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 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]

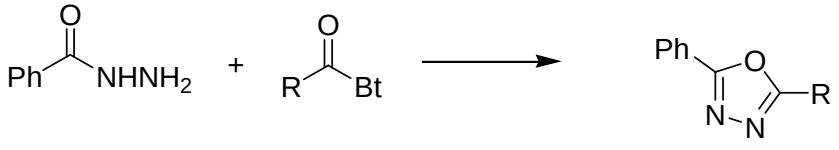
Herein, we report the efficient one pot synthesis of 1, 3, 4-oxadiazoles from *N*-acylbenzotriazoles and acyl hydrazides.

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 CBr_4 (1 mmol) and Ph_3P (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 ^{1}H 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 ^{13}C 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 colleagues[39], 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.

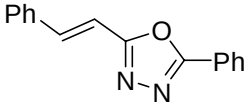
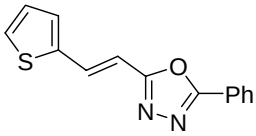
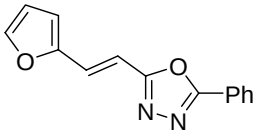
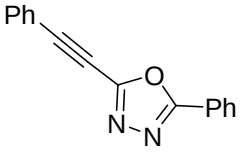
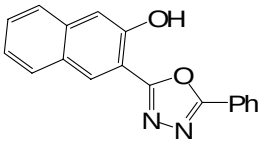
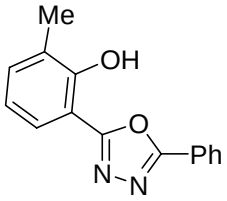
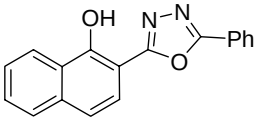
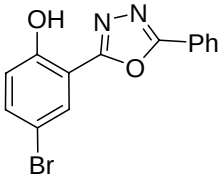


1 **2a-h** **3a-h**

Bt = benzotriazol-1-yl

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 $C_{14}H_{10}N_2OS$: 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* = 1.8Hz, 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, $CDCl_3$): δ = 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 $C_{14}H_{10}N_2O_2$: 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, $CDCl_3$): δ = 8.13–8.10 (m, 2H), 7.68–7.65 (m, 2H), 7.60–7.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 $C_{16}H_{10}N_2O$: 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{18}H_{12}N_2O_2$: 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{15}H_{13}ClN_2O_2$: 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{18}H_{12}N_2O_2$: 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{14}H_9BrN_2O_2$: C, 53.02; H, 2.86; N, 8.83. Found: C, 52.69; H, 2.79; N, 8.54.

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References and Notes

1. Hashem, A. I.; Youssef, A. S. A.; Kandeel, K. A.; Abou-Elmagd, W. S. I. *Eur. J. Med. Chem*. **2007**, *42*, 934.
2. Kuecuekguezel, S. G.; Kuecuekguezel, I.; Tatar, E.; Rollas, S.; Sahin, F.; Guelluece, M.; De Clercq, E.; Kabasakal, L. *Eur. J. Med. Chem*. **2007**, *42*, 893.
3. Kadi, A. A.; El-Brollosy, N. R.; Al-Deeb, O. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Eur. J. Med. Chem*. **2007**, *42*, 235.
4. Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem*. **2000**, *65*, 8210 and the references there in.
5. Cesarini, S.; Colombo, N.; Pulici, M.; Felder, E. R.; Brill, W. K.-D. *Tetrahedron* **2006**, *62*, 10223.
6. Kangani, C. O.; Kelley, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6497.
7. Rajapakse, H. A.; Zhu, H.; Young, M. B.; Mott, B. T. *Tetrahedron Lett.* **2006**, *47*, 4827.
8. Wang, Y.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 105.
9. Vasil'ev, N. V.; Romanov, D. V.; Bazhenov, A. A.; Lyssenko, K. A.; Zatonsky, G. V. *J. Fluorine Chem*. **2007**, *128*, 740.
10. Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361.
11. Wolarz, E.; Chrzumnicka, E.; Fischer, T.; Stumpe, J. *Dyes Pigments* **2007**, *75*, 753.
12. Qian, Y.; Lu, Z.; Lu, C.; Chen, Z.; Cui, Y. *Dyes Pigments* **2007**, *75*, 641.
13. Inoue, H.; Egawa, M.; Seo, S. U.S. Patent 2007085073. *Chem. Abstr*. **2007**, *146*, 402092.
14. Souldozi, A.; Ramazani, A. *Tetrahedron Lett*. **2007**, *48*, 1549.
15. Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Bahramnejad, M. *Synth. Commun*. **2007**, *37*, 1201.
16. Li, Z.; Xing, Y.; Ma, X.; Xiao, S.; Lu, Z. *Synth. Commun*. **2006**, *36*, 3287.
17. Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656.
18. Katritzky, A. R.; Meher, N. K.; Cai, C.; Singh, S. K. *Rev. Soc. Quim. Mex.* **2004**, *48*, 275.
19. Katritzky, A. R.; Angrish, P. *Steroids* **2006**, *71*, 660.
20. Katritzky, A. R.; Angrish, P. *Synthesis* **2006**, 4135.
21. Zou, X.; Wang, X.; Cheng, C.; Kong, L.; Mao, H. *Tetrahedron Lett*. **2006**, *47*, 3767.
22. Katritzky, A. R.; Jiang, R.; Suzuki, K. *J. Org. Chem*. **2005**, *70*, 4993.
23. Katritzky, A. R.; Meher, N. K.; Singh, S. K. *J. Org. Chem*. **2005**, *70*, 7792.
24. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Akhmedova, R. G. *Arkivoc* **2005**, (*vi)*, 329.
25. Katritzky, A. R.; Angrish, P.; Suzuki, K. *Synthesis* **2006**, 411.
26. Katritzky, A. R.; Todadze, E.; Cusido, J.; Angrish, P.; Shestopalov, A. A. *Chem. Biol. Drug Des*. **2006**, *68*, 37.
27. Katritzky, A. R.; Todadze, E.; Shestopalov, A. A.; Cusido, J.; Angrish, P. *Chem. Biol. Drug Des*. **2006**, *68*, 42.
28. Katritzky, A. R.; Meher, G.; Angrish, P. *Chem. Biol. Drug Des.* **2006**, *68*, 326.

29. Katritzky, A. R.; Tao, H.; Jiang, R.; Suzuki, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 407.
30. Katritzky, A. R.; Mohapatra, P. P.; Fedoseyenko, D.; Duncton, M.; Steel, P. J. *J. Org. Chem.* **2007**, *72*, 4268.
31. Katritzky, A. R.; Angrish, P.; Narindoshvili, T. *Biocon. Chem.* **2007**, *18*, 994.
32. Katritzky, A. R.; Todadze, E.; Angrish, P.; Draghici, B. *J. Org. Chem.* **2007**, *72*, 5794.
33. Katritzky, A. R.; Singh, S. K.; Cai, C.; Bobrov, S. *J. Org. Chem.* **2006**, *71*, 3364.
34. Katritzky, A. R.; Singh, S. K.; Akhmedova, R.; Cai, C.; Bobrov, S. *Arkivoc* **2007**, (*vi)*, 6.
35. Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem*. **2006**, *71*, 9861.
36. Katritzky, A. R.; Le, K. N. B.; Mohapatra, P. P. S*ynthesis* **2007**, 3141.
37. Katritzky, A. R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 5802.
38. Karakhanov, R. A.; Kelarev, V. I.; Koshelev, V. N.; Morozova, G. V.; Dibi, A. *Chem. Heterocycl. Compounds* **1995**, *31*, 208.
39. Wang, X.; Yu, H.; Xu, P.; Zheng, R. *J.Chem. Res.* **2005**, *9*, 595.