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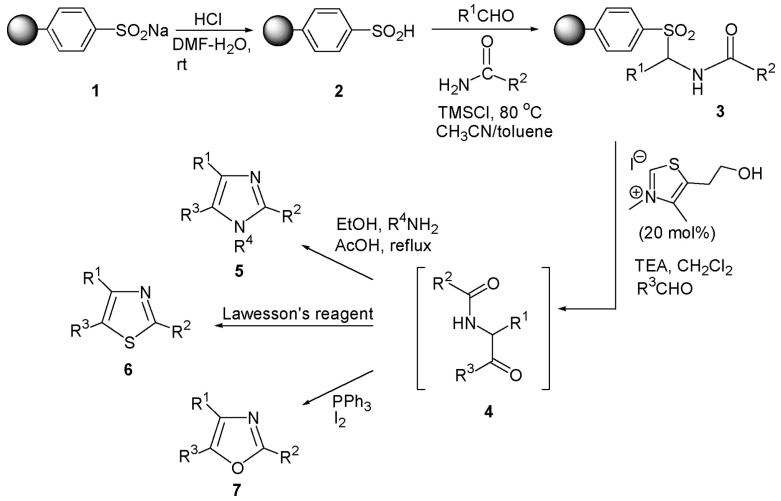

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Articles

A Facile Solid-Phase Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles Using Sodium Benzenesulfinate as a Traceless Linker

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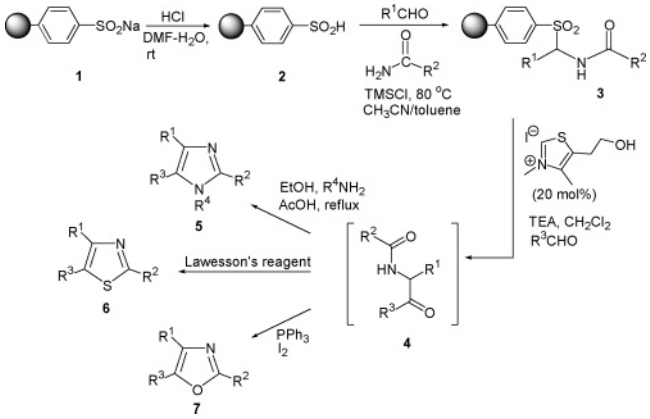
The preparation of substituted imidazoles, thiazoles, and oxazoles using traceless solid-phase sulfone linker strategy is described. Key steps involved are (i) sulfinate acidification, (ii) sulfinic acid condensation with aldehyde and amine, and (iii) traceless product release by a one-pot elimination-cyclization reaction. The elimination reaction was carried out in the presence of a thiazolium catalyst that facilitated the in situ formation of the α-ketoamide, which was subsequently converted to the corresponding imidazoles, oxazoles, and thiazoles by treatment with amines, PPh_3/I_2 or Lawesson's reagent. A library of 18 compounds was synthesized.

Introduction

The imidazole moiety, as part of the side chain in histidine, plays a major role in the biological functions of many peptides and proteins. Functionalized imidazoles also comprise an important class of pharmacologically active compounds with a wide range of interesting properties. Members of this class of compounds are known to possess NO synthase inhibition[1] and antifungal,[2] antimycotic,[3] antibiotic,[4] antiulcerative,[5] and CB_1 receptor antagonistic activities.[6] Consequently, methodologies for the preparation of imidazoles have attracted much attention from both industry and academia, and numerous solution-phase syntheses of these compounds have been reported.[7] In recent years, synthetic methods for the preparation of imidazoles on solid-phase have been examined;[8] however, only one of these reports concerns the construction of 1,2,4,5-tetrasubstituted imidazoles. In this report, 1,2,4,5-tetrasubstituted imidazoles were prepared via a seven-step traceless synthesis strategy based on benzylic acylammonium chloride reactivity.[8c] Thus, new methods providing rapid access to this class of compounds would be of interest.

A promising alternative approach involves the synthesis of imidazoles through the cyclization of α-ketoamides with amines. α-Ketoamides could be achieved through the coupling of aldehydes with acylamines, and the latter could, in turn, be obtained from arylsulfonylamides through the elimination of sulfinic acid.[9] To our knowledge, this methodology has not been employed for solid-phase imidazole synthesis. We herein describe a rapid, solid-phase approach to 1,2,4,5-tetrasubstituted imidazoles via arylsulfonylamides on resin. Key steps in the synthesis include (i) sulfinate acidification, (ii) sulfinic acid condensation with aldehyde and amine, and (iii) traceless product release by a one-pot elimination−cyclization reaction (Scheme 1). Since a variety of reagents can be used in steps ii and iii, the overall strategy appears to be applicable for library generation.

Scheme 1. SPOS of 1,2,4,5-Tetrasubstituted Imidazoles, 2,4,5-Trisubstituted Oxazoles, and Thiazoles



Results and Discussion

Solution-Phase Synthesis of Imidazoles. Prior to the solid-phase synthesis, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications for the solid-phase synthesis. To begin our investigation, *N*-(benzenesulfonylphenylmethyl)-benzamide (**10**) was prepared by treating sodium benzenesulfinate with HCl in water at room temperature to give benzenesulfinic acid (**9**) in 93% yield (Scheme 2).[10] Subsequent condensation of **9**, benzaldehyde, and benzamide according to a procedure from Sisko and co-workers[11] provided **10** in 87% yield. Coupling of **10** with pyridine-4-

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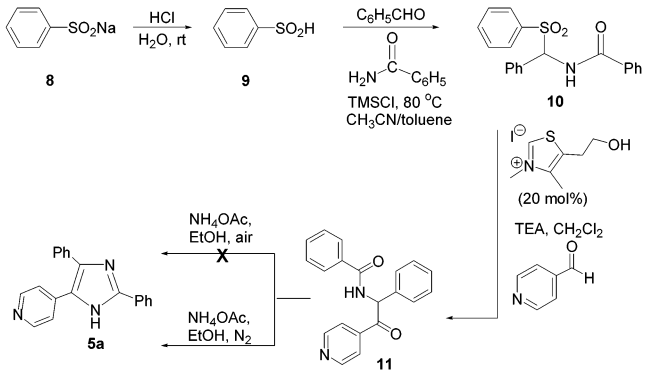
Scheme 2. Solution-Phase Synthesis of Imidazoles



carbaldehyde in the presence of triethylamine and 20 mol % thiazolium catalyst gave the α-ketoamide, *N*-(2-oxo-1-phenyl-2-pyridin-4-ylethyl)benzamide (**11**), in good yield (92%).[9] Attempts to cyclize **11** with NH_4OAc/EtOH in air did not provide the imidazole **5a**, and **11** was recovered.[12] However, when the reaction proceeded under nitrogen, **5a** was formed in 85% yield.

Solid-Phase Synthesis of Imidazoles, Oxazoles, and Thiazoles. With the solution-phase pathway established, we proceeded to develop the solid-phase route to these compounds. Due to the poor swelling ability of the resin in water, a DMF−H_2O (v/v, 3:1) mixture was used as the solvent for the preparation of **2**. Polystyrene/1% divinylbenzene sodium sulfinate (**1**, 100−200 mesh) in DMF−H_2O was allowed to react with HCl at room temperature (Scheme 1). The formation of **2** was amenable to KBr FTIR monitoring (i.e., appearance of sulfone stretch at 1443, 1287 cm^{-1}). Condensation of **2** with an aldehyde and an amide gave resin **3**, which was monitored with FTIR (appearance of the carbonyl stretch at 1650 cm^{-1}). We next proceeded to generate the α-ketoamide in situ by treating resin **3** with excess TEA and an aldehyde in the presence of a thiazolium catalyst in CH_2Cl_2 at 35 °C for 10 h. Concentration of the reaction mixture followed by the addition of ethanol/amine, and refluxing under nitrogen condition gave **5**. The overall yields obtained were 24−40% (Table 1), indicating an average yield of >70% for each step of the four solid-phase reactions.

In addition to the synthesis of imidazoles, we have also examined the application of this methodology for the synthesis of oxazoles and thiazoles. The α-ketoamide generated in situ from resin **3** was treated with PPh_3/I_2 or Lawesson's reagent to furnish the corresponding oxazole or thiazole in 19−32% overall yield (Table 1).

In summary, we have demonstrated a traceless solid-phase synthesis of substituted imidazoles, oxazoles, and thiazoles. The use of a sulfone moiety as a linker in the reaction benefits the solid-phase synthetic route because it not only provides a short synthetic route to the desired products but its chemical versatility also adds to the diversity of the library.

Experimental Section

General Procedures. Polystyrene/1% divinylbenzene sodium sulfinate was purchased from Tianjin Nankai Hecheng Science and Technology Co. (100−200 mesh, Catalog no. HC8201-1). All chemicals were obtained from commercial suppliers and used without purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 230−400 mesh). NMR spectra (^1H and ^{13}C) were recorded at 298 K on a Bruker DPX300 spectrometer. Chemical shifts are expressed in δ (parts per million), relative to the internal standard of tetramethylsilane (TMS). Mass spectra were performed on a VG Micromass 7035 spectrometer under EI or ESI.

Table 1. Library of Imidazoles, Thiazoles, and Oxazoles

compd	R^1	R^2	R^3	R^4	yield (%)[a]
5a	C_6H_5	C_6H_5	C_5H_4N	H	37
5b	C_6H_5	C_6H_5	C_5H_4N	CH_2CH_2OH	35
5c	C_6H_5	C_6H_5	C_5H_4N	C_4H_9	34
5d	C_6H_5	H	C_5H_4N	H	39
5e	C_6H_5	H	C_5H_4N	CH_2CH_2OH	40
5f	C_6H_5	CH_3	C_5H_4N	C_4H_9	31
5g	C_6H_5	CH_3	$CH{=}CHC_6H_5$	C_4H_9	24
5h	*p*-FC_6H_4	C_6H_5	C_5H_4N	C_4H_9	27
5i	C_6H_5	CH_3	C_5H_4N	$CHCH_3(C_2H_5)$	30
5j	C_6H_5	C_6H_{11}	$CH{=}CHC_6H_5$	H	24
5k	$CH_2CH(CH_3)_2$	C_6H_5	C_5H_4N	C_4H_9	27
5l	C_2H_5	C_6H_5	C_5H_4N	CH_2CH_2OH	24
6a	C_6H_5	C_6H_5	C_5H_4N		27
6b	C_6H_5	C_6H_{11}	C_5H_4N		24
6c	*p*-FC_6H_4	C_6H_5	$CH{=}CHC_6H_5$		19
7a	C_6H_5	C_6H_5	C_5H_4N		32
7b	C_6H_5	C_6H_{11}	C_5H_4N		30
7c	*p*-FC_6H_4	C_6H_5	$CH{=}CHC_6H_5$		22

[a] Purified overall yield calculated on the basis of the loading of the resin. Purities of >95% as evaluated by NMR.

General Procedure for the Preparation of Polymer-Supported Phenylsulfinic Acid (2). Compound **1** (1.0 g, 2.1 mmol) was swollen in a mixture of 15 mL of DMF and 5 mL of H_2O by gently stirring the resin−DMF−H_2O mixture at room temperature for 0.5 h. Concentrated HCl (6 equiv) was added, and the reaction mixture was stirred at room temperature for 4 h, after which the mixture was filtered, and the resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2) and dried for 2 h in a vacuum oven at 40 °C to afford resin **2**.

General Procedure for the Synthesis of Polymer Supported Arylsulfonylamide (3). Resin **2** (1.0 g) was swollen in a mixture of 25 mL of anhydrous acetonitrile and 25 mL of anhydrous toluene at room temperature for 0.5 h. The resin was sequentially treated with aldehyde (6 equiv), amide (15 equiv), and chlorotrimethylsilane (6.6 equiv). The reaction mixture was gently stirred at 50 °C for 8 h, after which the mixture was filtered, and the resin was washed sequentially with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), DCM (20 mL × 2), and ether (20 mL × 2) and dried overnight in a vacuum oven at 40 °C to afford resin **3**.

General Procedure for the Synthesis of 1,2,4,5-Tetrasubsituted Imidazoles (5). A 50-mL flask was charged with resin **3** (0.5 g, 1 equiv) and the thiazolium catalyst (20 mol %) and purged with nitrogen for 15 min. To the flask was added CH_2Cl_2 (25 mL), followed by the aldehyde (8 equiv),

and the resulting mixture was gently stirred at 35 °C for 10 h, after which the solvent was removed by concentration, and the residual mixture was treated sequentially with ethanol (25 mL), acetic acid (8 equiv), and amine (8 equiv). The reaction mixture was then refluxed for an additional 12 h. The resin was filtered and washed with MeOH (20 mL × 3). The combined organic layer was concentrated on a rotavapor and purified by flash column chromatography to give **5**.

4-(2,5-Diphenyl-3*H*-imidazol-4-yl)pyridine (5a). White solid. ^{1}H NMR ($CDCl_3$): δ 8.44 (m, 2H, ArH), 8.02 (m, 2H, ArH), 7.98−7.95 (m, 2H, ArH), 7.59−7.48 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$): δ 150.7, 150.5, 142.9, 138.1, 133.0, 132.1, 131.0, 130.8, 130.6, 129.1, 128.7, 128.3, 127.0, 124.8. HRMS (EI) calcd for $C_{20}H_{15}N_3$, 297.1266; found, 297.1266.

2-(2,4-Diphenyl-5-pyridin-4-yl-imidazol-1-yl)ethanol (5b). White solid. ^{1}H NMR ($CDCl_3$): δ 8.59 (m, 2H, ArH), 7.46−7.35 (m, 6H, ArH), 7.32 (m, 2H, ArH), 7.23−7.21 (m, 4H, ArH), 4.06 (t, J = 5.9 Hz, 2H, CH_2), 3.42 (t, J = 5.9 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 150.1, 149.2, 139.8, 139.3, 133.5, 130.9, 130.8, 130.4, 129.3, 128.7, 128.3, 127.5, 127.1, 125.6, 60.8, 46.7. HRMS (EI) calcd for $C_{22}H_{19}N_3O$, 341.1528; found, 341.1528.

4-(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-yl)pyridine (5c). White solid. ^{1}H NMR ($CDCl_3$): δ 8.59 (m, 2H, ArH), 7.69 (m, 2H, ArH), 7.50−7.46 (m, 5H, ArH), 7.35 (m, 2H, ArH), 7.26−7.23 (m, 3H, ArH), 3.96 (t, J = 8.0 Hz, 2H, CH_2), 1.29 (m, 2H, CH_2), 0.97 (m, 2H, CH_2), 0.62 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 150.6, 149.1, 139.9, 139.4, 133.8, 131.0, 130.8, 129.2, 129.1, 128.7, 128.2, 127.3, 126.9, 125.3, 44.8, 32.5, 19.4, 13.2. HRMS (EI) calcd for $C_{24}H_{23}N_3$, 353.1892; found, 353.1893.

4-(4-Phenyl-1*H*-imidazol-5-yl)pyridine (5d). White solid. ^{1}H NMR (DMSO-d_6): δ 12.74 (1H, br, NH), 8.44 (m, 2H, ArH), 7.88 (s, 1H, CH), 7.45 (m, 7H, ArH). ^{13}C NMR (DMSO-d_6): δ 149.7, 149.0, 142.3, 136.5, 134.7, 128.8, 128.3, 127.9, 120.8, 120.5. HRMS (EI) calcd for $C_{14}H_{11}N_3$, 221.0953; found, 221.0955.

2-(4-Phenyl-5-(pyridin-4-yl)-1*H*-imidazol-1-yl)ethanol (5e). White solid. ^{1}H NMR (DMSO-d_6): δ 8.68 (m, 2H, ArH), 7.89 (s, 1H, CH), 7.41 (m, 2H, ArH), 7.32 (m, 2H, ArH), 7.25−7.15 (m, 3H, ArH), 4.99 (t, J = 5.2 Hz, 1H, OH), 3.91 (t, J = 5.6 Hz, 2H, CH_2), 3.48 (dd, J = 5.2, 5.6 Hz, 2H, CH_2). ^{13}C NMR (DMSO-d_6): δ 150.4, 138.9, 138.8, 138.0, 134.5, 130.5, 128.3, 126.5, 125.7, 125.5, 60.1, 47.2. HRMS (EI) calcd for $C_{16}H_{15}N_3O$, 265.1215; found, 265.1215.

4-(3-Butyl-2-methyl-5-phenyl-3*H*-imidazol-4-yl)pyridine (5f). White solid. ^{1}H NMR ($CDCl_3$): δ 8.72 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.38−7.23 (m, 5H, ArH), 3.82 (t, J = 7.7 Hz, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.50 (m, 2H, CH_2), 1.21 (m, 2H, CH_2), 0.81 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 150.6, 150.3, 145.3, 138.7, 136.0, 131.7, 128.4, 127.4, 127.1, 125.2, 44.2, 32.3, 19.6, 13.3, 12.9. HRMS (EI) calcd for $C_{19}H_{21}N_3$, 291.1735; found, 291.1739.

1-Butyl-2-methyl-4-phenyl-5-styryl-1*H*-imidazole (5g). White solid. ^{1}H NMR ($CDCl_3$): δ 7.82 (m, 1H, ArH), 7.71 (m, 2H, ArH), 7.38−7.27 (m, 7H, ArH), 6.96 (d, J = 16.5 Hz, 1H, CH), 6.75 (d, J = 16.5 Hz, 1H, CH), 3.96 (t, J = 7.6 Hz, 2H, CH_2), 2.47 (s, 3H, CH_3), 1.76 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 0.99 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 147.6, 137.6, 134.5, 131.5, 131.4, 131.0, 129.1, 129.0, 128.7, 128.5, 128.0, 126.8, 126.1, 44.4, 32.4, 19.4, 13.2, 12.8. HRMS (EI) calcd for $C_{22}H_{24}N_2$, 316.1939; found, 316.1938.

4-[3-Butyl-5-(4-fluoropenyl)-2-phenyl-3*H*-imidazol-4-yl]-pyridine (5h). White solid. ^{1}H NMR ($CDCl_3$): δ 8.72 (m, 2H, ArH), 7.66 (m, 2H, ArH), 7.47−7.41 (m, 5H, ArH), 7.35 (m, 2H, ArH), 6.95 (m, 2H, ArH), 3.97 (t, J = 8.0 Hz, 2H, CH_2), 1.26 (m, 2H, CH_2), 0.97 (m, 2H, CH_2), 0.61 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 162.9, 150.2, 130.5, 129.7, 129.1, 129.0, 128.9, 128.8, 128.6, 125.1, 117.5, 117.2, 115.2, 114.9, 44.7, 32.3, 19.2, 13.0. HRMS (EI) calcd for $C_{24}H_{22}N_3F$, 371.1798; found, 371.1799.

4-(3-*sec*-Butyl-2-methyl-5-phenyl-3*H*-imidazol-4-yl)pyridine (5i). White solid. ^{1}H NMR ($CDCl_3$): δ 8.69 (m, 2H, ArH), 7.33 (m, 2H, ArH), 7.26−7.23 (m, 3H, ArH), 7.18 (m, 2H, ArH), 3.94 (m, 1H, CH), 2.59 (s, 3H, CH_3), 1.86−1.70 (m, 2H, CH_2), 1.44 (d, J = 6.9 Hz, 3H, CH_3), 0.78 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 150.5, 150.4, 144.9, 140.9, 129.2, 128.2, 126.9, 126.6, 126.2, 121.5, 53.8, 28.7, 20.5, 15.7, 11.1. HRMS (EI) calcd for $C_{19}H_{21}N_3$, 291.1753; found, 291.1738.

2-(2-Cyclohexyl-4-phenyl-5-styrylimidazol-1-yl)ethanol (5j). White solid. ^{1}H NMR ($CDCl_3$): δ 7.59−7.51 (m, 7H, ArH), 7.41−7.38 (m, 3H, ArH), 6.99 (d, J = 16.5 Hz, 1H, CH), 6.81 (d, J = 16.5 Hz, 1H, CH), 2.90 (m, 1H, CH), 2.20−2.13 (m, 2H), 1.94−1.86 (m, 2H), 1.79−1.62 (m, 3H), 1.50−1.26 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 136.0, 134.5, 132.7, 130.1, 129.4, 129.2, 128.8, 128.6, 128.1, 127.6, 127.2, 126.7, 112.6, 37.8, 30.8, 25.9, 25.7. HRMS (EI) calcd for $C_{23}H_{24}N_2$, 328.1939; found, 328.1932.

4-(3-Butyl-5-isobutyl-2-phenyl-3*H*-imidazol-4-yl)pyridine (5k). White solid. ^{1}H NMR ($CDCl_3$): δ 8.71 (m, 2H, ArH), 7.52 (m, 5H, ArH), 7.28 (m, 2H, ArH), 3.98 (d, J = 7.3 Hz, 2H, CH_2), 2.44 (d, J = 7.3 Hz, 2H, CH_2), 1.19 (m, 2H, CH_2), 0.97 (m, 3H, CH and CH_2), 0.84 (d, J = 6.6 Hz, 6H, CH_3), 0.58 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 150.1, 149.6, 140.8, 131.8, 129.1, 128.8, 127.3, 127.0, 124.5, 121.8, 44.9, 36.2, 32.3, 28.9, 22.4, 19.1, 13.1. HRMS (EI) calcd for $C_{22}H_{27}N_3$, 333.2205; found, 333.2211.

2-(4-Ethyl-2-phenyl-5-pyridin-4-yl-imidazol-1-yl)ethanol (5l). White solid. ^{1}H NMR ($CDCl_3$): δ 8.58 (m, 2H, ArH), 7.70 (m, 2H, ArH), 7.34 (m, 5H, ArH), 3.63 (t, J = 5.6 Hz, 2H, CH_2), 3.43 (t, J = 5.6 Hz, 2H, CH_2), 3.09 (q, J = 7.3 Hz, 2H, CH_2), 1.21 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 150.9, 149.7, 143.9, 131.4, 129.4, 126.8, 124.8, 124.5, 123.0, 116.8, 61.3, 47.8, 43.6, 9.2. HRMS (EI) calcd for $C_{18}H_{19}N_3O$, 293.1528; found, 293.1521.

General Procedure for the Synthesis of 2,4,5-Trisubstituted Thiazoles (6). A 50-mL flask was charged with resin **3** (0.5 g) and the thiazolium catalyst (20 mol %) and purged with nitrogen for 15 min. To the flask was added anhydrous CH_2Cl_2 (25 mL), followed by the aldehyde (8 equiv), and the resulting mixture was stirred at 35 °C for 11 h. Triethylamine (20 equiv) was added via a syringe, and the reaction mixture was allowed to continue stirring overnight

at 35 °C, after which the solvent was removed by simple concentration followed by the addition of toluene (25 mL) and Lawesson's reagent (6 equiv). The reaction mixture was then refluxed overnight. The resin was removed by filtration and washed with MeOH (20 mL × 3). The combined organic layer was concentrated on a rotavapor and purified by flash column chromatography to give **6**.

4-(2,4-Diphenyl-thiazol-5-yl)pyridine (6a). White solid. ^{1}H NMR ($CDCl_3$): δ 8.61 (m, 2H, ArH), 7.71−7.69 (m, 2H, ArH), 7.41−7.37 (m, 6H, ArH), 7.30 (m, 2H, ArH), 7.24 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 177.1, 151.9, 150.8, 140.9, 140.7, 134.6, 132.5, 132.2, 129.2, 128.6, 128.5, 128.1, 127.9, 123.6. HRMS (EI) calcd for $C_{20}H_{14}N_2S$, 314.0878; found, 314.0879.

4-(2-Cyclohexyl-4-phenyl-thiazol-5-yl)-pyridine (6b). White solid. ^{1}H NMR ($CDCl_3$): δ 8.51 (m, 2H, ArH), 7.50−7.49 (m, 2H, ArH), 7.35−7.33 (m, 3H, ArH), 7.23 (m, 2H, ArH), 3.13−3.03 (m, 1H, CH), 2.28−2.18 (m, 2H), 1.93−1.72 (m, 3H), 1.68−1.27 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 176.6, 151.4, 150.1, 140.4, 134.6, 129.2, 128.6, 128.5, 128.4, 123.9, 43.1, 33.8, 26.1, 25.8. HRMS (EI) calcd for $C_{22}H_{20}N_2S$, 320.1347; found, 320.1349.

4-(4-Fluorophenyl)-2-phenyl-5-styrylthiazole (6c). White solid. ^{1}H NMR ($CDCl_3$): δ 7.48−7.42 (m, 6H, ArH), 7.30−7.11 (m, 9H, ArH and CH), 6.95 (d, J = 16.6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 168.2, 162.7, 151.4, 142.9, 136.0, 134.5, 133.1, 129.5, 129.2, 128.9, 128.7, 128.5, 128.2, 127.9, 127.6, 123.5, 123.1. HRMS (EI) calcd for $C_{23}H_{16}NFS$, 357.0987; found, 357.0989.

General Procedure for the Synthesis of 2,4,5-Trisubstituted Oxazoles (7). A 50-mL flask was charged with resin **3** (0.5 g) and the thiazolium catalyst (20 mol %) and purged with nitrogen for 15 min. To the flask was added anhydrous CH_2Cl_2 (25 mL), followed by the aldehyde (8 equiv), and the resulting mixture was stirred at 35 °C for 11 h. Triethylamine (20 equiv) was added via a syringe, and the reaction mixture was allowed to continue stirring overnight at 35 °C, after which iodine (5 equiv) and triphenylphosphine (5 equiv) were added, and the mixture was stirred at ambient temperature for another 20 h. The resin was then removed by filtration and washed with MeOH (20 mL × 3). The combined organic layer was concentrated on a rotavapor and purified by flash column chromatography to give **7**.

4-(2,4-Diphenyl-oxazol-5-yl)pyridine (7a). White solid. ^{1}H NMR ($CDCl_3$): δ 8.66 (m, 2H, ArH), 7.75−7.72 (m, 2H, ArH), 7.45−7.43 (m, 6H, ArH), 7.33 (m, 2H, ArH), 7.27 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 168.3, 150.2, 142.0, 138.9, 136.4, 132.0, 129.6, 129.0, 128.6, 128.4, 127.1, 126.8, 121.7, 121.4. HRMS (EI) calcd for $C_{20}H_{14}N_2O$, 298.1106; found, 298.1109.

4-(2-Cyclohexyl-4-phenyloxazol-5-yl)pyridine (7b). White solid. ^{1}H NMR ($CDCl_3$): δ 8.56 (m, 2H, ArH), 7.65−7.62 (m, 2H, ArH), 7.45 (m, 2H, ArH), 7.44−7.40 (m, 3H, ArH), 2.91 (m, 1H, CH), 2.21−2.11 (m, 2H, CH_2), 1.95−1.84 (m, 2H, CH_2), 1.80−1.62 (m, 3H), 1.50−1.26 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 168.2, 150.2, 142.0, 138.9, 136.4, 132.1, 128.9, 128.8, 128.3, 119.4, 37.7, 30.7, 25.9, 25.6. HRMS (EI) calcd for $C_{22}H_{20}N_2O$, 304.1576; found, 304.1579.

4-(4-Fluorophenyl)-2-phenyl-5-styryloxazole (7c). White solid. ^{1}H NMR ($CDCl_3$): δ 7.50−7.38 (m, 7H, ArH), 7.34−7.15 (m, 8H, ArH and CH), 7.06 (d, J = 16.6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 166.1, 163.4, 150.2, 142.0, 135.9, 134.4, 132.7, 130.7, 130.2, 129.4, 129.2, 128.8, 128.7, 128.3, 127.5, 127.3, 119.4. HRMS (EI) calcd for $C_{23}H_{16}NFO$, 341.1216; found, 341.1216.

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Supporting Information Available. Crystallographic files of **5c**, **5e**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sennequier, N.; Wolan, D.; Stuehr, D. J. *J. Biol. Chem.* **1999**, *274*, 930−938.
(2) Tafi, A.; Costi, R.; Botta, M.; Di Santo, R.; Corelli, F.; Massa, S.; Ciacci, A.; Manetti, F.; Artico, M. *J. Med. Chem.* **2002**, *45*, 2720−2732.
(3) Niwano, Y.; Seo, A.; Kanai, K.; Hamaguchi, H.; Uchida, K.; Yamaguchi, H. *Antimicrob. Agents Chemother.* **1994**, *38*, 2204−2206.
(4) Brogden, R. N.; Heel, R. C.; Speigt, T. M. *Drugs* **1978**, *16*, 387−417.
(5) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, C.; Gamellin, C. R.; Parsons, M. E. *J. Int. Med. Res.* **1975**, *3*, 86−92.
(6) Dyck, B.; Goodfellow, V. S.; Phillips, T.; Grey, J.; Haddach, M.; Rowbottom, M.; Naeve, G. S.; Brown, B.; Saunders, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1151−1154. (b) Hunkeler, W.; Möhler, H.; Pieri, L.; Polc, P.; Bonetti, E. P.; Cumin, R.; Schaffner, R.; Haefely, W. *Nature* **1981**, *290*, 514−516.
(7) Grimmett, M. R. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1980; Vol. 27, p 241. (b) Sisko, J. *J. Org. Chem.* **1998**, *63*, 4529−4531. (c) Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449−8454. (d) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843−846. (e) Nunami, K.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635−7642. (f) Lantos, I.; Zhang, W. Y.; Shui, X.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 7092−7095. (g) Reiter, L. A. *J. Org. Chem.* **1987**, *52*, 2714−2726.
(8) Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835−838. (b) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800−2801. (c) Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323−326. (d) Cobb, J. M.; Grimster, N.; Khan, N.; Lai, J. Y. Q.; Payne, H. J.; Payne, L. J.; Raynham, T.; Taylor, J. *Tetrahedron Lett.* **2002**, *43*, 7557−7560. (e) Henkel, B. *Tetrahedron Lett.* **2004**, *45*, 2219−2221.
(9) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.
(10) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Org. Syntheses* **2000**, *77*, 198−205.
(11) Sisko, J.; Mellinger, M.; Sheldrake, P. W.; Baine, N. H. *Tetrahedron Lett.* **1996**, *37*, 8113−8116.
(12) Structure of **11** has been confirmed by X-ray crystallography.

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