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Rapid Multistep Synthesis of 1,2,4-Oxadiazoles in a Single Continuous Microreactor Sequence

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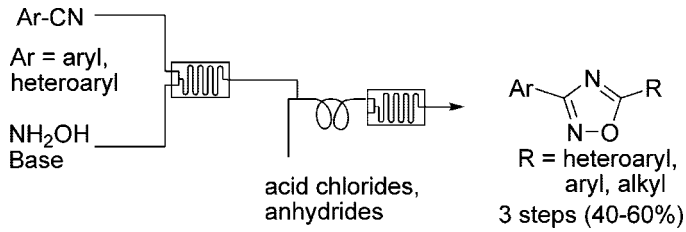

A general method for the synthesis of bis-substituted 1,2,4-oxadiazoles from readily available arylnitriles and activated carbonyls in a single continuous microreactor sequence is described. The synthesis incorporates three sequential microreactors to produce 1,2,4-oxadiazoles in ~30 min in quantities (40−80 mg) sufficient for full characterization and rapid library supply.

Introduction

There is a continual need for the development of new technologies that enable the rapid and efficient construction of biologically interesting small molecules.[1] The application of automated methods to the synthesis of focused libraries[2] to populate screening collections is an important field of research, particularly for the biopharmaceutical sector and increasingly for the academic community.[3] Reports on the use of microreactors (microfluidic chips) as an alternative to "in flask" chemistry have recently started to appear in the scientific literature.[4−7] Microreactors afford efficient mixing and precise temperature control,[8] allowing the development of useful variations of traditionally low temperature reactions such as the Swern oxidation[9] and oligosaccharide couplings,[10] both of which can be performed at ambient temperature in a microreactor. Furthermore, the size of the microreactor also allows the chemist to more easily achieve forcing conditions (high temperature and pressure), analogous to sealed tube reactions but without the dangers and difficulties inherently associated with this type of chemistry.

Although examples of multistep organic transformations using flow methods have been reported,[11] these sequences involve reagent packed columns[12,13] or are broken into segments involving workup and purification.[14,15] While introduction of reagents to a flow reaction via solid support in a packed column allows for clean reactions without incorporation of byproduct into the reaction stream, or involving changes in concentration, it introduces the problem of having to renew, replace, or repack the reagent columns as they are consumed. Recently, we have become interested in the use of microreactors for the rapid synthesis of focused libraries via combinations of multiple organic transformations into single unbroken microreactor sequences. This strategy maximizes the speed and efficiency of synthesis by eliminating the need for handling of the

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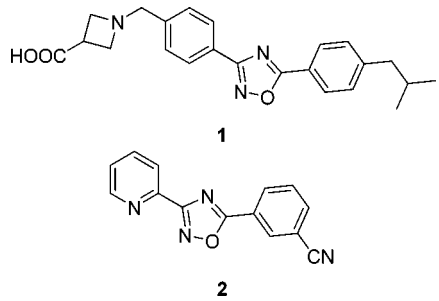
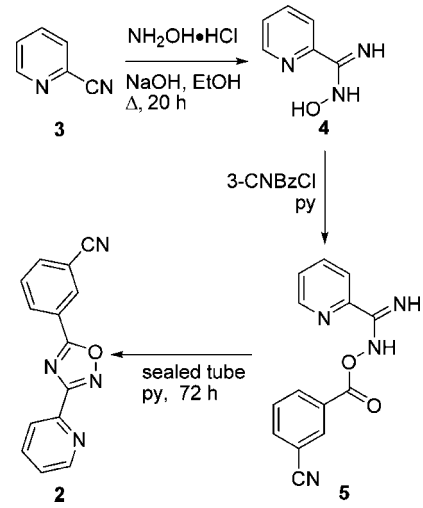


FIGURE 1. Biologically active bis-substituted oxadiazoles.

intermediates by a chemist. Once a sequence has been developed, the synthesis is simply a matter of preparing starting material solutions and introducing them to the system. Ultimately, the use of this strategy to prepare compounds whose traditional syntheses involve long reaction times and forcing conditions will greatly facilitate the population of previously sparsely populated chemical space.[16]

The 1,2,4-oxadiazole scaffold is a class of heterocycle commonly found in biologically active molecules. This motif is often used as an amide or ester bioisostere[17,18] and is found in several drugs and drug leads[19] including the potent S1P1 agonist **1**[20] (Figure 1) and the metabotropic glutamate subtype 5 (mGlu5) receptor antagonist **2**.[21,22] The synthesis of oxadiazoles has typically been carried out by reacting arylnitriles with hydroxylamine to give the amidoxime in moderate yields (Scheme 1).[21−23] Cyclization of the *O*-acyl amidoxime formed from reaction of the amidoxime with an acyl chloride is generally the most difficult and time-consuming step and often requires sealed tube conditions and long reaction times. In an attempt to improve on these procedures, microwave-assisted methods for this cyclization have recently been reported.[24−26] Herein we report the rapid synthesis of bis-substituted 1,2,4-oxadiazoles from arylnitriles in a single, unbroken microreactor sequence, utilizing three microreactors, two of which involve superheating of the solvent. In this way, we have shortened a multiday, multistep sequence to a highly efficient procedure lasting less than 30 min.[27]

SCHEME 1. "In Flask" Synthesis of 2[22]

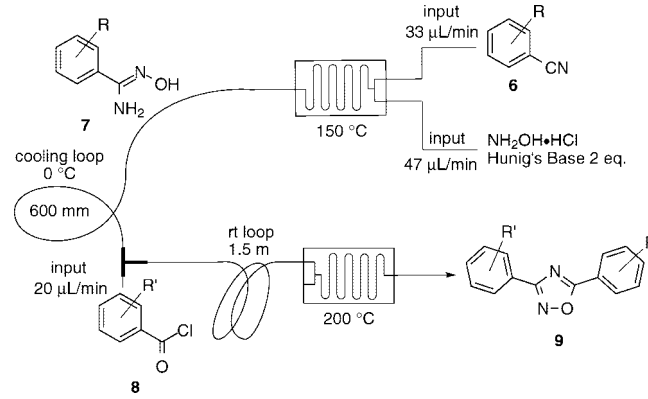


Results and Discussion

One of the chief concerns in any microfluidic experiment is the formation of solid in the microreactor. This problem can be exacerbated by the need to use relatively concentrated reagent streams essential for efficiency, especially when several solutions are combined over a multistep sequence. For these reasons, as well as its high boiling point, DMF was selected as the solvent for our initial studies. The arylnitriles may be introduced into the system in concentrations of up to 1.0 M, although 0.5 M solutions provided more uniform solubility of the arylnitriles used in these experiments. However, the $NH_2OH \cdot HCl$/Hunig's base solution cannot exceed a concentration greater than 0.4 M because of solubility issues. In initial experiments, LCMS analysis showed that the conversion of nitriles to the corresponding amidoximes was complete after only 6 min at 150 °C. Similarly, the dehydrative cyclization of the *O*-acyl amidoxime goes to completion in 10 min in a microreactor at 200 °C and 7.5−9.0 bar in DMF.

The integration of both of these reactions into a continuous sequence proved challenging. Interestingly, the condensation of the amidoxime with the acid chloride proved to be the most problematic step. The stream containing the amidoxime, exiting the first microreactor,[28] was combined with a solution of acid

SCHEME 2. Continuous Microfluidic Sequence for the Synthesis of 1,2,4-Oxadiazoles



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(27) All microfluidic experiments were performed using a Syrris AFRICA microfluidic apparatus.

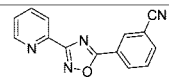
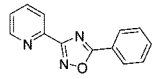
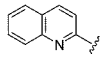
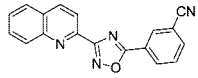
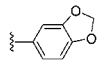
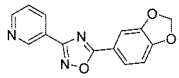
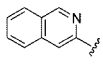
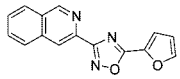
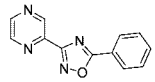
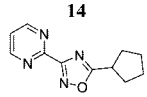
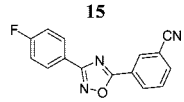
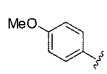
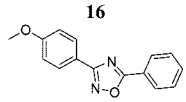
(28) It should be noted that while the conversion of nitrile to the amidoxime requires only 6 min, in the continuous system the time of the reaction mixture on the final 200 °C chip dictates the flow rates for the entire system; thus, the reaction mixture remains on the first chip for 12 min.

TABLE 1. Optimization of Molar Ratios for the Synthesis of 2 in a Continuous Microreactor Sequence

entry	2-CNPy:NH_2OH/Hunig's base[a]:3-CNBzCl	yield[b] (%)
1	1:1:1	45
2	1:1.2:1.2	45
3	1:1.5:1.5	21
4	1:1:1.5	11
5	1:2:2	32

[a] 3:1 molar ratio of $NH_2OH \cdot HCl$ to Hunig's base. [b] Yield determined by LCMS using an internal standard (chlorpromazine) added to the arylnitrile reactant solution.

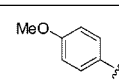
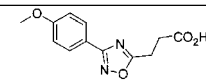
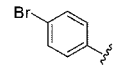
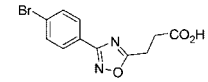
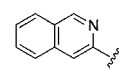
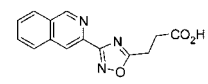
TABLE 2. Synthesis of Bis-Substituted 1,2,4-Oxadiazoles via a Continuous Microreactor Sequence from Arylnitriles and Acyl Chlorides

entry	ArCN	RCOCl	product	yield[a] (%)
1			 **2**	45
2			 **10**	45
3			 **11**	63
4			 **12**	47
5			 **13**	51
6			 **14**	45
7			 **15**	57
8			 **16**	63
9			 **17**	40

[a] Isolated yield of pure product after purification of crude reaction mixture using preparative HPLC.

chloride (1.0 M) in a T-fitting before the combined streams entered the microreactor at 200 °C (Scheme 2). After initial attempts proved unsuccessful, subsequent experimentation showed that the stream exiting the first microreactor must be cooled before meeting the acyl chloride stream. This was accomplished by insertion of a 600 mm loop of capillary which

TABLE 3. Microfluidic Synthesis of 3-(1,2,4-Oxadiazol-5-yl)propanoic Acids from Arylnitriles and Succinic Anhydride

entry	ArCN	product	yield[a] (%)
1		 **18**	46
2		 **19**	45
3		 **20**	62

[a] Isolated yield of pure product after purification of crude reaction mixture using preparative HPLC.

was submerged in an ice bath before the T-fitting. It was also imperative that the combined streams be allowed to react at room temperature for at least 2 min before entering the final microreactor at 200 °C. For this purpose, a 1500 mm coil of 0.05 mm PTFE capillary tubing was placed between the T-fitting and the final microreactor. This coil holds a volume of 250 μL and essentially acts as a room temperature microreactor. The final optimized microreactor sequence is shown in Scheme 2 and consists of three microreactors at three different temperatures in addition to a cooling loop.

In order to optimize the molar ratio of reactants, experiments were performed to compare the effects of various molar ratios on yield (Table 1). We found that there was no benefit to increasing the molar equivalents of hydroxylamine/Hunig's base or acid chloride in relation to arylnitrile. However, for the final synthetic procedure we selected a ratio of 1:1.2:1.2 to offset the loss of reagent by decomposition in the reactant reservoir. Under these conditons, the isolated yield of the entire sequence (45%) is comparable to the reported "in flask" yield[22] and corresponds to an average yield of 76% per step. A typical 35 min run involves the collection of 3.5 mL of reaction mixture, i.e., 0.5 mmol of product. Upon isolation by HPLC, this provides 40−80 mg of purifed product depending on yield and formula weight. The generality of this sequence was demonstrated by the synthesis of a number of bis-substituted 1,2,4-oxadiazoles (Table 2). The isolated yields over the multistep synthesis ranged from 40% to 63% and the conditions were applicable to a variety of scaffolds. For example, heteroaryl and arylnitriles, both electron deficient and electron rich, reacted with aroyl, heteroaroyl, or alkanoyl chlorides to form the corresponding oxadiazole.

The same microfluidic sequence also proved applicable to the preparation of 3-(3-aryl-1,2,4-oxadiazol-5-yl)propanoic acids. In this case succinic anhydride was used in place of the acyl chloride reagent (Table 3). The reaction proceeded under similar conditions, although DMA was used as a solvent in place of DMF, due to competitive formation of the dimethyl amide.

Ostensibly, this was the result of the slight decomposition of DMF at high temperature.

Conclusion

We have described the rapid and efficient synthesis of 1,2,4-oxadiazoles in a continuous microreactor sequence. In this way, a multiday, multistep preparative procedure has been shortened to a matter of minutes, demonstrating proof-of-concept for the rapid synthesis of focused libraries of small molecule heterocycles based on this scaffold.

Experimental Section

General Procedure for Synthesis of 1,2,4-Oxadiazoles in a Continuous Microfluidic System. Streams of the arylnitrile (32.5 μL/min, 0.5 M, DMF) and a solution of $NH_2OH \cdot HCl$ (0.4 M, DMF) and diisopropylethylamine (1.2 M, DMF) (47.5 μL/min) were combined in a 1000 μL chip at 150 °C. The reaction mixture was then cooled by flowing through 60 mm of capillary submerged in an ice bath before meeting the electrophile (20.0 μL/min, 1.0 M, DMF) in a simple T-fitting. Following the T-fitting, the reaction mixture flowed through 1500 mm of capillary before entering the final 1000 μL chip at 200 °C. The stream exiting the chip was collected after passing though the back pressure regulator. This sequence was carried out with the back pressure maintained between 7.5 and 8.5 bar. The reaction mixture was then evaporated to remove the solvent before being dissolved in 1.5 mL of DMF and purified by preparative HPLC. Note: Due to conversion of product carboxylic acids (**11**, **12**, and **13**) to the corresponding dimethylamides ostensibly from byproduct of DMF decomposition at high temperature, reactions in which succinic anhydride is used as electrophile were carried out in DMA.

5-(3-Cyanophenyl)-3-(pyridin-2-yl)-1,2,4-oxadiazole (2).[21,22] A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (54 mg, 45%). Mp: 148−149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, J = 4.8, 7.8 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.92−8.00 (m, 2H), 8.27 (d, J = 8.4 Hz, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.61 (s, 1H), 8.90 (dd, J = 0.9, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.2, 117.6, 123.8, 125.5, 126.3, 130.5, 132.0, 132.4, 136.2, 138.0, 145.8, 150.5, 169.0, 174.7. LRMS (ESI): m/z calcd for $C_{14}H_8N_4O$ $(M + H)^+$ 249.08, found 248.95.

5-Phenyl-3-(pyridin-2-yl)-1,2,4-oxadiazole (10).[29−31] A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (48 mg, 45%). Mp: 128−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (ddd, J = 1.4, 4.8, 7.8 Hz, 1H), 7.56−7.65 (m, 3H), 7.91 (dt, J = 2.0, 7.8 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 6.8 Hz, 2H), 8.87 (d, J = 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 176.8, 169.0, 150.7, 146.7, 137.3, 133.2, 129.4, 128.6, 125.8, 124.3, 123.5. HRMS (ESI): m/z calcd for $C_{13}H_9N_3O$ $(M + H)^+$ 224.0818, found 224.0821.

5-(3-Cyanophenyl)-3-(quinolin-2-yl)-1,2,4-oxadiazole (11).[22] A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (90 mg, 63%). Mp: 153 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (t, J = 7.2 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 7.85 (t, J = 7.2 Hz, 1H), 7.95 (d, J = 7.8 Hz, 2H), 8.33 (d, J = 8.7 Hz, 1H), 8.39−8.43 (m, 2H), 8.58 (d, J = 7.8, 1H), 8.66 (s, 1H). NMR (75 MHz, $CDCl_3$): δ 114.2, 117.7, 120.4, 125.5, 127.9, 128.5, 129.2, 130.5, 130.6, 130.8, 132.2, 132.5, 136.2, 137.9, 146.0, 148.3, 169.5, 174.9. LRMS (ESI): m/z calcd for $C_{18}H_{10}N_4O$ $(M + H)^+$ 299.09, found 298.95.

5-Piperonyl-3-(pyridin-3′-yl)-1,2,4-oxadiazole (12). A sample of the reaction mixture (2.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (40 mg, 47%). Mp: 192−195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.14 (s, 2H), 7.01 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 4.8, 7.8 Hz, 1H), 7.67 (dd, J = 2.8, 8.4 Hz, 1H), 8.55 (dt, J = 3.0, 7.8 Hz), 8.83 (dd, J = 2.5, 5.4 Hz, 1H), 9.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.4, 108.3, 109.3, 117.9, 124.3, 124.4, 136.1, 147.8, 148.7, 150.9, 152.1, 166.7, 175.3. HRMS (ESI): m/z calcd for $C_{14}H_9N_3O_3$ $(M + H)^+$ 268.0717, found 268.0720.

5-(Furan-2-yl)-3-(isoquinolin-3-yl)-1,2,4-oxadiazole (13). A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (64 mg, 51%). Mp: 178−180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (dd, J = 1.5, 3.3 Hz, 1H), 7.49 (dd J = 1.2, 3.3 Hz, 1H), 7.71−7.84 (m, 3H), 7.99 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 9.43 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 112.9, 117.3, 121.4, 127.8, 128.1, 129.2, 129.7, 131.5, 136.0, 140.0, 140.4, 147.1, 153.6, 168.2, 169.1. HRMS (ESI): m/z calcd for $C_{15}H_9N_3O_2$ $(M + H)^+$ 264.0767, found 264.0773.

5-Phenyl-3-(pyrazin-2-yl)-1,2,4-oxadiazole (14).[32] A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (48 mg, 45%). Mp: 143−145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54−7.67 (m, 3H), 8.28 (d, J = 7.8 Hz, 2H), 8.76 (d, J = 2.5 Hz, 1H), 8.80 (s, 1H), 8.46 (d, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 123.9, 128.6, 129.5, 133.5, 142.7, 144.7, 145.1, 146.7, 167.3, 177.1. HRMS (ESI): m/z calcd for $C_{12}H_8N_4O$ $(M + H)^+$ 225.0771, found 225.0770.

5-Cyclopentyl-3-(pyrimidin-2-yl)-1,2,4-oxadiazole (15). A sample of the reaction mixture (2.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a colorless crystal (45 mg, 57%). Mp: 67−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72−1.89 (m, 2H), 2.06−2.23 (m, 2H), 3.48 (p, J = 8.1 Hz, 1H), 7.47 (t, J = 4.8 Hz, 1H), 8.98 (d, J = 4.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 31.8, 37.4, 122.3, 156.5, 158.2, 167.7, 185.4. HRMS (ESI): m/z calcd for $C_{11}H_{12}N_4O$ $(M + H)^+$ 217.1084, found 217.1085.

5-(3-Cyanophenyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (16). A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (80 mg, 63%). Mp: 197−198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−7.27 (m, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.93 (dt, J = 1.0, 7.8 Hz, 1H), 8.18−8.23 (m, 2H), 8.46 (dt, J = 1.0, 7.5 Hz, 1H), 8.55 (t, J = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 114.1, 116.3, 116.6, 117.7, 122.87, 122.90, 125.8, 130.0, 130.1, 130.5, 131.9, 132.2, 136.0, 163.4, 166.7, 168.7, 174.0. HRMS (ESI): m/z calcd for $C_{15}H_8FN_3O$ $(M + H)^+$ 266.0724, found 266.0719.

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (17).[33] A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (46 mg, 40%). Mp: 98−99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.55−7.64 (m, 3H), 8.15 (d, J = 9.0 Hz, 2H), 8.25 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7, 114.5, 119.7, 124.7, 128.4, 129.3, 129.4, 132.9, 162.2, 168.9, 175.7. LRMS (ESI): m/z calcd for $C_{15}H_{12}N_2O_2$ $(M + H)^+$ 253.1, found 252.95.

3-(3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)propanoic Acid (18). A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a colorless crystal (54 mg, 46%). Mp: 135−137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.04 (t, J = 7.2 Hz, 2H), 3.28 (t, J

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= 7.2 Hz, 2H), 3.90 (s, 3H), 7.01 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.0, 29.0, 55.6, 114.5, 119.3, 129.3, 162.2, 168.2, 176.5, 178.0. HRMS (ESI): m/z calcd for $C_{12}H_{12}N_2O_4$ $(M + H)^+$ 249.0870, found 249.0972.

3-(3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)propanoic Acid (19). A sample of the reaction mixture (3.0 mL) was collected, and this was purified using preparative HPLC, carried out on only 2.5 mL of the reaction mixture due to solubility issues, to provide the title compound as a colorless crystal (48 mg, 45%). Mp: 156−157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 3.03 (d, J = 7.5 Hz, 2H), 3.28 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, DMSO): 27.2, 35.3, 130.5, 130.9, 134.4, 137.8, 172.2, 178.2,185.5. HRMS (ESI): m/z calcd for $C_{11}H_9BrN_2O_3$ $(M + H)^+$ 296.9869, found 296.9873.

3-(3-(Isoquinol-3-yl)-1,2,4-oxadiazol-5-yl)propanoic Acid (20). A sample of the reaction mixture (3.5 mL) was collected, and this was purified using preparative HPLC to provide the title compound as a white solid (93 mg, 62%). Mp: 210 °C dec. ^{1}H NMR (300 MHz, DMSO): 2.89 (t, J = 6.9 Hz, 2H), 3.24 (t, J = 6.9 Hz, 2H), 7.82 (t, J = 8.1 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 8.21 (d, J = 8.7 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.59 (s, 1H), 9.46 (s, 1H). ^{13}C NMR (75 MHz, DMSO): 27.2, 35.3, 126.2, 133.1, 133.3, 134.3, 134.7, 137.0, 140.6, 145.0, 158.8, 173.3, 178.3, 185.2. HRMS (ESI): m/z calcd for $C_{14}H_{11}N_3O_3$ $(M + H)^+$ 270.0873, found 270.0875.

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Supporting Information Available: Additional experimental procedures; ^{1}H and ^{13}C NMR spectra of oxadiazoles **2** and **10**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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