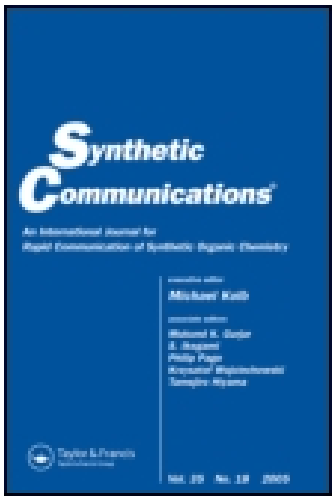

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A Preferred Synthesis of 1,2,4-Oxadiazoles

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A Preferred Synthesis of 1,2,4-Oxadiazoles

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ABSTRACT

An efficient and high-yielding one-pot synthesis of 1,2,4-oxadiazoles from carboxylic acids and amidoximes is described. Activation of the carboxylic acid using hydroxybenzotriazole (HOBt) and EDC/HCl followed by reaction with an amidoxime generates an oxime ester. Without isolation, the oxime ester is dehydrated to give the oxadiazole ring.

Key Words: 1,2,4-Oxadiazoles; Carboxylic acids; Hydroxybenzotriazole; High-yielding synthesis.

INTRODUCTION

Substituted 1,2,4-oxadiazoles are important pharmacophores found in pharmaceutical candidates, which are often used to replace ester or amide

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functions. Starting from acid (**I**), an efficient and high-yielding synthesis of 3-methyl-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole[1] suitable for large-scale production was required (Sch. 1). Several different approaches starting from the carboxylic acid and using a variety of peptide coupling reagents were explored. These methods included carbonyl activation using CDI,[2] DCC,[3] formation of an acid chloride,[4] or anhydride.[5] None of these approaches were applicable to large-scale synthesis, because, most were low yielding or required isolation by chromatography to afford product with acceptable purity. An optimized procedure was developed which involved activation of 4-(methylsulfonyl)phenylacetic acid using standard peptide coupling reagents EDC/HCl and hydroxybenzotriazole (HOBt)[6] followed by displacement with methylamidoxime.[7] Cyclization and dehydration took place upon heating, without the addition of other reagents. Compound **3** was produced on a 30 kg scale in 90% yield employing this method.

We report herein the results from our studies on the application of this procedure using these peptide-coupling reagents to form a wide range of oxadiazoles. A series of carboxylic acids (Table 1) was successfully activated using a combination of HOBt and EDC/HCl. Displacement of HOBt from the ester intermediate by methylamidoxime or commercially available 4-fluorobenzamidoxime occurred readily at room temperature in acetonitrile. It was critical to ensure that the active ester formation was complete before addition of the amidoxime. Low conversion of the starting carboxylic acid was observed when all the reagents were charged at once, possibly due to the reaction of the amidoxime with EDC/HCl. Other peptide coupling reagents such as 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) were not effective even when used in excess (greater than 2 equiv.), and generated impurities due to side reactions.

The *Z*-isomer of the *O*-acylated intermediate **II** was isolated for structural confirmation by NMR, and was found to be consistent with previously reported structures.[3,4] Cyclodehydration of **II** to form the oxadiazole occurred on heating. In some cases, water removal was necessary to avoid the competing hydrolysis of the oxime ester which regenerates the starting carboxylic acid. On laboratory scale, water removal was accomplished by heating to reflux and returning the condensate through a bed of molecular sieves which were contained in an addition funnel.[a] Aromatic compounds containing an electron donating group para to the carboxylic acid were more sensitive to hydrolysis compared to those containing an electron withdrawing group such as cyano. The compounds containing an electron donating group

[a]A Soxhlet apparatus was not as efficient in water removal.

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Scheme 1.

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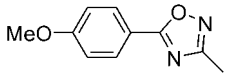
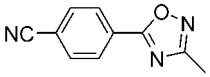
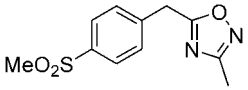
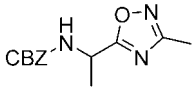
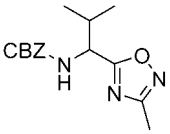
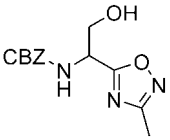
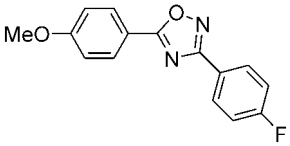
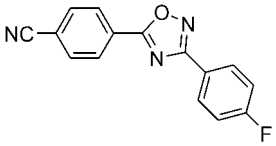
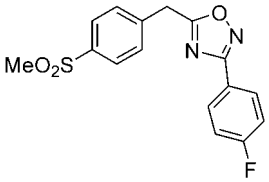
Table 1. Yields of 1,2,4-oxadiazoles.

Entry	Oxadiazole	Method[a]	Isolated yield (%)	Lit. yield (%)
1		A	70	68,[8] 53[2]
2		B	88	60[2]
3		A	90	—
4		B	76	—
5		B	70	—
6		B	69	—
7		A	60	51[2]
8		B	93	63[2]
9		A	78	—

(*continued*)

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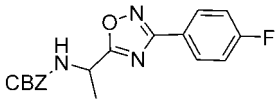
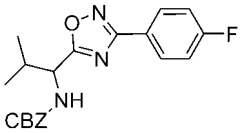
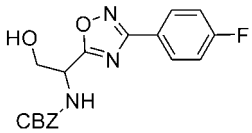
Table 1. Continued.

Entry	Oxadiazole	Method[a]	Isolated yield (%)	Lit. yield (%)
10		B	93	—
11		B	76	—
12		B	73	—

[a]*Method A:* In acetonitrile, the mixture was heated to reflux and the condensate dried over a bed of sieves. *Method B:* Reaction mixture was solvent switched from acetonitrile to diethoxyethane after formation of the oxime ester.

also required a longer reaction time for cyclization, thus, making the uncyclized intermediate available for hydrolysis in the presence of water generated during cyclization. In such cases, we found that switching the solvent from acetonitrile to a higher boiling solvent such as diethoxyethane or toluene compensated for this rate decrease. The poor solubility of EDC/HCl in diethoxyethane and toluene precluded the use of these solvents in the initial stage of the reaction, because, a gummy material formed in the mixture so that reaction in these solvents was not conducive to scale-up. Therefore, the formation of the oxime ester was carried out in acetonitrile and then the reaction solvent was switched to toluene or diethoxyethane. For those substrates containing an electron withdrawing group, the entire reaction sequence was carried out in acetonitrile and the cyclization went to completion cleanly and in high yield (Table 1).

Excellent stereochemical retention was also demonstrated starting from an amino acid with this method. When the oxadiazole was formed from CBZ-L-serine and methylamidoxime, the product was obtained in $>95\%$ ee. In the case of CBZ-L-serine and 4-fluorobenzamidoxime, there was complete retention of stereochemistry.

In conclusion, this communication describes an optimized, high-yielding synthesis of 1,2,4-oxadiazoles. The process is easily scalable, as was demonstrated on 30 kg and is suitable for use in preparation of a wide variety of substrates.

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EXPERIMENTAL

Overall yields were determined by evaporation to dryness and were corrected based on quantitative assay by HPLC against a standard of known purity. Yields were reproducible and structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, HPLC and elemental analysis. NMR spectra were recorded on a Bruker DPX 400.

Typical Procedures

Method A: A carboxylic acid (20 mmol) and HOBt (24 mmol) are slurried in dry acetonitrile (50 mL). Addition of EDC/HCl (23 mmol) to this mixture at room temperature generates the HOBt ester. Methylamidoxime or 4-fluorobenzamidoxime is added and the mixture is heated to reflux. The condensate is returned through a bed of molecular sieves, which are contained in an addition funnel. After concentration of the reaction mixture, the oxadiazole is isolated by partitioning with ethyl acetate and aqueous bicarbonate solution. Concentration of the separated organics is followed by crystallization of the oxadiazole from isopropanol or isopropanol/hexane.

Method B: Ester formation as above. In cases where hydrolysis of the HOBt ester occurs readily, the reaction mixture solvent is switched at this point from acetonitrile to a higher boiling solvent such as diethoxyethane and the resulting solution is heated to reflux. When using this procedure, the reaction goes to completion in 4–6 hr without the use of sieves to remove water. The reaction workup is the same as above.

3-Methyl-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole (3). ^{1}H-NMR ($CDCl_3$) δ 7.90 (m, 2H), 7.52 (m, 2H), 4.27 (s, 2H), 3.02 (s, 3H), 2.35 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 176.3, 167.4, 139.9, 139.6, 129.9, 127.9, 44.4, 32.6, 11.4. Analytical Calculated: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.34; H, 4.69; N, 11.00; mp 90–91°C (dec).

Benzyl[1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]carbamate (4). ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.56 (d, $J = 6.4$, 1H), 5.13 (m, 3H), 2.37 (s, 3H), 1.57 (d, $J = 7.2$, 3H); ^{13}C-NMR ($CDCl_3$) δ 179.5, 167.2, 155.5, 136.1, 128.6, 128.3, 128.2, 67.3, 44.6, 19.9, 11.5. Analytical Calculated: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.64; H, 5.83; N, 16.25.

Benzyl[2-methyl-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]carbamate (5). ^{1}H-NMR ($CDCl_3$) δ 7.36 (m, 5H), 5.47 (d, $J = 9.2$, 1H), 5.15, 5.11 (AB quartet, $J = 12.2$, 2H), 4.97 (dd, $J = 9.2$, $J = 5.9$, 1H), 2.39 (s, 3H), 2.25 (m, 1H), 0.96 (d, $J = 7.2$, 6H); ^{13}C-NMR ($CDCl_3$) δ 178.4, 167.0, 155.9, 136.0, 128.5, 128.3, 128.2, 67.3, 54.0, 32.5, 18.6, 17.8, 11.5. Analytical Calculated: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.57; H, 6.63; N, 14.35; mp.

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Benzyl[2-hydroxy-1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl]carbamate (6). ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H), 6.05 (d, $J = 8.6$, 1H), 5.12 (m, 3H), 4.06 (dd, $J = 11.3$, 3.1, 1H), 3.95 (dd, $J = 11.3$, 4.0, 1H), 2.97 (br s, 1H), 2.36 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 177.1, 167.1, 156.0, 135.8, 128.6, 128.3, 128.2, 67.5, 63.2, 50.5, 11.4. Analytical Calculated: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.44; H, 5.33; N, 15.05; mp 116–117°C (dec).

3-(4-Fluorophenyl)-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole (9). ^{1}H-NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.97 (m, 2H), 7.45 (m, 2H), 7.18 (m, 2H), 4.40 (s, 2H), 3.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 176.8, 167.8, 164.6 (d, $J = 251.7$), 140.1, 139.6, 130.1, 129.6 (d, $J = 8.8$), 128.1, 122.7 (d, $J = 3.1$), 116.1 (d, $J = 22.0$), 44.5, 32.8. Analytical Calculated: C, 57.82; H, 3.94; N, 8.43. Found: C, 57.87, H, 3.80, N, 8.46; mp 129–130°C (dec).

Benzyl{1-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate (10). ^{1}H-NMR ($CDCl_3$) δ 8.07 (m, 5H), 7.38 (m, 2H), 7.17 (m, 2H), 5.51 (d, $J = 7.4$, 1H), 5.24 (m, 1H), 5.17, 5.15 (AB quartet, $J = 12.5$, 2H), 1.66 (d, $J = 7.2$, 3H); ^{13}C-NMR ($CDCl_3$) δ 179.8, 167.6, 164.7 (d, $J = 251.8$), 155.5, 136.0, 129.8 (d, $J = 8.8$), 128.7, 128.4, 128.3, 122.8 (d, $J = 3.2$), 116.1 (d, $J = 21.7$), 67.4, 44.8, 20.1. Analytical Calculated: C, 63.34; H, 4.72; N, 12.31. Found: C, 63.30; H, 4.58; N, 12.30; mp 110–111°C (dec).

Benzyl{1-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-2-methylpropyl} carbamate (11). ^{1}H-NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.38 (m, 5H), 7.17 (m, 2H), 5.47 (d, $J = 8.9$, 1H), 5.17, 5.15 (AB quartet, $J = 12.5$, 2H), 5.07 (dd, $J = 8.9$, 5.85, 1H), 2.32 (m, 1H), 1.01 (d, $J = 6.8$, 6H); ^{13}C-NMR ($CDCl_3$) δ 178.8, 167.4, 164.7 (d, $J = 251.8$), 156.0, 136.1, 129.8 (d, $J = 8.7$), 128.7, 128.4, 128.3, 122.9 (d, $J = 3.2$), 116.1 (d, $J = 22.0$), 67.5, 54.3, 32.7, 18.7, 17.9. Analytical Calculated: C, 65.03; H, 5.46; N, 11.38. Found: C, 64.90; H, 5.19; N, 11.29; mp 82–84°C (dec).

Benzyl{1-[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]-2-hydroxyethyl} carbamate (12). ^{1}H-NMR ($CDCl_3$) δ 8.04 (m, 2H), 7.36 (m, 5H), 7.15 (m, 2H), 6.0 (d, $J = 8.8$, 1H), 5.23 (m, 1H), 5.16 (s, 2H), 4.17 (dd, $J = 11.2$, 2.8, 1H), 4.05 (dd, $J = 11.2$, 3.6, 1H), 2.59 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 177.4, 167.5, 164.7 (d, $J = 252.2$), 155.9, 135.8, 129.7 (d, $J = 8.8$), 128.6, 128.4, 128.2, 122.4 (d, $J = 3.2$), 116.1 (d, $J = 22.3$), 67.6, 63.4, 50.6. Analytical Calculated: C, 60.50; H, 4.51; N, 11.76. Found: C, 60.55; H, 4.31; N, 11.77; mp 104–105°C (dec).

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