), 6.08 (d, 1H, J = 7.3 Hz), 7.06 (d, 1H, J = 7.3 Hz), 7.71 (t, 1H, J = 8.2 Hz), 8.32–8.47 (m, 2H), 8.84 (t, 1H, J = 1.9 Hz). ^{13}C NMR δ 13.38, 19.69, 30.90, 49.59, 110.83, 124.17, 127.07, 130.13, 130.42, 134.81, 148.48, 151.24, 159.19. MS (EI): m/z = 325 (M^+, 6%), 153 (100%). HRMS (EI): m/z (M^+): Calcd. for $C_{13}H_{15}N_3O_5S$; 325.0733, Found 325.0715.

N-Butyl-3-(3-nitrophenyl)-5-isoxazolesulfonamide (**4b**)

M.p. 121–122°C. ^{1}H NMR δ 0.92 (t, 3H, J = 7.3 Hz), 1.35–1.42 (m, 2H), 1.47–1.58 (m, 2H), 3.24 (t, 2H, J

= 6.7 Hz), 5.35 (br, 1H), 7.25 (s, 1H), 7.13 (t, 1H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 7.8 Hz), 8.29 (d, 1H, *J* = 7.8 Hz), 8.60 (s, 1H). ^{13}C NMR δ 13.43, 19.51, 31.62, 43.40, 105.41, 121.91, 125.43, 129.19, 130.42, 132.59, 148.63, 160.80, 167.73. IR (KBr) *v* 3272 (s), 2958 (w), 2934 (m), 2872 (m), 1539 (m), 1346 (s), 1166 (s). MS (EI): *m/z* = 325 (M^+, 7%), 153 (100%). HRMS (EI): *m/z* (M^+): Calcd. for $C_{13}H_{15}N_3O_5S$; 325.0733, Found 325.0753. Anal. Calcd. For $C_{13}H_{15}N_3O_5S$: C 48.00, H 4.62, N 12.92; Found: C 47.96, H 4.70, N 12.95.

4-Butyl-3-phenyl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3c**)

^{1}H NMR δ 0.84 (t, 3H, *J* = 7.3 Hz), 1.26–1.36 (m, 2H), 1.47–1.57 (m, 2H), 3.51 (t, 2H, *J* = 7.6 Hz), 6.01 (d, 1H, *J* = 7.1 Hz), 7.00 (d, 1H, *J* = 7.1 Hz), 7.42–7.50 (m, 2H), 7.52–7.58 (m, 1H), 7.93–7.97 (m, 1H). ^{13}C NMR δ 13.43, 19.64, 31.13, 49.14, 111.00, 128.74, 128.95, 129.64, 132.80, 151.60, 161.26. IR (NaCl) *v* 3065 (s), 2958 (s), 2932 (s), 2855 (m), 1610 (s), 1559 (w), 1450 (w), 1240 (w), 1154 (s), 1039 (m).

N-Butyl-3-phenyl-5-isoxazolesulfonamide (**4c**)

M.p. 86–87°C. ^{1}H NMR δ 0.88 (t, 3H, *J* = 7.3 Hz), 1.21–1.40 (m, 2H), 1.48–1.58 (m, 2H), 3.19 (q, 2H, *J* = 7.0 Hz), 5.09 (t, 1H, *J* = 5.9 Hz), 7.11 (s, 1H), 7.43–7.51 (m, 3H), 7.76–7.87 (m, 2H), ^{13}C NMR δ 13.44, 19.55, 31.66, 43.39, 105.66, 126.93, 127.39, 129.03, 130.91, 162.59, 166.69. IR (KBr) *v* 3280 (s), 3159 (w), 2961 (m), 2872 (m), 1462 (m), 1435 (s), 1345 (s), 1171 (s), 1118 (s), 1069 (m).

4-t-Butyl-3-phenyl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3d**)

^{1}H NMR δ 1.49 (s, 9H), 6.06 (d, 2H, *J* = 6.9 Hz), 6.95 (d, 2H, 6.9 Hz), 7.41–7.47 (m, 2H), 7.50–7.56 (m, 1H), 7.99–8.03 (m, 2H). ^{13}C NMR δ 29.85, 64.47, 114.32, 128.88, 129.67, 131.54, 132.57, 150.92, 162.47.

N-t-Butyl-3-phenyl-5-isoxazolesulfonamide (**4d**)

M.p. 92–93°C. ^{1}H NMR δ 1.36 (s, 9H), 5.09 (br, 1H), 7.10 (s, 1H), 7.43–7.55 (m, 1H), 7.77–7.85 (m, 1H). ^{13}C NMR δ 29.87, 62.24, 105.67, 126.72, 127.43, 129.03, 130.93, 162.62, 166.67.

4-Butyl-3-(3-chlorophenyl)-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3e**)

^{1}H NMR δ 0.84 (t, 3H, *J* = 7.2 Hz), 1.24–1.34 (m, 2H), 1.46–1.56 (m, 2H), 3.58 (t, 2H, *J* = 7.6 Hz), 5.99 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 7.2 Hz), 7.38–7.49 (m, 2H), 7.81–7.94 (m, 2H). ^{13}C NMR δ 13.50, 19.73, 31.06, 49.36, 110.92, 127.69, 129.30, 130.13, 130.63, 132.82, 135.05, 151.40, 160.04.

N-Butyl-3-(3-chlorophenyl)-5-isoxazolesulfonamide (**4e**)

M.p. 67–68°C. ^{1}H NMR δ 0.83 (t, 3H, *J* = 7.3 Hz), 1.21–1.37 (m, 2H), 1.42–1.59 (m, 2H), 3.15 (q, 2H, *J* = 6.8 Hz), 5.47 (br, 1H), 7.09 (s, 1H), 7.32–7.45 (m, 2H), 7.60–7.70 (m, 1H), 7.72–7.82 (m, 1H). ^{13}C NMR δ 13.40, 19.48, 31.54, 43.30, 105.45, 124.97, 126.87, 128.94, 130.39, 130.85, 135.10, 161.40, 166.97. IR (KBr) *v* 3274 (s), 3156 (w), 2957 (m), 2931 (m), 2873 (m), 1609 (s), 1527 (m), 1427 (s), 1347 (s), 1264 (s) 1173 (s).

4-Butyl-3-thienyl-4,5-dihydro-1,5,2,4-oxathiadiazepine-5,5-dione (**3f**)

^{1}H NMR δ 0.88 (t, 3H, *J* = 7.5 Hz), 1.33–1.41 (m, 2H), 1.57–1.66 (m, 2H), 3.65 (t, 2H, *J* = 7.7 Hz), 5.98 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 7.2 Hz), 7.10–7.15 (m, 1H), 7.55–7.57 (m, 1H), 7.72–7.74 (m, 1H). ^{13}C NMR δ 13.56, 19.84, 31.13, 49.97, 110.77, 128.18, 134.11, 132.95, 134.37, 151.57, 156.90.

N-Butyl-3-thienyl-5-isoxazolesulfonamide (**4f**)

M.p. 44–45°C. ^{1}H NMR δ 0.89 (t, 3H, *J* = 7.5 Hz), 1.24–1.39 (m, 2H), 1.47–1.59 (m, 2H), 3.36 (q, 2H, *J* = 7.5 Hz), 4.92 (br, 1H), 7.02 (s, 1H), 7.22–7.26 (m, 1H), 7.46–7.50 (m, 2H). ^{13}C NMR δ 13.43, 19.70, 31.03, 44.30, 105.63, 125.43, 131.33, 134.67, 151.53, 162.10, 167.38.

REFERENCES AND NOTES

[1] (a) Torssel, K. B. G. Organic Nitro Chemistry: Organic Nitile Oxides, Nitrones, and Nitronates in Organic Synthesis, Feuer, H., Ed.; VCH Publishers: New York, 1998; pp 1–71; (b) Caramell, P.; Grunannger, P. 1,3-Dipolar Cycloaddition Chemistry, Padwa, A., Ed.; Wiley and Sons: New York, vol. 1, 291–392, 1984.

[2] (a) Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. Chem Ber 1973, 106, 3258; (b) Christl, M.; Huisgen, R. Chem Ber 1973, 106, 3345; (c) Kim, J. N.; Ryu, E. K. Heterocycles 1992, 34, 1423; (d) Shishido, K.; Umimoto, K. Heterocytes 1993, 36, 345; (e) Martin, S. F.; Dupre, B. Tet Lett; 1983, 24, 1337; (f) Caramella, P.; Albini, E.; Bandiera, T.; Coda, A. C.; Grunanger, P.; Albini, F. M. Tetrahedron 1983, 39 (4), 689; (g) Caramella, P.; Bandiera, T.; Grunanger, P.; Albini, F. M. Tetrahedron 1984, 40 (2), 441; (h) Bianchi, G.; Micheli, C. D.; Gandolfi, R.; Grunanger, P.; Finzi, P. V.; de Pava, O. V. J Chem Soc Perkin 1 1973, 1148.

[3] Liu, K. L.; Shelton, B. R.; Howe, R. K. J Org Chem 1980, 45, 3916.