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Synthesis of 4-(5-Aryl-1,3,4-oxadiazol-2-yl)phenyl-hydrazine Derivatives from 3-(4-Hydrazinocarbonyl-phenyl)sydnones

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ABSTRACT: *The synthesis of potential fluorescent active 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives was accomplished in three steps. The key step was the dehydration cyclization of 1,2-diacylhydrazines to form the 1,3,4-oxadiazole ring by use of acetic anhydride/perchloric acid mixture as the dehydrating agent. The sydnone moiety served as the masked hydrazines, which could be demasked by HCl for further application.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:438–442, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20318

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INTRODUCTION

1,3,4-Oxidiazoles have been reported to be biologically versatile compounds displaying a variety of biological effects [1–5]. 1,3,4-Oxadiazole-based heterocyclic compounds are also the most widely studied class of electron-injection and/or hole-blocking organic electroluminescent materials [6]. The most common synthetic approach to 1,3,4-oxidiazoles involves cyclodehydration of 1,2-diacylhydrazines by use of a dehydrating agent [11–15]. An alternative route to 1,3,4-oxidiazoles by oxidative cyclization from the corresponding aldehyde *N*-acylhydrazones proceeds with an oxidating agent [12–17]. Herein, we reported the synthesis of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives from 3-(4-hydrazinocarbonylphenyl)sydnones in three steps to prepare the precursor of the 1,3,4-oxadiazol derivatives as electroluminescent materials. Description of the formation of the 1,3,4-oxidiazole ring can be found in a previous work, where a mixture of acetic anhydride

and perchloric acid was used as the dehydrating agent [18].

Sydnones attract attention owing to their widely useful properties, including biological and pharmaceutical usage [19], synthetic application [20], photochromic properties [21], and preparation of electroluminescent materials [22]. In this work, sydnones were considered as the masked hydrazines, which could be demasked by HCl for further application [23].

RESULTS AND DISCUSSION

The synthetic pathway of the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c** is depicted in Scheme 1. 4-Hydrazinocarbonylphenylsydnone **1a–1c** were prepared by the published procedure [24]. The sydnone compounds **1a–1c** were easily converted to the 1,2-diacylhydrazines **2a–2c** by reacting with benozyl chloride (*para*-$R^1 = H$, Cl, and OMe) in CH_2Cl_2 solution for 3.0 h. The isolated yields and the results are shown in Table 1.

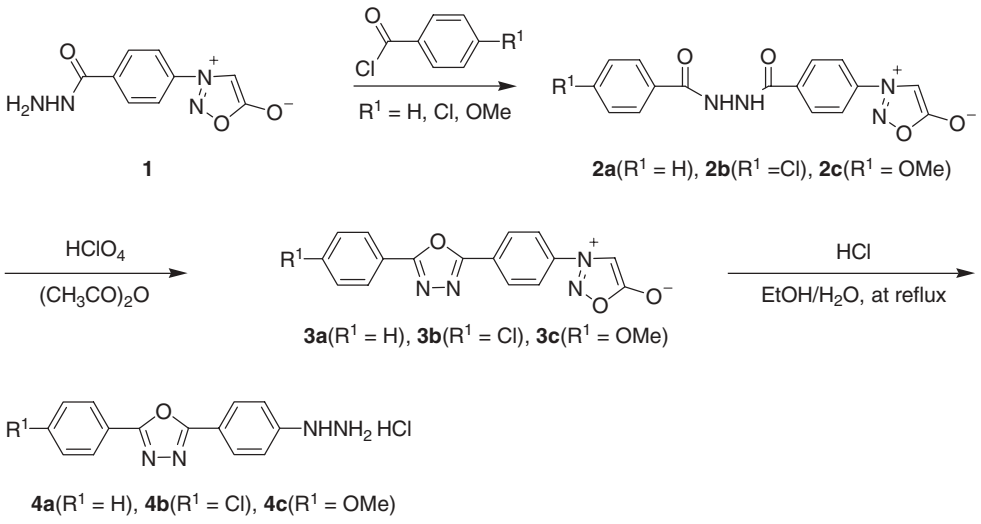
Treatment of the various 1,2-diacylhydrazines **2a–2c** (*para*-$R^1 = H$, Cl, and OMe) with the acetic anhydride/perchloric acid mixture gave the 1,3,4-oxadiazole–sydnone hybrids **3a–3c** in 52%–60% yields (see Table 1). The proposed dehydration–cyclization mechanism is shown in Scheme 2. Upon addition of perchloric acid to the acetic anhydride solution, the sequence of the reaction can be generated using the $CH_3CO^{+-}ClO_4$ and acetic acid species [25]. 1,2-Diacylhydrazines **5** can be reacted with $CH_3CO^{+-}ClO_4$ in the acidic condition to afford the acetyl hydrazone intermediate (**7**) [26]. Further dehydration–cyclization was smoothly performed to yield the 1,3,4-oxidiazole ring (**6**). Finally, reaction of 1,3,4-oxadiazole–sydnone hybrids **3a–3c** with HCl gave products derived from cleavage of the sydnone ring to the corresponding hydrazines **4a–4c**.

In conclusion, we have developed a synthetic route for the precursor of electroluminescent materials of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives in three steps. The key dehydration cyclization of 1,2-diacylhydrazines was performed with acetic anhydride/perchloric acid mixture to provide the 1,3,4-oxadiazole ring. In the last step, the cleavage of sydnone ring was reacted with HCl aqueous solution to afford the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazines.

EXPERIMENTAL

General

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker-300 (300 MHz) spectrometer by use of $CDCl_3$ and-d_6-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Varian Bruker-300 (75 MHz)



SCHEME 1 The synthetic route of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c**.

TABLE 1 The Yields of Aldehyde *N*-Acylhydrazones **2a–2c**, 1,3,4-Oxidiazole–sydnone Hybrids **3a–3c**, and 4-(5-Aryl-1,3,4-oxadiazol-2-yl)phenylhydrazines **4a–4c**

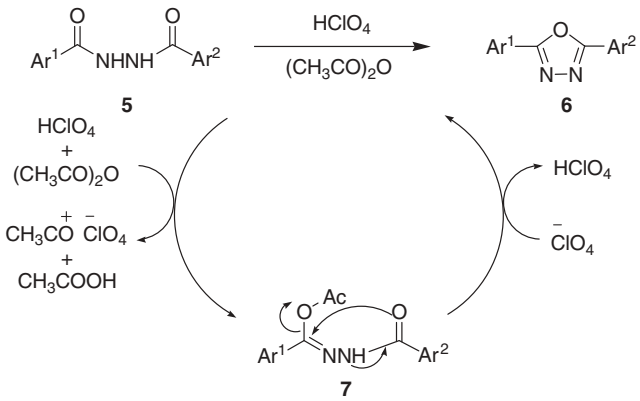
Entry R^1	*Compounds* ***2***	*Yield (%)*	*Compounds* ***3***	*Yield (%)*	*Compounds* ***4***	*Yield (%)*
H	**2a**	87	**3a**	52	**4a**	68
Cl	**2b**	90	**3b**	60	**4b**	77
Ome	**2c**	91	**3c**	57	**4c**	70

spectrometer by use of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard Procedure for the Substitution Reaction

To a solution of 4-hydrazinocarbonylphenylsydnones (**1**, 0.38 g, 6.00 mmol, 1.0 equiv.) and benzoyl chloride (0.80 mL, 6.00 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was stirred at room temperature for 3 h. After the reaction was completed, the resultant precipitate was filtrated, washed with cold CH_2Cl_2 (10 mL × 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOAc to give pure 1,2-diacylhydrazines **2a–2c** as light-yellow powder in 87%–91% yields.

3-[4-(N′-Benzoylhydrazinocarbonyl)phenyl]sydnone **2a**. mp (recrystallized from EtOAc): 214–216°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.48–7.61 (m, 3H), 7.89 (s, 1H), 7.90–7.99 (m, 2H), 8.12 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 8.8 Hz), 10.63 (s, 1H), 10.83 (s, 1H); IR (KBr) 3220 (s, NH), 3130 (s), 1695 (m, C=O) cm^{-1}; FABMS m/z (relative intensity): 325 (M + 1, 20), 324 (M$^+$, 16); Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.32; H, 3.84; N, 17.27.



SCHEME 2 The proposed mechanism of the oxidative cyclization.

3-[4-(N′-4-Chlorobenzoylhydrazinocarbonyl)phenyl]sydnone **2b**. mp (recrystallized from EtOAc): 199–201°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.60 (d, 2H, J = 8.8 Hz), 7.88 (s, 1H), 7.90 (d, 2H, J = 8.8 Hz), 8.09 (d, 2H, J = 8.8 Hz), 8.18 (d, 2H, J = 8.8 Hz), 10.74 (s, 1H), 10.87 (s, 1H); IR (KBr) 3214 (s, NH), 3136 (s), 1746 (m, C=O) cm^{-1}; FABMS m/z (relative intensity): 361 (M + 3, 10), 360 (M + 2, 8), 359 (M + 1, 32), 358 (M$^+$, 20); Anal. Calcd for $C_{16}H_{11}N_4O_4Cl$: C, 53.57; H, 3.09; N, 15.62. Found: C, 53.70; H, 3.21; N, 15.43.

3-[4-(N′-4-Methoxylbenzoylhydrazinocarbonyl)-phenyl]sydnone **2c**. mp (recrystallized from EtOAc): 250–252°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.84 (s, 3H, CH_3), 7.05 (d, 2H, J = 8.9 Hz), 7.88 (s, 1H), 7.90 (d, 2H, J = 8.8 Hz), 7.91 (d, 2H, J = 8.9 Hz), 8.10 (d, 2H, J = 8.8 Hz), 8.19 (d, 2H, J = 8.8 Hz), 10.47 (s, 1H), 10.74 (s, 1H); IR (KBr) 3214 (s, NH), 3130 (s), 1749 (m, C=O) cm^{-1}; FABMS m/z (relative intensity): 355 (M + 1, 31), 354 (M$^+$, 22); Anal. Calcd for $C_{17}H_{14}N_4O_5$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.50; H, 4.23; N, 16.69.

Standard Procedure for the Dehydration–Cyclization

1,2-Diacylhydrazines **2a–2c** (0.32 g, 1.00 mmol, 1.0 equiv.) was dissolved in acetic anhydride (5.0 mL) and added to 4 drops of 60% perchloric acid aqueous solution ($HClO_{4aq}$). The reaction mixture was stirred at room temperature for 36 h. After the reaction was completed, the reaction mixture was filtrated to remove the solid residue. The filtrate was mixed with cold water (10.0 mL) and the resultant precipitate was filtrated, washed with cold EtOAc (10 mL × 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOAc to give the 1,3,4-oxadiazole–sydnone hybrids **3a–3c** as light-yellow powder in 52%–60% yields.

3-[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)phenyl]sydnone **3a**. mp (recrystallized from EtOAc) > 250°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.61–7.67 (m, 3H),

7.93 (s, 1H), 8.15–8.22 (m, 4H), 8.43 (d, 2H, $J = 8.8$ Hz), IR (KBr) 3124 (s), 1770 (m, C=O) cm^{-1}; MS *m/z* (relative intensity): 306 (M^+, 3), 280 (4), 276 (11), 248 (100), 221 (10), 164 (21), 105 (53), 88 (33), 77 (63); Anal. Calcd for $C_{16}H_{10}N_4O_3$: C, 62.74; H, 3.29; N, 18.29. Found: C, 62.83; H, 3.14; N, 18.18.

3-[4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-phenyl]sydnone **3b**. mp (recrystallized from EtOAc) > 250°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.70 (d, 2H, $J = 8.5$ Hz), 7.92 (s, 1H), 8.15 (d, 2H, $J = 8.7$ Hz), 8.18 (d, 2H, $J = 8.5$ Hz), 8.41 (d, 2H, $J = 8.7$ Hz); IR (KBr) 3124 (s), 1755 (m, C=O) cm^{-1}; MS *m/z* (relative intensity): 340 (M^+, 10), 310 (11), 282 (100), 255 (15), 198 (15), 164 (16), 139 (40), 90 (39); Anal. Calcd for $C_{16}H_9N_4O_3Cl$: C, 56.40; H, 2.66; N, 16.44. Found: C, 56.30; H, 2.67; N, 16.45.

3-[4-(5-(4-Methoxylphenyl)-1,3,4-oxadiazol-2-yl)-phenyl]sydnone **3c**. mp (recrystallized from EtOAc): 241–243°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.87 (s, 3H, CH_3), 7.18 (d, 2H, $J = 8.9$ Hz), 7.92 (s, 1H), 8.10 (d, 2H, $J = 8.9$ Hz), 8.18 (d, 2H, $J = 8.9$ Hz), 8.40 (d, 2H, $J = 8.7$ Hz); IR (KBr) 3142 (s), 1743 (m, C=O) cm^{-1}; MS *m/z* (relative intensity): 336 (M^+, 3), 306 (13), 278 (100), 251 (18), 208 (7), 194 (14), 152 (18), 135(85), 90 (35); Anal. Calcd for $C_{17}H_{12}N_4O_4$: C, 60.71; H, 3.59; N, 16.66. Found: C, 60.53; H, 3.38; N, 16.37.

Standard Procedure for the Demasking Reaction [16]:

1,3,4-Oxadiazole–sydnone hybrids **3a–3c** (1.80 g, 5.88 mmol, 1.0 equiv.) was stirred in EtOH solution (60 mL) and added to 3.0 mL of 37% HCl aqueous solution. The reaction mixture was stirred at reflux for 4 h. After the reaction was completed, the resultant precipitate was filtrated, washed with cold EtOH (10 mL × 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOH to afford the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c** as light-yellow powder in 68%–77% yields.

4-(5-Phenyl-1,3,4-oxadiazol-2-yl)phenylhydrazine Hydrochloride **4a**. mp (recrystallized from EtOH): 247–249°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.18 (d, 2H, $J = 8.8$ Hz), 7.57–7.61 (m, 3H), 7.86 (d, 2H, $J = 8.8$ Hz), 8.02–8.12 (m, 3H), 9.03 (br, 1H), 10.58 (br, 3H); IR (KBr) 3184 (s, NH) cm^{-1}; MS *m/z* (relative intensity): 252 (M^+ −36, 59), 180 (9), 165 (17), 135 (100), 119 (16), 105 (46), 90 (22), 77 (72); Anal. Calcd for $C_{14}H_{13}N_4OCl$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.35; H, 4.47; N, 19.40.

4-(5-(4-Chlorophenyl-1,3,4-oxadiazol-2-yl)phenyl-hydrazine Hydrochloride **4b**. mp (recrystallized from EtOH) > 250°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.12 (d, 2H, $J = 8.7$ Hz), 8.95 (br, 1H), 10.47 (br, 3H), IR (KBr) 3208 (s, NH) cm^{-1}; MS *m/z* (relative intensity): 286 (M^+ – 36, 76), 256 (7), 165 (18), 139 (41), 135 (100), 111 (34), 90 (27), 75 (32); Anal. Calcd for $C_{14}H_{12}N_4OCl_2$: C, 52.03; H, 3.74; N, 17.33. Found: C, 52.05; H, 3.70; N, 17.51.

4-(5-(4-Methoxylphenyl-1,3,4-oxadiazol-2-yl)phenyl-hydrazine Hydrochloride **4c**. mp (recrystallized from EtOH): 228–230°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.83 (s, 3H, CH_3), 7.13 (d, 2H, $J = 8.8$ Hz), 7.15 (d, 2H, $J = 8.8$ Hz), 8.01 (d, 2H, $J = 8.8$ Hz), 8.03 (d, 2H, $J = 8.8$ Hz), 8.95 (br, 1H), 10.52 (br, 3H); IR (KBr) 3214 (s, NH) cm^{-1}; MS *m/z* (relative intensity): 282 (M^+ −36, 65), 267 (63), 252 (9), 210 (24), 196 (27), 135 (100), 120 (83), 77 (62); Anal. Calcd for $C_{15}H_{15}N_4O_2Cl$: C, 56.56; H, 4.74; N, 17.58. Found: C, 56.35; H, 4.68; N, 17.39.

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