Efficient Synthesis of Trisubstituted Pyrazoles and Isoxazoles Using a Traceless "Catch and Release" Solid-Phase Strategy

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An efficient three-component, two-step "catch and release" solid-phase synthesis of 3,4,5-trisubstituted pyrazoles and isoxazoles has been developed. The first step involves a base-promoted condensation of a 2-sulfonyl- or a 2-carbonyl-acetonitrile derivative (**1** or **7**) with an isothiocyanate **2** and in situ immobilization of the resulting thiolate anion on Merrifield resin. Reaction of the resin-bound sulfonyl intermediate **4** with hydrazine or hydroxylamine, followed by release from the resin and intramolecular cyclization, affords 3,5-diamino-4-(arylsulfonyl)-1*H*-pyrazoles **5** or isoxazoles **6**, respectively. Reaction of the resin-bound carbonyl intermediate **9** with hydrazine, on the other hand, leads to 3-(arylamino)-5-aryl-1*H*-pyrazole-4-carbonitriles **10**.

Introduction

Solid-phase parallel synthesis (SPPS) has become an essential tool in drug discovery not only for producing focused libraries of drug-like molecules for biological screening but also for optimizing the potency, selectivity, metabolic stability, and physicochemical properties of lead compounds.[1] Given the prevalence of heterocyclic scaffolds in biologically active molecules, it is not surprising that there is a continuing interest in developing novel solid-phase parallel syntheses of diversely substituted heterocycles. We report here the successful development of a three-component, two-step "catch and release" solid-phase strategy for the preparation of 3,4,5-trisubstituted pyrazoles and isoxazoles.

The standard approach to preparing pyrazoles involves the condensation of a 1,3-dicarbonyl compound or its synthetic equivalent with hydrazine.[2] Several solid-phase methods have been reported in the literature;[3] however, in most of them, the starting material is anchored to the resin via a functional group that remains in the product once this is released into solution. A limitation of this approach is that all compounds in the library end up having the same substituent, whether it is desirable or not. To circumvent this problem, we investigated an alternative route for synthesizing 3,4,5-trisubstituted pyrazoles involving a traceless cleavage from the solid support.

Ketene dithioacetals are useful intermediates for the preparation of a large number of heterocyclic scaffolds.[4] These compounds undergo nucleophilic displacement of one of the alkylthio groups by various nucleophiles and subsequent cyclization of the resulting intermediate. We decided to extend this strategy to the synthesis of 5-aminopyrazoles by coupling an isothiocyanate with an activated acetonitrile derivative (e.g., **1**, Scheme 1) and trapping the resulting thiolate anion with Merrifield resin.[5] Treatment of the solid-bound intermediate **4** with hydrazine would then afford the 3,5-diamino-4-(arylsulfonyl)-1*H*-pyrazoles **5** after release from the solid support and intramolecular cyclization. Also, reaction of **4** with a different nucleophile such as hydroxylamine would provide an entry into the corresponding 3,5-diamino-4-(arylsulfonyl)isoxazoles **6**.

Results and Discussion

The synthetic procedure for the preparation of 3,5-diamino-4-(arylsulfonyl)-1*H*-pyrazoles **5** begins with commercially available 2-sulfonylacetonitriles **1**. These reagents were deprotonated with Et_3N (or NaH, vide infra) in THF and reacted with isothiocyanates to give thiolate anions **3**, which

Scheme 1. Traceless Solid-Phase Synthesis of 3,5-Diamino-4-(arylsulfonyl)-1*H*-pyrazoles **5** and 3,5-Diamino-4-(arylsulfonyl)isoxazoles **6**

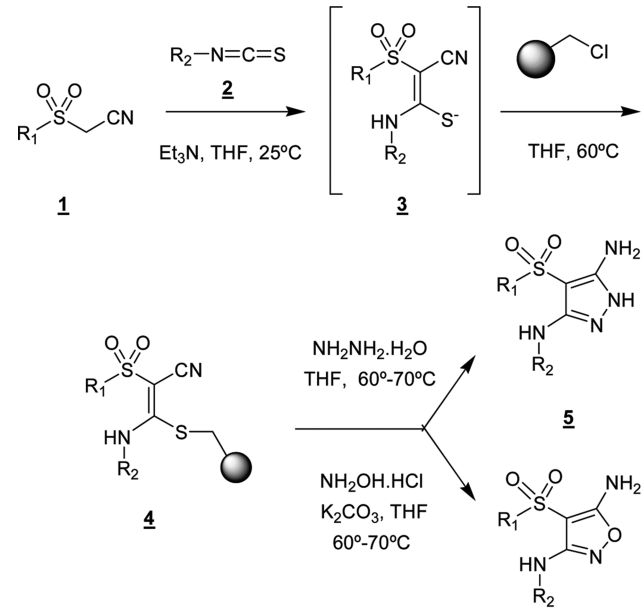

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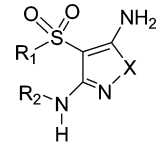
Table 1. 3,5-Diamino-4-(arylsulfonyl)-1*H*- pyrazoles (**5a**−**ak**) and 3,5-Diamino-4-(arylsulfonyl)-isoxazoles (**6a**−**h**)



5, X = NH
6, X = O

entry	compound	R_1	R_2	X	purity (%)	yield (%)	note
1	**5a**	Ph	2-Cl-Ph	NH	91	89	
2	**5b**	Ph	3-Cl-Ph	NH	77	69	
3	**5c**	Ph	4-Cl-Ph	NH	84	71	
4	**5d**	Ph	4-PhO-Ph	NH	97	96	
5	**5e**	Ph	2-F-Ph	NH	76	76	*a*
6	**5f**	Ph	2-CN-Ph	NH	84	69	*a*
7	**5g**	Ph	3-CN-Ph	NH	99	66	*a*
8	**5h**	Ph	4-CN-Ph	NH	91	44	
9	**5i**	Ph	2-CF_3-Ph	NH	97	99	
10	**5j**	Ph	3-CF_3-Ph	NH	59	34	*a*
11	**5k**	Ph	4-CF_3-Ph	NH	52	29	*a*
12	**5l**	Ph	2-biphenyl	NH	98	85	
13	**5m**	Ph	3,4-methylenedioxyphenyl	NH	96	88	
14	**5n**	Ph	CH_3	NH	97	94	*b*
15	**5o**	Ph	$PhCH_2$	NH	98	93	*b*
16	**5p**	Ph	$(CH_3)_2CHCH_2$	NH	92	94	*b*
17	**5q**	Ph	(tetrahydrofuran-2-yl)CH_2	NH	98	92	*b*
18	**5r**	4-Cl-Ph	2-Cl-Ph	NH	83	80	
19	**5s**	4-Cl-Ph	3-Cl-Ph	NH	67	51	*a*
20	**5t**	4-Cl-Ph	4-Cl-Ph	NH	71	51	*a*
21	**5u**	4-Cl-Ph	2-F-Ph	NH	74	65	*a*
22	**5v**	4-Cl-Ph	3-F-Ph	NH	79	59	*a*
23	**5w**	4-Cl-Ph	4-F-Ph	NH	94	90	
24	**5x**	4-Cl-Ph	2-CH_3-Ph	NH	92	74	
25	**5y**	4-Cl-Ph	3-CH_3-Ph	NH	99	89	
26	**5z**	4-Cl-Ph	4-CH_3- Ph	NH	97	74	
27	**5aa**	4-Cl-Ph	2-OCH_3-Ph	NH	98	65	
28	**5ab**	4-Cl-Ph	3-OCH_3-Ph	NH	97	80	
29	**5ac**	4-Cl-Ph	4-OCH_3-Ph	NH	95	75	
30	**5ad**	4-Cl-Ph	2-CF_3-Ph	NH	97	99	
31	**5ae**	4-Cl-Ph	3-CF_3-Ph	NH	72	54	*a*
32	**5af**	4-Cl-Ph	4-CF_3-Ph	NH	59	41	*a*
33	**5ag**	4-Cl-Ph	2-biphenyl	NH	98	87	
34	**5ah**	4-Cl-Ph	Ph	NH	86	74	
35	**5ai**	4-Cl-Ph	4-PhO-Ph	NH	93	90	
36	**5aj**	4-Cl-Ph	3,4-methylenedioxyphenyl	NH	99	96	
37	**6a**	Ph	Ph	O	99	73	*a,b*
38	**6b**	Ph	4-CH_3O-Ph	O	99	52	*a,b*
39	**6c**	Ph	3-CH_3O-Ph	O	99	69	*a,b*
40	**6d**	Ph	2-CH_3O-Ph	O	99	65	*a,b*
41	**6e**	Ph	4-CH_3-Ph	O	99	61	*a,b*
42	**6f**	Ph	3-CH_3-Ph	O	99	65	*a,b*
43	**6g**	Ph	2-CH_3-Ph	O	99	54	*a,b*
44	**6h**	Ph	4-F-Ph	O	99	52	*a,b*
45	**6i**	Ph	3-F-Ph	O	99	65	*a,b*
46	**6j**	Ph	2-F-Ph	O	99	73	*a,b*
47	**6k**	Ph	4-NO_2-Ph	O	99	57	*a,b*

[a] Purity and yield after SPE purification. [b] NaH was used as base instead of Et_3N.

were trapped in situ with Merrifield resin in THF at 60−70 °C (Scheme 1). After filtration and thorough washing, the resin-bound thioethers **4** were treated with hydrazine monohydrate in THF at 60−70 °C, which effected cleavage from the resin and ensuing nucleophilic attack on the nitrile group to deliver the corresponding pyrazoles **5** (Table 1). The crude pyrazoles were usually the predominant product of this reaction, as determined by LC/MS, and were isolated by simple filtration.

In order to increase the scope of this "catch and release" strategy, we also examined the use of other nucleophilic reagents. As expected, reaction of **4** with hydroxylamine gave the corresponding 3,5-diamino-4-(arylsulfonyl)isoxazoles **6** (Table 1). For this series, the products were easily purified by filtration through an SPE silica plug.

Among the aryl isothiocyanates investigated, those containing electron-donating substituents such as methyl, methoxy, phenyl, phenoxy, and 3,4-methylenedioxy gave products with high purity and in good chemical yield. Aryl isothiocyanates with electron-withdrawing substituents such as fluoro-, chloro-, and trifluoromethyl, on the other hand, gave less-consistent results in terms of yield and purity. The poor yield obtained with cyano-substituted aryl thioisocyanates (cf., **5f**, **5g** and **5h**) was attributed to the interference of the additional nitrile group in the reaction with hydrazine.

Scheme 2. Traceless Solid-Phase Synthesis of 3-(Arylamino)-5-aryl-1*H*-pyrazole-4-carbonitriles **10**

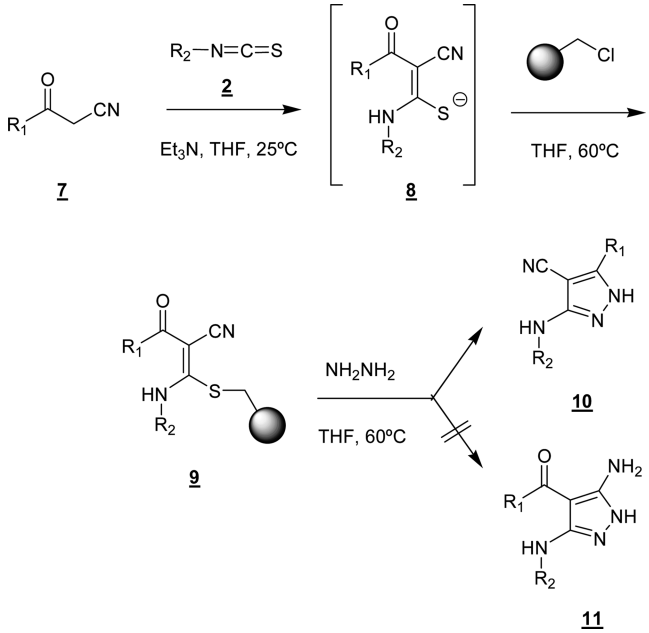
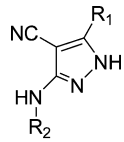


Table 2. 3-(4-Chlorophenylamino)-5-aryl-1*H*-pyrazole-4-carbonitriles (**10a**−**d**)



10

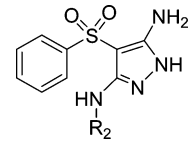
entry	compound	R_1	R_2	purity (%)	yield (%)
1	**10a**	4-Cl-Ph	2-CH_3-Ph	93	96
2	**10b**	4-Cl-Ph	3-CH_3-Ph	90	96
3	**10c**	4-Cl-Ph	4-CH_3-Ph	93	81
4	**10d**	4-Cl-Ph	Ph	96	98

We also examined the effect of replacing the sulfonyl group in the starting acetonitrile by a carbonyl group, as shown in Scheme 2. In this case, 3-(arylamino)-5-aryl-1*H*-pyrazole-4-carbonitriles **10** were obtained in good purity and yield (Table 2), with no evidence for the formation of the corresponding 3-amino-5-arylamino-4-carbonyl derivatives **11**. This result can be rationalized in terms of the higher reactivity of the carbonyl group of **9** toward hydrazine compared to the cyano group.

The effect of different experimental conditions on the chemical yield and purity of the final products was also examined. The use of excess reagents (i.e., 5−10 equiv relative to the amount of Merrifield resin) and carrying out the resin-loading and product-releasing steps at slightly elevated temperatures (∼60−70 °C), generally provided higher yields of product. Sodium hydride was found to be superior to triethylamine during the initial condensation step in terms of providing products of higher purity (Table 3), as was the use of tetrahydrofuran instead of dimethylformamide in both the initial condensation and product-releasing steps.

One unanticipated problem initially observed was the presence of small amounts of unknown impurities in the final products. These impurities did not show UV absorption at 254 nm and generally had high-field signals in the ^{1}H NMR spectrum. We postulated that these impurities were present in the resin itself and examined different batches of Merrifield resin; however, we were not able to prove or disprove that this was the source of the problem. Therefore, we subjected any final product with a purity of less than 80% (as determined by HPLC-UV analysis at 220 nm) to an additional aqueous workup. This simple treatment significantly improved the purity of the final product. In the case of the isoxazoles, it was found more efficient to filter the crude product through a Solid phase Extraction (SPE) silica plug. Tables 1 and 2 summarize the results obtained for 3,5-diamino-4-(arylsulfonyl)-1*H*-pyrazoles **5a**−**aj**, 3,5-diamino-4-(arylsulfonyl)isoxazoles **6a**−**k** and 3-(4-chlorophenylamino)-5-aryl-1*H*-pyrazole-4-carbonitriles **10a**−**d** using these procedures.

Table 3. Comparison of NaH and Et_3N as the Base for the Synthesis of 3,5-Diamino-4-(phenylsulfonyl)-1*H*-pyrazoles



entry	compound	R_2	base	crude purity (%)	yield (%)
1	**12**	4-NO_2-Ph	Et_3N	37	<10
2			NaH	52	39
3	**13**	3-NO_2-Ph	Et_3N	65	<10
4			NaH	96	82
5	**5k**	4-CF_3-Ph	Et_3N	52	29
6			NaH	98	88
7	**5j**	3-CF_3-Ph	Et_3N	59	34
8			NaH	99	91

Conclusions

The method described here allows the preparation of 3,4,5-trisubstituted pyrazoles and isozaxoles in a high-throughput parallel format and in excellent yield and chemical purity. A major benefit of this "catch and release" strategy is that immobilizing the thiol intermediate on a solid support circumvents the production of reactive cyanoketene *S,N*-acetals in solution, thus simplifying the purification of the final products. Also, the three components used in this synthetic approach, namely, activated acetonitriles, isothiocyanates, and nucleophilic reagents such as hydrazine or hydroxylamine, can be independently varied to provide compound libraries with broad structural diversity. The synthesis of other heterocyclic scaffolds using this methodology will be reported elsewhere.

Experimental Section

Materials and Methods. Merrifield resin (styrene-1% DVB copolymer, 100−200 mesh, 2.0 mmol/g) was obtained from NovaBiochem (Catalog No. 01−64−5007). Solvents were purchased from EM Science, J.T. Baker, or Aldrich and were anhydrous or HPLC grade. Reactions were performed in an Argonaut First Mate parallel synthesizer using 16 × 150 mm glass tubes. Resin rinses and filtrations were carried out in polypropylene tubes

(Pharmacia Biotech, Catalog No. 17-0435-01) on a multiport vacuum manifold (Supelco Visiprep, Catalog No. 5-7030). Scintillation vials (Wheaton Scientific-VWR, Catalog No. 986541) were used for filtrate collections and extractions. Solvent evaporation was performed in a GeneVac HT-4X centrifugal evaporator. Purity and molecular parent ion identity were determined on an Agilent 1100 LC/MSD instrument using a Zorbax Eclipse XDB-C8 column (2.1 × 50 mm, 3.5 μm, Catalog No. PN 971700-906), a 10 mM aqueous ammonium acetate: acetonitrile mobile phase (95:5 to 10:90 v/v gradient with 0.1% acetic acid as a modifier) at a flow rate of 0.4 mL/min, UV detection at 254 nm, and atmospheric-pressure electrospray ionization (API-ES) in either a negative or positive mode. The structures of the final products were confirmed by ^{1}H NMR on a Varian Mercury-400 instrument; chemical shifts are reported in ppm downfield from internal tetramethylsilane.

General Procedure for the Synthesis of Pyrazoles. The sulfonylacetonitrile (2.0 mmol) was dissolved in tetrahydrofuran (2 mL) and treated with triethylamine (2.0 mmol) in a nitrogen-purged glass tube at room temperature for one hour. A solution of the isothiocyanate (2.0 mmol) in tetrahydrofuran (0.5 mL) was added, and the mixture was stirred at room temperature for an additional two hours before adding Merrifield resin (100 mg, 0.2 mmol). The reaction tube was purged with nitrogen and heated at 60 °C for sixteen hours. The resulting mixture was transferred to a fritted polypropylene tube, and the resin was rinsed with tetrahydrofuran, isopropanol, and dichloromethane (3 × 10 mL each) and finally placed under high vacuum for two hours. The dried resin was transferred into a glass tube and swollen with tetrahydrofuran (2.5 mL). Hydrazine monohydrate (2.0 mmol) was added; the mixture was purged once again with nitrogen and then heated at 60 °C for twenty-four hours. The resin was filtered through a fritted polypropylene tube and the filtrate collected in a 20 mL scintillation vial, along with a *N,N*-dimethylformamide rinse (4 mL). The solvent was evaporated in a GeneVac centrifugal evaporator to obtain a viscous oil. Additional workup involved solubilizing the crude product in ethyl acetate (6 mL), washing this solution with saturated sodium bicarbonate (8 mL), decanting the organic layer, drying it with anhydrous magnesium sulfate, and filtering it into a 20 mL scintillation vial. The solvent was then evaporated under vacuum to obtain the final product, usually as a semicrystalline solid.

5a: 68 mg, 91% pure by LC/MS, 89% yield; ^{1}H NMR (DMSO-d_6) δ 6.26 (2H, s), 6.90 (1H, t, J = 7.8 Hz), 7.27 (1H, t, J = 7.0 Hz), 7.46 (1H, d, J = 7.8 Hz), 7.58−7.67 (3H, m), 7.95 (2H, d, J = 8.2 Hz), 8.15 (1H, s), 8.31 (1H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES$^+$) m/z 349 (M + H).

5b: 62 mg, 77% pure by LC/MS, 69% yield; ^{1}H NMR (DMSO-d_6) δ 6.20 (2H, s), 6.87 (1H, d, J = 7.8 Hz), 7.23 (1H, t, J = 7.8 Hz), 7.38−7.42 (2H, m), 7.52−7.67 (3H, m), 7.83 (1H, s), 8.00 (2H, d, J = 7.4 Hz), 11.4 (1H, s); MS (ES$^+$) m/z 349 (M + H).

5c: 59 mg, 84% pure by LC/MS, 71% yield; ^{1}H NMR (DMSO-d_6) δ 6.16 (2H, s), 7.26 (2H, d, J = 8.6 Hz), 7.57−7.63 (6H, m), 7.99 (2H, d, J = 8.2 Hz), 11.4 (1H, s); MS (ES$^+$) m/z 349 (M + H).

5d: 80 mg, 97% pure by LC/MS, 96% yield; ^{1}H NMR (DMSO-d_6) δ 6.14 (2H, s), 6.91−6.96 (4H, m), 7.06 (1H, t, J = 7.4 Hz), 7.34 (2H, t, J = 7.4 Hz), 7.48 (1H, s), 7.56−7.66 (5H, m), 8.00 (2H, d, J = 7.8 Hz), 11.3 (1H, s); MS (ES$^+$) m/z 407 (M + H).

5e: 66 mg, 76% pure by LC/MS, 76% yield; ^{1}H NMR (DMSO-d_6) δ 6.22 (2H, s), 6.82 − 6.87 (1H, m), 7.11 (1H, t, J = 7.4 Hz), 7.19−7.24 (1H, m), 7.55−7.64 (3H, m), 7.76 (1H, d, J = 7.4 Hz), 7.93 (2H, d, J = 7.0 Hz), 8.18 (1H, t, J = 8.6 Hz), 11.4 (1H, s); MS (ES$^+$) m/z 333 (M + H).

5f: 72 mg, 84% pure by LC/MS, 69% yield; ^{1}H NMR (DMSO-d_6) δ 6.29 (2H, s), 7.30 (1H, t, J = 7.8 Hz), 7.52−7.57 (3H, m), 7.65−7.74 (2H, m), 8.08−8.11 (2H, m), 8.30 (1H, d, J = 8.2 Hz); MS (ES$^+$) m/z 340 (M + H).

5g: 59 mg, 99% pure by LC/MS, 66% yield; ^{1}H NMR (DMSO-d_6) δ 6.20 (2H, s), 7.23 (1H, d, J = 7.4 Hz), 7.39 (1H, t, J = 7.8 Hz), 7.53−7.62 (3H, m), 7.78−7.81 (2H, m), 7.98 (2H, d, J = 7.0 Hz), 8.08 (1H, s), 11.4 (1H, s); MS (ES$^+$) m/z 340 (M + H).

5h: 56 mg, 91% pure by LC/MS, 44% yield; ^{1}H NMR (DMSO-d_6) δ 6.22 (2H, s), 7.54−7.67 (7H, m), 7.98 (2H, d, J = 7.4 Hz), 8.04 (1H, s), 11.6 (1H, s); MS (ES$^+$) m/z 340 (M + H).

5i: 78 mg, 97% pure by LC/MS, 99% yield; ^{1}H NMR (DMSO-d_6) δ 6.28 (2H, s), 7.04 (1H, t, J = 7.4 Hz), 7.55−7.67 (5H, m), 7.91 (2H, d, J = 7.8 Hz), 8.07 (1H, s), 8.48 (1H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES$^+$) m/z 383 (M + H).

5j: 44 mg, 59% pure by LC/MS, 34% yield; ^{1}H NMR (DMSO-d_6) δ 6.22 (2H, s), 7.15 (1H, d, J = 7.4 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.54−7.64 (3H, m), 7.73 (1H, d, J = 8.6 Hz), 7.83 (1H, s), 8.02 (2H, d, J = 7.8 Hz), 8.12 (1H, s), 11.5 (1H, s); MS (ES$^+$) m/z 383 (M + H).

5k: 42 mg, 52% pure by LC/MS, 29% yield; ^{1}H NMR (DMSO-d_6) δ 6.16 (2H, s), 7.52−7.64 (5H, m), 7.66 (2H, d, J = 8.2 Hz), 7.86 (1H, s), 7.95 (2H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES$^+$) m/z 383 (M + H).

5l: 68 mg, 98% pure by LC/MS, 85% yield; ^{1}H NMR (DMSO-d_6) δ 6.12 (2H, s), 6.94 (1H, t, J = 7.4 Hz), 7.14 (1H, d, J = 7.4 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.42−7.52 (7H, m), 7.56−7.62 (3H, m), 7.95 (1H, S), 8.31 (1H, d, J = 8.2 Hz), 11.3 (1H, s); MS (ES$^+$) m/z 391 (M + H).

5m: 66 mg, 96% pure by LC/MS, 88% yield; ^{1}H NMR (DMSO-d_6) δ 5.93 (2H, s), 6.12 (2H, s), 6.78 (1H, d, J = 8.2 Hz), 6.95 (1H, d, J = 8.2 Hz), 7.32−7.33 (2H, m), 7.56−7.65 (3H, m), 7.99 (2H, d, J = 8.2 Hz), 11.3 (1H, s); MS (ES$^+$) m/z 358 (M + H).

5n: 49 mg, 97% pure by LC/MS, 94% yield; ^{1}H NMR (DMSO-d_6) δ 2.68 (3H, d, J = 5.1 Hz), 7.56−7.60 (3H, m), 7.85−7.95 (2H, m); MS (ES$^+$) m/z 253 (M + H).

5o: 62 mg, 98% pure by LC/MS, 93% yield; ^{1}H NMR (DMSO-d_6) δ 4.29 (2H, d, J = 6.2 Hz), 7.18−7.21 (1H, m), 7.24−7.27 (4H, m), 7.54−7.65 (3H, m), 7.92−7.94 (2H, m); MS (ES$^+$) m/z 329 (M + H).

5p: 61 mg, 92% pure by LC/MS, 94% yield; ^{1}H NMR (DMSO-d_6) δ 0.83 (6H, d, J = 6.6 Hz), 1.76−1.86 (1H, m),

2.86−2.91 (2H, m), 7.54−7.63 (3H, m), 7.89−7.92 (2H, m); MS (ES^+) *m/z* 295 (M + H).

5q: 60 mg, 98% pure by LC/MS, 92% yield; ^{1}H NMR (DMSO-d_6) δ 1.46−1.54 (1H, m), 1.77−1.90 (3H, m), 3.03−3.09 (1H, m), 3.15−3.21 (1H, m), 3.62−3.67 (1H, m), 3.75−3.80 (1H, m), 3.93−3.99 (1H, m), 7.54−7.63 (3H, m), 7.87−7.90 (2H, m), 10.90−11.00 (1H, br s); MS (ES^+) *m/z* 323 (M + H).

5r: 74 mg, 83% pure by LC/MS, 80% yield; ^{1}H NMR (DMSO-d_6) δ 6.31 (2H, s), 6.89 (1H, t, J = 7.8 Hz), 7.27 (1H, t, J = 7.4 Hz), 7.46 (1H, d, J = 8.2 Hz), 7.69 (2H, d, J = 8.2 Hz), 7.95 (2H, d, J = 8.2 Hz), 8.11 (1H, s), 8.30 (1H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES^+) *m/z* 384 (M + H).

5s: 59 mg, 67% pure by LC/MS, 51% yield; ^{1}H NMR (DMSO-d_6) δ 6.25 (2H, s), 6.87 (1H, d, J = 7.8 Hz), 7.23 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 8.2 Hz), 7.62−7.67 (3H, m), 7.81 (1H, s), 8.01 (2H, d, J = 8.6 Hz), 11.4 (1H, s); MS (ES^+) *m/z* 384 (M + H).

5t: 55 mg, 71% pure by LC/MS, 51% yield; ^{1}H NMR (DMSO-d_6) δ 6.18 (2H, s), 7.23 (2H, d, J = 9.0 Hz), 7.50−7.58 (3H, m), 7.63 (2H, d, J = 8.6 Hz), 7.98 (2H, d, J = 8.6 Hz), 11.4 (1H, s); MS (ES^+) *m/z* 384 (M + H).

5u: 64 mg, 74% pure by LC/MS, 65% yield; ^{1}H NMR (DMSO-d_6) δ 6.28 (2H, s), 6.86−6.90 (1H, m), 7.11 (1H, t, J = 7.4 Hz), 7.21−7.26 (1H, m), 7.68 (2H, d, J = 8.6 Hz), 7.74 (1H, d, J = 3.9 Hz), 7.93 (2H, d, J = 9.0 Hz), 8.17 (1H, t, J = 8.2 Hz), 11.5 (1H, s); MS (ES^+) *m/z* 367 (M + H).

5v: 55 mg, 79% pure by LC/MS, 59% yield; ^{1}H NMR (DMSO-d_6) δ 6.21 (2H, s), 6.5−6.64 (1H, m), 7.17−7.24 (2H, m), 7.53−7.566 (1H, m), 7.61−7.64 (3H, m), 7.98 (2H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES^+) *m/z* 367 (M + H).

5w: 70 mg, 94% pure by LC/MS, 90% yield; ^{1}H NMR (DMSO-d_6) δ 6.19 (2H, s), 7.06 (2H, t, J = 8.6 Hz), 7.46 (1H, s), 7.52−7.58 (2H, m), 7.66 (2H, d, J = 8.6 Hz), 8.01 (2H, d, J = 8.6 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 367 (M + H).

5x: 58 mg, 92% pure by LC/MS, 74% yield; ^{1}H NMR (DMSO-d_6) δ 3.34 (3H, s), 6.23 (2H, s), 6.80 (1H, t, J = 7.2 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.16 (1H, d, J = 7.4 Hz), 7.48 (1H, s), 7.68 (2H, d, J = 8.2 Hz), 7.97 (2H, d, J = 8.2 Hz), 8.09 (1H, d, J = 8.2 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 363 (M + H).

5y: 65 mg, 99% pure by LC/MS, 89% yield; ^{1}H NMR (DMSO-d_6) δ 3.34 (3H, s), 6.20 (2H, s), 6.67 (1H, d, J = 7.4 Hz), 7.11 (1H, t, J = 7.1 Hz), 7.31−7.34 (2H, m), 7.39 (1H, s), 7.66 (2H, d, J = 8.6 Hz), 7.99 (2H, d, J = 8.6 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 363 (M + H).

5z: 55 mg, 97% pure by LC/MS, 74% yield; ^{1}H NMR (DMSO-d_6) δ 3.34 (3H, s), 6.17 (2H, s), 7.04 (2H, d, J = 8.6 Hz), 7.34 (1H, s) 7.42 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.2 Hz), 7.99 (2H, d, J = 8.2 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 363 (M + H).

5aa: 50 mg, 98% pure by LC/MS, 65% yield; ^{1}H NMR (DMSO-d_6) δ 3.92 (3H, s), 6.20 (2H, s), 6.80−6.84 (2H, m), 6.99 (1H, d, J = 7.4 Hz), 7.68 (2H, d, J = 8.2 Hz), 7.91 (2H, d, J = 8.6 Hz), 7.95 (1H, s), 8.07 (1H, d, J = 7.4 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 379 (M + H).

5ab: 62 mg, 97% pure by LC/MS, 80% yield; ^{1}H NMR (DMSO-d_6) δ 3.73 (3H, s), 6.21 (1H, s), 6.43 (1H, d, J = 7.8 Hz), 7.05−7.15 (2H, m), 7.25 (1H, s), 7.47 (1H, s), 7.66 (2H, d, J = 8.6 Hz), 7.96 (1H, s), 8.00 (2H, d, J = 8.6 Hz), 11.4 (1H, s); MS (ES^+) *m/z* 379 (M + H).

5ac: 60 mg, 95% pure by LC/MS, 75% yield; ^{1}H NMR (DMSO-d_6) δ 3.70 (3H, s), 6.15 (2H, s), 6.82 (2H, d, J = 8.6 Hz), 7.24 (1H, bs), 7.46 (2H, d, J = 9.0 Hz), 7.66 (2H, d, J = 8.6 Hz), 7.99 (2H, d, J = 8.2 Hz), 11.2 (1H, s); MS (ES^+) *m/z* 379 (M + H).

5ad: 85 mg, 97% pure by LC/MS, 99% yield; ^{1}H NMR (DMSO-d_6) δ 6.33 (2H, s), 7.05 (1H, t, J = 7.4 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.70 (2H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 8.04 (1H, s), 8.47 (1H, d, J = 8.6 Hz), 11.5 (1H, s); MS (ES^+) *m/z* 417 (M + H).

5ae: 62 mg, 72% pure by LC/MS, 54% yield; ^{1}H NMR (DMSO-d_6) δ 6.27 (2H, s), 7.16 (1H, d, J = 7.4 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.65 (2H, d, J = 8.2 Hz), 7.73 (1H, d, J = 7.8 Hz), 7.83 (1H, s), 8.03 (2H, d, J = 8.6 Hz), 8.10 (1H, s), 11.5 (1H, s); MS (ES^+) *m/z* 417 (M + H).

5af: 58 mg, 59% pure by LC/MS, 41% yield; ^{1}H NMR (DMSO-d_6) δ 6.23 (2H, s), 7.52 (2H, d, J = 8.6 Hz), 7.60−7.66 (4H, m), 7.87 (1H, s), 7.98 (2H, d, J = 8.2 Hz), 11.5 (1H, s); MS (ES^+) *m/z* 417 (M + H).

5ag: 75 mg, 98% pure by LC/MS, 87% yield; ^{1}H NMR (DMSO-d_6) δ 6.18 (2H, s), 6.95 (1H, t, J = 7.4 Hz), 7.14 (1H, d, J = 7.4 Hz), 7.29 (1H, t, J = 7.4 Hz), 7.38−7.52 (6H, m), 7.58−7.63 (4H, m), 8.30 (1H, d, J = 8.6 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 425 (M + H).

5ah: 60 mg, 86% pure by LC/MS, 74% yield; ^{1}H NMR (DMSO-d_6) δ 6.20 (2H, s), 6.85 (1H, t, J = 7.0 Hz), 7.23 (2H, t, J = 7.8 Hz), 7.45 (1H, s), 7.53 (2H, d, J = 7.8 Hz), 7.66 (2H, d, J = 8.2 Hz), 8.00 (2H, d, J = 8.6 Hz), 11.4 (1H, s); MS (ES^+) *m/z* 349 (M + H).

5ai: 85 mg, 93% pure by LC/MS, 90% yield; ^{1}H NMR (DMSO-d_6) δ 6.19 (2H, s), 6.94 (4H, t, J = 8.6 Hz), 7.06 (1H, t, J = 7.4 Hz), 7.34 (2H, t, J = 7.8 Hz), 7.47 (1H, s), 7.59 (2H, d, J = 8.6 Hz), 7.67 (2H, d, J = 8.2 Hz), 8.02 (2H, d, J = 8.6 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 441 (M + H).

5aj: 76 mg, 99% pure by LC/MS, 96% yield; ^{1}H NMR (DMSO-d_6) δ 5.93 (2H, s), 6.17 (2H, s), 6.78 (1H, d, J = 8.6 Hz), 6.96 (1H, d, J = 8.6 Hz), 7.30−7.31 (2H, m), 7.66 (2H, d, J = 7.8 Hz), 8.00 (2H, d, J = 7.8 Hz), 11.3 (1H, s); MS (ES^+) *m/z* 392 (M + H).

10a: 69 mg, 93% pure by LC-MS, 96% yield; ^{1}H NMR (DMSO-d_6) δ 2.10 (3H, s), 6.95−6.99 (1H, m), 7.12−7.21 (3H, m), 7.57−7.63 (2H, m), 7.84−7.86 (2H, m); MS (ES^+) *m/z* 309 (M + H).

10b: 71 mg, 90% pure by LC-MS, 96% yield; ^{1}H NMR (DMSO-d_6) δ 2.10 (3H, s), 6.70 (1H, d, J = 8.0 Hz), 7.11−7.25 (3H, m), 7.66 (2H, d, J = 8.0 Hz), 7.84−7.86 (2H, m), 8.90 (1H, bs); MS (ES^+) *m/z* 309 (M + H).

10c: 59 mg, 93% pure by LC-MS, 81% yield; ^{1}H NMR (DMSO-d_6) δ 2.20 (3H, s), 7.06 (2H, d, J= 8.2 Hz), 7.26−7.34 (2H, m), 7.66 (2H, d, J = 8.2 Hz), 7.82−7.85 (2H, m), 8.84 (1H, bs); MS (ES^+) *m/z* 309 (M + H).

10d: 65 mg, 96% pure by LC-MS, 98% yield; ^{1}H NMR (DMSO-d_6) δ 6.86 (1H, t), 7.26 (2H, t, J= 7.8 Hz), 7.34−7.46 (2H, m), 7.66 (2H, d, J = 8.2 Hz), 7.84 (2H, d, J =8.6 Hz), 8.96 (1H, bs), 13.30−13.60 (1H, br s); MS (ES^+) *m/z* 295 (M + H).

General Procedure for the Synthesis of Isoxazoles. A solution of 2-(phenylsulfonyl)acetonitrile (1.5 mmol) in anhydrous tetrahydrofuran (3 mL) in a glass tube precooled in an ice bath was treated with sodium hydride (1.5 mmol, 60% dispersion in mineral oil). After the mixture was stirred at room temperature for two hours, a solution of isothiocyanate (1.5 mmol) in anhydrous tetrahydrofuran (2 mL) was added, and the mixture stirred for an additional two hours. Merrifield resin (0.25 mmol, 2.5 mmol/g) preswollen in dichloromethane was then added; the tube was repurged with nitrogen, and the mixture was heated at 60 °C for sixteen hours. The resulting mixture was transferred to a fritted polypropylene tube, and the resin was rinsed with tetrahydrofuran, isopropanol, and dichloromethane (3 × 10 mL each). The washed resin was then transferred back to a glass tube and treated with anhydrous tetrahydrofuran (3 mL), hydroxylamine hydrochloride (2.5 mmol) and potassium carbonate (2.5 mmol). The mixture was heated at 60 °C for twenty-four hours and transferred to a fritted polypropylene tube, and the filtrate was collected in a 20 mL scintillation vial along with a THF rinse (2 mL). The solvents were evaporated under vacuum, and the crude product was loaded onto an SPE tube (6 mL tube prepacked with 0.5 g SiO_2) and eluted with 1:1 Hexane/EtOAc. The combined eluents were evaporated to afford the product, usually as an off-white solid.

6a: 50 mg, 99% pure by HPLC, 73% yield; ^{1}H NMR (DMSO) δ 6.97 (1H, t, $J = 7.4$ Hz), 7.30 (2H, t, $J = 7.5$ Hz), 7.49−7.51 (2H, m), 7.61−7.70 (4H, m), 8.09−8.12 (3H, m); MS (ES^+) *m*/*z* 316 (M + H).

6b: 45 mg, 99% pure by HPLC, 52% yield; ^{1}H NMR (DMSO) δ (ppm): 3.71 (3H, s), 6.88 (2H, d, $J = 9.0$ Hz), 7.41 (2H, d,$J = 9.0$ Hz), 7.47 (1H, bs), 7.61−7.65 (2H, m), 7.68−7.70 (1H, m), 8.05 (2H, bs), 8.10 (2H, d, $J = 8.6$ Hz); MS (ES^+) *m*/*z* 346 (M + H).

6c: 59 mg, 99% pure by HPLC, 69% yield; ^{1}H NMR (DMSO) δ (ppm): 3.75 (3H, s), 6.54−6.57 (1H, m), 7.07−7.09 (1H, m), 7.15−7.22 (2H, m), 7.62−7.71 (4H, m), 8.09−8.12 (4H, m); MS (ES^+) *m*/*z* 346 (M + H).

6d: 56 mg, 99% pure by HPLC, 65% yield; ^{1}H NMR (DMSO) δ (ppm): 3.98 (3H, s), 6.92−6.96 (2H, m), 7.06−7.09 (1H, m), 7.63−7.76 (4H, m), 7.97−8.00 (2H, m), 8.12 (1H, s), 8.16 (2H, bs); MS (ES^+) *m*/*z* 346 (M + H).

6e: 50 mg, 99% pure by HPLC, 61% yield; ^{1} H NMR (DMSO) δ (ppm): 2.24 (3H, s), 7.11 (2H, d, J= 8.5 Hz), 7.38 (2H, d, $J = 8.5$ Hz),7.55 (1H, bs), 7.61−7.70 (3H, m), 8.08−8.10 (4H, m); MS (ES^+) *m*/*z* 330 (M + H).

6f: 53 mg, 99% pure by HPLC, 65% yield; ^{1} H NMR (DMSO) δ (ppm): 2.28 (3H, s), 6.79 (1H, d, J= 7.4 Hz), 7.16−7.20 (1H, m), 7.30−7.31 (2H, m), 7.58 (1H, bs), 7.61−7.70 (3H, m), 8.08−8.13 (4H, m); MS (ES^+) *m*/*z* 330 (M + H).

6g: 44 mg, 99% pure by HPLC, 54% yield; ^{1}H NMR (DMSO) δ (ppm): 2.33 (3H, s), 6.91−6.93 (1H, m), 7.17−7.24 (2H, m), 7.63−7.67 (3H, m), 7.69−7.73 (2H, m), 8.04−8.07 (2H, m), 8.16 (2H, bs); MS (ES^+) *m*/*z* 330 (M + H).

6h: 43 mg, 99% pure by HPLC, 52% yield; ^{1}H NMR (DMSO) δ (ppm): 7.12−7.16 (2H, m), 7.52−7.56 (2H, m), 7.62−7.65 (2H, m), 7.69−7.70 (2H, m), 8.10−8.12 (4H, m); MS (ES^+) *m*/*z* 334 (M + H).

6i: 54 mg, 99% pure by HPLC, 65% yield; ^{1}H NMR (DMSO) δ (ppm): 6.78−6.82 (1H, m), 7.31−7.35 (2H, m), 7.44−7.48 (1H, m), 7.61−7.70 (3H, m), 7.87 (1H, bs), 8.10−8.12 (2H, m), 8.16 (2H, bs); MS (ES^+) *m*/*z* 334 (M + H).

6j: 59 mg, 99% pure by HPLC, 73% yield; ^{1}H NMR (DMSO) δ (ppm): 7.00−7.05 (1H, m), 7.17−7.20 (1H, t, $J = 7.2$ Hz), 7.29−7.34 (1H, m), 7.63−7.74 (3H, m), 7.82−7.86 (1H, m), 7.90 (1H, d, $J = 3.6$ Hz), 8.00−8.03 (2H, m), 8.24 (2H, bs); MS (ES^+) *m*/*z* 334 (M + H).

6k: 51 mg, 99% pure by HPLC, 57% yield; ^{1}H NMR (DMSO) δ (ppm): 7.61−7.77 (m, 5H), 8.10−8.13 (2H, m), 8.19−8.22 (2H, m), 8.26 (2H, bs), 8.42 (1H, bs); MS (ES^+) *m*/*z* 361.25 (M + H).

Supporting Information Available. Spectroscopic characterization (LC/MS and ^{1}H NMR) for compounds **5a**−**5aj**, **6a**−**6k**, and **10a**−**10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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