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. 1,3,4-Oxadiazoles are also important starting materials for cycloaddition reactions 9 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-(5-phenyl-1,3,4-oxadiazol-2-yl)-naphthalen-1-ol 3e 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, 1H-benzotriazol-1-yl(1-hydroxy-2-naphthalenyl)-methanone 2g and 1H-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](image-url)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Product Structure</th>
<th>Yield(^a), %</th>
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<tr>
<td>1</td>
<td>3a</td>
<td>![Structure of 3a]</td>
<td>84(^b)</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>![Structure of 3b]</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>![Structure of 3c]</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>![Structure of 3d]</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
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<td>76</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>![Structure of 3f]</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>![Structure of 3g]</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>![Structure of 3h]</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\) 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 \(\pi\)-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 \(^1\)H (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 \((\mathcal{E})\)-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\(_3\)P (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-((\(\mathcal{E}\))-styryl)-1,3,4-oxadiazole (104 mg, 84% yield) as a white solid.

2-Phenyl-5-((\(\mathcal{E}\))-styryl)-1,3,4-oxadiazole (3a). Yield 104 mg (84%); white microcrystals; m. p. 125–127 °C (lit.\(^7\) m. p. 128–130 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.14–8.12\) (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\(_3\)): \(\delta = 164.5, 164.2, 139.1, 135.0, 132.0, 129.3, 129.2, 127.7, 127.2, 124.0, 110.2\).

2-Phenyl-5-((\(\mathcal{E}\))-2-thiophen-2-yl-vinyl)-1,3,4-oxadiazole (3b). Yield 104 mg (82%); yellow microcrystals; m. p. 110–114 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.13\) (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\(_3\)): \(\delta = 164.2, 164.2, 140.3, 132.0, 131.8, 130.0, 129.3, 128.4, 128.2, 127.2, 124.1, 109.1\). Anal. Calcd for C\(_{14}\)H\(_{10}\)N\(_2\)OS: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.01; H, 3.85; N, 10.95.

2-((\(\mathcal{E}\))-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); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.11\) (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 C$_{14}$H$_{10}$N$_2$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; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.13–8.10 (m, 2H), 7.68–7.65 (m, 2H), 7.60–7.40 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 165.1, 163.2, 156.2, 136.2, 132.2, 129.4, 128.5, 127.4, 126.4, 124.9, 123.9, 123.6, 121.8, 120.1, 101.4. Anal. Calcd for C$_{16}$H$_{10}$N$_2$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; $^1$H 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 C$_{18}$H$_{12}$N$_2$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; $^1$H 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), 7.63–7.55 (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 C$_{15}$H$_{13}$ClN$_2$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; $^1$H 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 C$_{18}$H$_{12}$N$_2$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; $^1$H 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 C$_{14}$H$_9$BrN$_2$O$_2$: C, 53.02; H, 2.86; N, 8.83. Found: C, 52.69; H, 2.79; N, 8.54.

Acknowledgements

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References and Notes