

1, 3, 4-Oxadiazoles from functionalized *N*-acylbenzotriazoles and acyl hydrazides

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Dedicated to Prof. Oleg Kulinkovich on the occasion of his 60th birthday

Abstract

N-Acylbenzotriazoles **2** react with acyl hydrazides **1** to afford the corresponding 1, 3, 4-oxadiazoles **3** in 66-89% yield.

Keywords: *N*-Acylbenzotriazoles, acyl hydrazides, 1, 3, 4-oxadiazoles

Introduction

1,3,4-Oxadiazole moieties are privileged structures in medicinal chemistry, and are in widespread use as pharmacophores.¹⁻⁸ 1,3,4-Oxadiazoles are also important starting materials for cycloaddition reactions⁹ in the synthesis of furans and natural products.¹⁰ 1,3,4-Oxadiazoles were recently tested for their possible use in organic light-emitting diodes (OLED).¹¹⁻¹³ 1,3,4-Oxadiazoles are commonly prepared by the coupling of acylhydrazides with carboxylic acids followed by a dehydration step.^{4-8, 14-16} Such syntheses of 2,5-disubstituted 1,3,4-oxadiazoles usually proceed under mild conditions in good yield; but carboxylic acids in which the carboxylic group is conjugated with Π -functionality, such as a styryl, gave low yields of 1,3,4-oxadiazole.⁷ Moreover, when nucleophilic functionality, such as a phenol moiety, was incorporated in the acid partner, the corresponding 1,3,4-oxadiazoles could not be obtained.⁷

N-Acylbenzotriazoles are easily prepared activated derivatives of carboxylic acids.^{17,18} Recent applications include (i) *N*-acylation, (ii) *O*-acylation,^{19,20} (iii) *C*-acylations,²¹⁻²⁴ and syntheses of (iv) peptides,²⁵⁻³² (v) esters,³³ (vi) benzodioxin-4-ones,³⁴ (viii) ketones,^{35,36} and (xi) acyl azides.³⁷

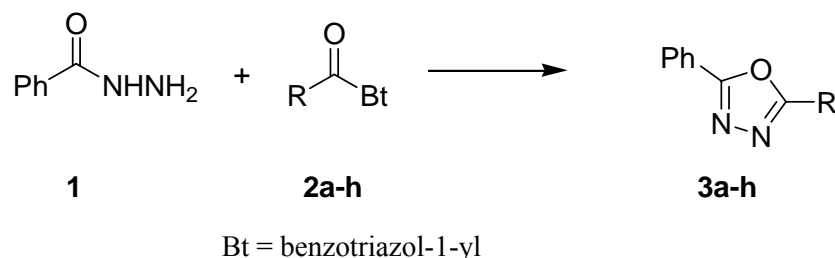
Herein, we report the efficient one pot synthesis of 1, 3, 4-oxadiazoles from *N*-acylbenzotriazoles and acyl hydrazides.

Results and Discussion

Reaction of (*E*)-1-benzotriazol-1-yl-3-phenylpropenone **2a** (0.5 mmol) with benzoic acid hydrazide (0.5 mmol) and sodium hydride (1 mmol) in dichloromethane at RT for 12 h followed by treatment with CBr₄ (1 mmol) and Ph₃P (1 mmol) at RT for 12 h gave 2-phenyl-5-((*E*)-styryl)-1,3,4-oxadiazole **3a** in 84% yield (lit.⁷ 23% yield). The ¹H NMR spectra of **3a** showed the disappearance of the benzotriazole signals in the aromatic region, indicating the loss of the benzotriazolyl group during the reaction. The ¹³C NMR spectra of **3a** showed two signals at 164.5 and 164.2 ppm corresponding to the two C=N groups of the product and the disappearance of the signal at 168.8 ppm belonging to the carbonyl group at the α position of the benzotriazolyl group in the starting material. We then explored reactions of benzoic acid hydrazide with a range of *N*-acylbenzotriazoles **2** to test the generality of this method. The results are shown in Table 1.

Reaction of heteroaryl-α,β-unsaturated acylbenzotriazoles such as (*E*)-1-benzotriazol-1-yl-3-thiophen-2-ylpropenone **2b** and (*E*)-1-benzotriazol-1-yl-3-furan-2-ylpropenone **2c** with benzoic acid hydrazide furnished novel 2-phenyl-5-((*E*)-2-thiophen-2-yl-vinyl)-1,3,4-oxadiazole **3b** and 2-((*E*)-2-furan-2-yl-vinyl)-5-phenyl-1,3,4-oxadiazole **3c** in 82% and 79% yields respectively. Similarly, reaction of 1-benzotriazol-1-yl-3-phenylpropynone **2d** and benzotriazol-1-yl-naphthalen-2-yl-methanone **2e** with benzoic acid hydrazide produced novel 2-phenyl-5-phenylethynyl-1,3,4-oxadiazole **3d** and 2-(5-phenyl-1,3,4-oxadiazol-2-yl)-naphthalen-1-ol **3e** in 73% and 76% yields respectively (Table 1).

Further reaction of hydroxyaryl acylbenzotriazoles including benzotriazol-1-yl-(2-hydroxy-3-methyl-phenyl)-methanone **2f**, 1*H*-benzotriazol-1-yl(1-hydroxy-2-naphthalenyl)-methanone **2g** and 1*H*-benzotriazol-1-yl(1-hydroxy-4-bromo-2-phenyl)methanone **2h** gave 2-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)-phenol hydrochloride **3f**, 2-(5-phenyl-1,3,4-oxadiazol-2-yl)-naphthalen-1-ol **3g** and novel 4-bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)-phenol **3h** in 86%, 66% and 89% yields respectively (Table 1). During the course of the present work, Wang and colleagues³⁹, prepared mono- and di-acylhydrazines by the reaction of hydrazine hydrate with acylbenzotriazoles; however, only symmetrical di-acylhydrazines were reported, no examples of unsymmetrical di-acylhydrazines are mentioned.



Scheme 1

Table 1. Reaction of *N*-acylbenzotriazoles **2a-h** with benzoic acid hydrazide **1**

Entry	Product	Product Structure	Yield ^a , %
1	3a		84 ^b
2	3b		82
3	3c		79
4	3d		73
5	3e		76
6	3f		86
7	3g		66
8	3h		89

^a Isolated yields after column purification and determined from a single experiment.

^b (lit.⁷ 23%).

Conclusions

A convenient route has been developed for the preparation of 1, 3, 4-oxadiazoles incorporating a π -functionality or a nucleophilic group in the side chain, most of which are not easily accessible by previous methods.

Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded in CDCl_3 with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz) unless otherwise stated. The elemental analyses were performed on a Carlo Erba EA-1108 instrument. Anhydrous THF was used freshly distilled from sodium/benzophenone. Column chromatography was conducted on silica gel 200-245 meshes.

Procedure for the synthesis of 1,3,4-oxadiazole 3

To a solution of (*E*)-1-benzotriazol-1-yl-3-phenyl-propenone (125 mg, 0.5 mmol) and benzoic acid hydrazide (68 mg, 0.5 mmol) in dichloromethane (5 mL) at RT was added sodium hydride (60% in mineral oil, 40 mg, 1 mmol). The coupling was allowed to proceed at RT for 12 h then CBr_4 (332 mg, 1 mmol) and Ph_3P (262 mg, 1 mmol) were added in one portion. The dehydration step was allowed to proceed at RT for 12 h and the reaction was poured onto a silica gel column for purification (silica gel, 10–15% EtOAc/hexanes) to afford 2-phenyl-5-((*E*)-styryl)-1,3,4-oxadiazole (104 mg, 84% yield) as a white solid.

2-Phenyl-5-((*E*)-styryl)-1,3,4-oxadiazole (3a). Yield 104 mg (84%); white microcrystals; m. p. 125–127 °C (lit.⁷ m. p. 128–130 °C); ^1H NMR (300 MHz, CDCl_3): δ = 8.14–8.12 (m, 2H), 7.64 (d, J = 16.9 Hz, 1H), 7.58–7.54 (m, 5H), 7.44–7.42 (m, 3H), 7.12 (d, J = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ = 164.5, 164.2, 139.1, 135.0, 132.0, 130.2, 129.3, 129.2, 127.7, 127.2, 124.0, 110.2.

2-Phenyl-5-((*E*)-2-thiophen-2-yl-vinyl)-1,3,4-oxadiazole (3b). Yield 104 mg (82%); yellow microcrystals; m. p. 110–114 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.13 (d, J = 1.8 Hz, 1H), 8.11 (d, J = 2.7 Hz, 1H), 7.75 (d, J = 16.2 Hz, 1H), 7.55–7.53 (m, 3H), 7.41 (d, J = 5.1 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.10 (dd, J = 5.1, 3.7 Hz, 1H), 6.91 (d, J = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ = 164.2, 164.2, 140.3, 132.0, 131.8, 130.0, 129.3, 128.4, 128.2, 127.2, 124.1, 109.1. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{OS}$: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.01; H, 3.85; N, 10.95.

2-((*E*)-2-Furan-2-yl-vinyl)-5-phenyl-1,3,4-oxadiazole (3c). Yield 94 mg (79%); white microcrystals; m. p. 115–117 °C (lit.³⁸ m. p. 118–119 °C); ^1H NMR (300 MHz, CDCl_3): δ = 8.11 (d, J = 1.8 Hz, 1H), 8.08 (d, J = 2.6 Hz, 1H), 7.54–7.47 (m, 4H), 7.39 (d, J = 16.2 Hz, 1H), 6.97

(d, $J = 16.2$ Hz, 1H), 6.62 (d, $J = 3.3$ Hz, 1H), 6.50 (dd, $J = 3.3, 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 164.4, 164.1, 155.2, 144.7, 131.9, 129.2, 127.1, 125.7, 124.0, 113.9, 112.5, 107.8$. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.36; H, 4.25; N, 11.81.

2-Phenyl-5-phenylethynyl-1,3,4-oxadiazole (3d). Yield 94 mg (73%); white microcrystals; m. p. 129–130 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 8.13\text{--}8.10$ (m, 2H), 7.68–7.65 (m, 2H), 7.60–7.40 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.1, 151.0, 132.6, 132.4, 130.9, 129.4, 128.9, 127.4, 123.6, 120.0, 97.4, 73.3$. Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}$: C, 78.03; H, 4.09; N, 11.38. Found: C, 77.75; H, 4.07; N, 11.28.

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)naphthalen-2-ol (3e). Yield 219 mg (76%); white microcrystals; m. p. 196–198 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 11.13$ (bs, 1H), 8.48 (d, $J = 7.7$ Hz, 1H), 8.18–8.16 (m, 2H), 7.84–7.80 (m, 2H), 7.63–7.56 (m, 5H), 7.47 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.1, 163.2, 156.2, 136.2, 132.2, 129.4, 129.3, 129.1, 127.8, 127.2, 127.1, 126.4, 124.9, 123.9, 123.6, 121.8, 120.1, 101.4$. Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.72; H, 4.00; N, 9.89.

2-Methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)phenol hydrochloride (3f). Yield 250 mg (86%); white microcrystals; m. p. 255–256 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 10.91$ (bs, 1H), 10.66 (bs, 1H), 7.97 (d, $J = 7.0$ Hz, 2H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.66–7.55 (m, 4H), 7.42 (d, $J = 7.1$ Hz, 1H), 6.89 (t, $J = 7.7$ Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 169.8, 165.7, 159.2, 135.1, 132.1, 132.0, 128.5, 127.4, 126.1, 124.5, 118.1, 111.9, 15.4$. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 63.86; H, 5.02; N, 9.89.

2-(5-Phenyl-1,3,4-oxadiazol-2-yl)naphthalen-1-ol (3g). Yield 190 mg (66%); pale green microcrystals; m. p. 196–198 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 11.13$ (bs, 1H), 8.48 (d, $J = 7.7$ Hz, 1H), 8.18–8.16 (m, 2H), 7.84–7.80 (m, 2H), 7.63–7.56 (m, 5H), 7.47 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.1, 163.2, 156.2, 136.2, 132.2, 129.4, 129.3, 129.1, 127.8, 127.2, 127.1, 126.4, 124.9, 123.9, 123.6, 121.8, 120.1, 101.4$. Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2\text{O}_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.72; H, 4.00; N, 9.89.

4-Bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenol (3h). Yield 282 mg (89%); off-white microcrystals; m. p. 146–148 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 10.15$ (bs, 1H), 8.08 (d, $J = 6.6$ Hz, 2H), 7.87 (d, $J = 2.2$ Hz, 1H), 7.57–7.44 (m, 4H), 6.98 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 163.6, 163.1, 156.7, 136.4, 132.5, 129.3, 128.7, 127.2, 123.0, 119.6, 111.7, 109.7$. Anal. Calcd for $\text{C}_{14}\text{H}_9\text{BrN}_2\text{O}_2$: C, 53.02; H, 2.86; N, 8.83. Found: C, 52.69; H, 2.79; N, 8.54.

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