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Synthesis of 3,4,5-Trisubstituted Isoxazoles via Sequential [3 + 2] Cycloaddition/ Silicon-Based Cross-Coupling Reactions

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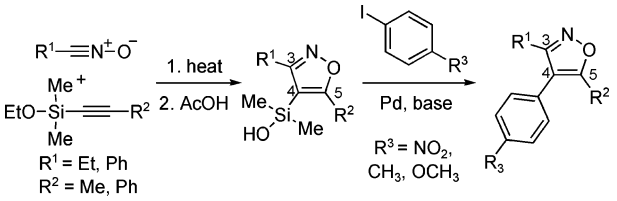
Received December 23, 2004



A [3 + 2] cycloaddition reaction between alkynyldimethylsilyl ethers and aryl and alkyl nitrile oxides to produce isoxazolylsilanols has been developed. The cross-coupling reactions of these heterocyclic silanols with a variety of aryl iodides affords 3,4,5-trisubstituted isoxazoles. This sequential process allows for rapid variation of substituents at the 3, 4, and 5 positions of the isoxazole.

Recent reports from these laboratories have described mild and selective methods for the introduction of silicon functional groups into carbon frameworks followed by transformation of these new organosilicon functions into carbon−carbon bonds by a palladium-catalyzed cross-coupling reaction.[1] This strategy has been demonstrated for a variety of processes such as the hydrosilylation[2a] and silylformylation of alkynes,[2b] silylation of aryl halides,[3] and ring-closing metathesis of vinyl silyl ethers.[4] These methods place the silicon functional group into a specific environment which is then primed for the cross-coupling reaction. Other powerful transformations that could install a silicon group to guide the construction of useful products are cycloaddition reactions. In the context of heterocycle synthesis, the [3 + 2] cycloaddition reaction of alkynylsilanes would provide highly substituted, silicon-containing five-membered heterocycles from acyclic precursors. A concern in the synthesis of these heterocycles is the regioselectivity of the cycloaddition (and consequently the substitution pattern) which is highly dependent on both steric and electronic features of the dipolarophile. Silicon-substituted dipolarophiles undergo the [3 + 2] cycloaddition with high regioselectivities.[5] We reasoned that in this sequential cycloaddition/cross-coupling process not only would the silicon group influence the regioselectivity of the cycloaddition but also would enable further functionalization of the heterocycle by a palladium-catalyzed, cross-coupling reaction.[6] The development of this process would allow for the synthesis of a wide array of heterocycles where the substituents could be selectively varied based on the choice of dipole or dipolarophile. Subsequent cross-coupling would provide another point of diversity in the synthesis of the substituted heterocycles.

Isoxazoles constitute an important family of five-membered heterocycles in view of their use in many natural products syntheses[7] and occurrence in pharmaceutical agents, such as the COX-2 inhibitor Bextra.[8] A powerful method for the construction of isoxazoles is the [3 + 2] dipolar cycloaddition between alkynes and nitrile oxides,[9] although regioselective construction of 3,4,5-trisubstituted isoxazoles is dependent on the substituents of the dipolarophile.[10] An alternative strategy to selectively prepare 3,4,5-trisubstituted isoxazoles is to employ a placeholder on the alkyne that biases the [3 + 2] cycloaddition and facilitates the construction of isomerically pure isoxazole. This concept has been reduced to practice with both tin-[11] and boron-substituted[12] alkynes that engage in [3 + 2] dipolar cycloadditions with nitrile oxides to afford substituted isoxazoles in moderate selectivities. In these cases, further manipulation of the newly formed isoxazoles via a Stille[13] or Suzuki[14] cross-coupling introduces a third substituent in a controlled manner, albeit with a limited variety of substituents on

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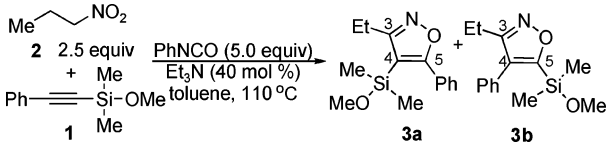
10.1021/jo047755z CCC: $30.25
Published on Web 02/24/2005

both the dipole and dipolarophile. We surmised that the [3 + 2] cycloaddition of silicon-substituted alkynes with nitrile oxides should proceed in a regioselective manner such that the silicon could facilitate further functionalization. In this paper, we report the cycloaddition of aryl- and alkyl-substituted alkynyldimethylsilyl ethers with aryl and alkyl nitrile oxides to generate a variety of differently functionalized 3,5-disubstituted 4-silylisoxazoles. A silicon-based cross-coupling reaction with aryl iodides creates a point for further diversification to afford 3,4,5-trisubstituted isoxazoles.

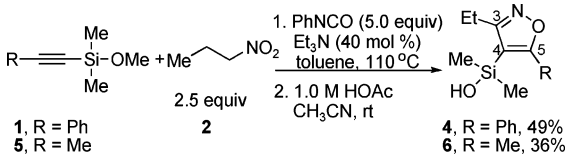
Studies on the [3 + 2] cycloaddition commenced with the reaction between phenylethynyl silyl ether, **1**, and ethyl nitrile oxide, which was generated *in situ* from 1-nitropropane, **2**, and phenyl isocyanate.[15] Most nitrile oxides must be prepared *in situ* from stable precursors to limit dimerization of the dipole.[9] Monitoring consumption of **1** and formation of the two possible isomeric isoxazoles, **3a** and **3b**, by ^{1}H NMR spectroscopy showed that slow addition of **2** to **1** was required for high conversion to **3a** and **3b**. Addition of 2.5 equiv of **2** to **1** over 5 h resulted in 89% conversion, based on the consumption of **1**, and a 3.4:1 mixture of **3a/3b** (Scheme 1).

SCHEME 1



Hydrolysis of the mixture of silyl ethers **3** to silanol **4** was effected with 1.0 M aqueous HOAc in CH_3CN[3] and afforded **4** in a 49% isolated yield (from **1**) as a single isomer. Only trace amounts of the silanol resulting from hydrolysis of **3b** could be isolated. Similarly, cycloaddition of **5** with **2** proceeded in a 3.3:1 regioselectivity of the isoxazole isomers with the silyl ether in the 4 and 5 positions, respectively. Hydrolysis of the crude mixture of silyl ethers afforded silanol **6** in a 36% yield (from **5**) as a 19:1 mixture of **6** to the 5-substituted silanol (Scheme 2).

SCHEME 2



To further explore substituent effects, the 3-phenyl-substituted isoxazoles were obtained by cycloaddition of silyl ethers **1** or **5** with benzonitrile oxide, generated *in situ* from chlorooxime **7** and $KHCO_3$ (Table 1). The addition of equimolar amounts of $KHCO_3$ and **7** to **1** resulted in the formation of isoxazole isomers **8a** and **8b** albeit with modest conversion. The yield of **8** could be improved by the portionwise addition of $KHCO_3$ and **7**. Addition of 2 equiv of both $KHCO_3$ and **7** to **1** in two portions in a 2 h interval improved the conversion to **8**; however, addition of a third portion of both $KHCO_3$ and

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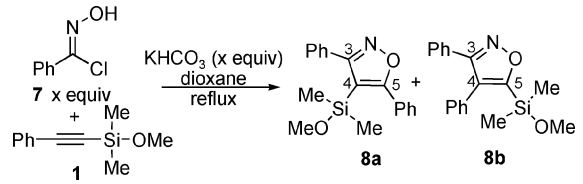
TABLE 1. Optimization of [3 + 2] Cycloaddition To Form 8a and 8b

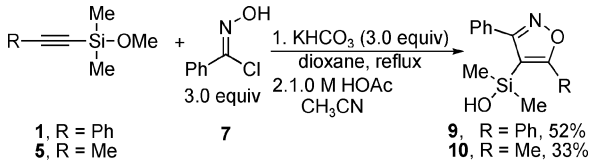


entry	**7**, equiv	no. of additions	interval,[a] h	time,[a] h	conversion,[b] %	**8a/8b**[c]
1	2.0	1		2	42	4.1:1
2	2.0	2	2	4	80	4.3:1
3	2.0	3	2	8	91	4.7:1
4	1.0	3	1	5	89	4.5:1

[a] See the Supporting Information for details. [b] Consumption of **1** measured by ^{1}H NMR spectroscopy vs hexamethylbenzene as an internal standard. [c] As determined by ^{1}H NMR spectroscopy.

7 after an additional 2 h interval had a negligible effect (Table 1, entries 1–3). Gratifyingly, addition of 1.0 equiv of both $KHCO_3$ and **7** in three portions with a 1 h interval provided an 89% conversion to **8a** and **8b** (entry 4). Under these conditions, cycloaddition of **1** with **7** afforded **8a** and **8b** in a 4.6:1 ratio. Hydrolysis of the resulting silyl ethers afforded silanol **9** in 52% yield as a single isomer. Likewise, cycloaddition of **5** with **7** produced a 1.8:1 ratio of the isoxazole isomers with the silyl ether in the 4- and 5-positions, respectively. Subsequent hydrolysis of this mixture afforded silanol **10** in a 33% yield as a single isomer (Scheme 3). In both of these cases the 5-substituted silanol was not isolated.

SCHEME 3

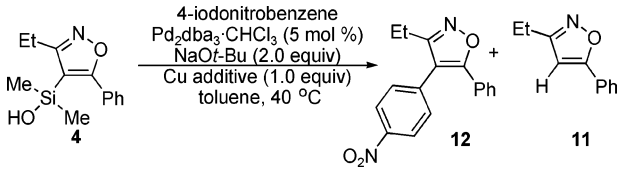


To further expand the utility of these cycloadducts, the cross-coupling reactions of silanols **4**, **6**, **9,** and **10** were investigated. Initial studies with **4** showed that significant amounts of the product of protodesilylation, **11**, was obtained with a variety of base and solvent combinations (NaO-*t*-Bu, KOTMS, Cs_2CO_3, K_3PO_4 in toluene, THF, DMF). Fortunately, the amount of **11** could be reduced by the use of copper salts[6] (Table 2). Addition of copper(I) iodide had little effect other than to significantly reduce the rate of the reaction (entries 1 and 2). Changing the additive to copper(II) salts showed both an increase in the rate of cross-coupling as well as an improvement in the ratio of **12** to **11**. Copper acetate was superior to all other salts surveyed in both conversion to **12** and selectivity (entries 3–5).

To further improve conversion of **4** to **12**, the amounts of base and copper were varied (Table 3). Decreasing the amount of base resulted in a large increase in the proportion of **11** (entry 2), whereas increasing the amount of base to 2.5 equiv resulted in a 97% conversion to **12** in less than 2 h with a high ratio of **12/11**. Decreasing the $Cu(OAc)_2$ loading to 25 mol % resulted in a slower reaction as well as a lower ratio of **12/11**.

Under these conditions, the cross-coupling reaction of **4** with 4-iodonitrobenzene afforded **12** in a 78% yield

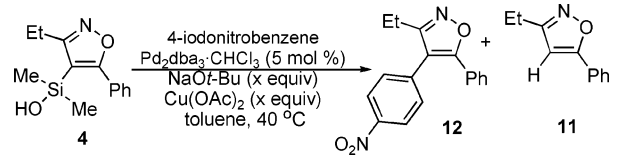
TABLE 2. Effect of Copper Source on the Cross-Coupling of 4 with 4-Iodonitrobenzene



entry	copper additive	time, h	**12**,[a] %	**12/11**[b]
1	none	4	47	7.9:1
2	CuI	4	19	7.7:1
3	$CuBr_2$	4	67	7.5:1
4	$Cu(OTf)_2$	4	74	20.0:1
5	$Cu(OAc)_2$	4	81	25.8:1

[a] Measured by ^{1}H NMR spectroscopy verses hexamethylbenzene as an internal standard. [b] As determined by ^{1}H NMR spectroscopy.

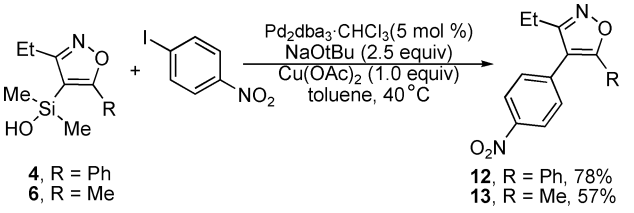
TABLE 3. Optimization of the Amount of Base and Copper Acetate



entry	NaO-*t*-Bu, equiv	$Cu(OAc)_2$, equiv	time, h	**12**,[a] %	**12/11**[b]
1	2.0	1.0	4	81	25.8:1
2	1.2	1.0	4	45	1.2:1
3	2.5	1.0	2	97	23.7:1
4	2.5	0.25	4	57	11.2:1
5	2.5	0.25	8	90	11.4:1

[a] Measured by ^{1}H NMR spectroscopy vs hexamethylbenzene as an internal standard. [b] As determined by ^{1}H NMR spectroscopy.

SCHEME 4



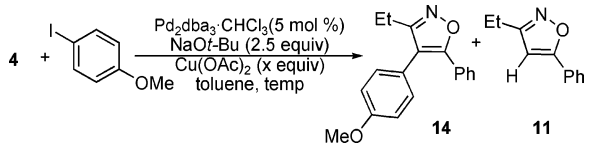
(Scheme 4). Reaction of **6** with 4-iodonitrobenzene afforded **13** in a 57% yield.

Next, the cross-coupling of **4** with an electron-rich aryl halide, 4-iodoanisole, was investigated. Using same cross-coupling conditions as above, significant amounts of protodesilylation product, **11**, was observed (Table 4, entry 1). Decreasing the $Cu(OAc)_2$ loading and increasing the reaction temperature improved conversion to product **14** while suppressing the formation of **11** (entries 2−4). Without $Cu(OAc)_2$, the rate of reaction was impractically slow and the amount of **11** was decreased only slightly (entry 5).

The cross-coupling reaction of **4** with 4-iodoanisole afforded **14** in a 62% yield (Table 5, entry 1) whereas the reaction of **4** with 4-iodotoluene afforded **15** in a 61% yield (entry 2). The use of silanol **6**, in which the 5-substituent is now a methyl group, resulted in consumption of the aryl iodide before consumption of **6**. When the amount of aryl iodide was increased to 1.25 equiv reaction of **6** afforded **16** in 52% yield (entry 3) and **17** in 56% yield (entry 4).

The cross-coupling of a sterically congested silanol bearing phenyl substituents at the C(3) and C(5) positions, substrate **9**, was studied. At 80 °C in toluene with 25 mol % of $Cu(OAc)_2$, a large amount of the product from protodesilylation, **19**, was observed (Table 6, entry 1). Changing the solvent to dioxane resulted in moderate

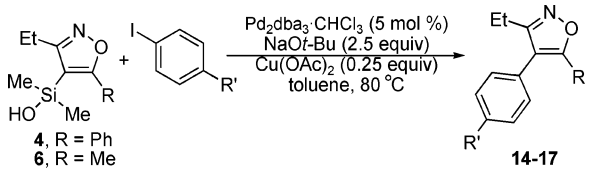
TABLE 4. Optimization of the Cross-Coupling of 4 with 4-Iodoanisole



entry	*T*, °C	$Cu(OAc)_2$, equiv	time, h	**14**,[a] %	**14/11**[b]
1	40	1.0	4	19	1:2.1
2	40	0.25	24	43	2.1:1
3	60	0.25	8	75	2.7:1
4	80	0.25	3	82	2.9:1
5	60	0	8	45	3.5:1

[a] Measured by ^{1}H NMR spectroscopy vs hexamethylbenzene as an internal standard. [b] As determined by ^{1}H NMR spectroscopy.

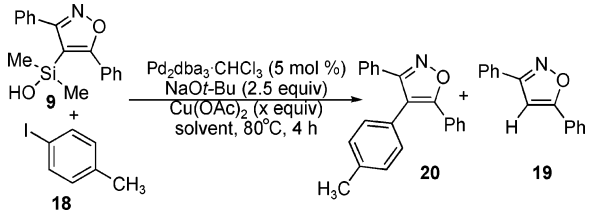
TABLE 5. Summary of Cross-Coupling Reactions of 4 and 6



entry	silanol	silanol equiv	R′	arylI, equiv	product	yield,[a] %
1	**4**	1.1	−OMe	1.0	**14**	62
2	**4**	1.1	−Me	1.0	**15**	61
3	**6**	1.0	−OMe	1.25	**16**	52
4	**6**	1.0	−Me	1.25	**17**	56

[a] Yield of analytically pure material.

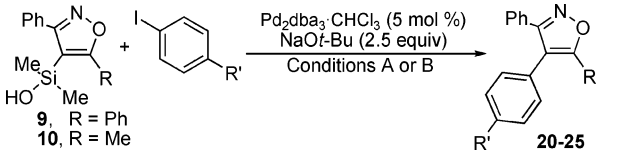
TABLE 6. Optimization of Cross-Couplings of 9 with 4-Iodotoluene



entry	**9**, equiv	**18**, equiv	solvent	$Cu(OAc)_2$, equiv	**20**,[a] %	**20/19**[b]
1	1.1	1.0	toluene	0.25	44	1:1.2
2	1.1	1.0	dioxane	0.25	51	1.3:1
3	1.1	1.0	dioxane	0	65	1.6:1
4	1.0	1.25	dioxane	0	72	2.5:1
5	1.0	1.5	dioxane	0	80	3.7:1
6	1.0	2.0	dioxane	0	76	3.2:1

[a] Measured by ^{1}H NMR spectroscopy vs hexamethylbenzene as an internal standard. [b] As determined by ^{1}H NMR spectroscopy.

TABLE 7. Summary of Cross-Coupling Reactions of 9 and 10



entry	silanol	method[a]	R′	product	yield,[b] %
1	**9**	A	−Me	**20**	69
2	**9**	A	−OMe	**21**	68
3	**9**	A	$-NO_2$	**24**	55
4	**10**	A	−Me	**22**	60
5	**10**	A	−OMe	**23**	63
6	**10**	B	$-NO_2$	**25**	63

[a] Method A: dioxane, 80 °C. Method B: toluene, 40 °C, 1.0 equiv of $Cu(OAc)_2$. [b] Yield of analytically pure material.

improvement, whereas elimination of $Cu(OAc)_2$ altogether further improved the ratio of **20/19** (entries 2 and 3). However, in dioxane, a significant amount of the aryl iodide homocoupling product was also observed. As was the case with **6**, using 1.5 equiv of aryl iodide improved the conversion to **20** (entries 4−6).

Employing these conditions in the cross-coupling of **9** and **10** with 4-iodotoluene, 4-iodoanisole, and 4-iodonitrobenzene afforded the products **20**−**25** in 55−69% yields (Table 7). The reactions of both **9** and **10** with 4-iodonitrobenzene in dioxane resulted in poorer ratios of product to protodesilylation. The cross-coupling of **10** with 4-iodonitrobenzene could be improved by carrying out the reaction in toluene at 40 °C with 1.0 equiv of $Cu(OAc)_2$ to afford **25** in 63% yield (entry 6).

In summary, we have developed sequential [3 + 2]-cycloaddition and cross-coupling reactions for the preparation of 3,4,5-trisubstituted isoxazoles. Reaction conditions for the two major classes of nitrile oxide cycloadditions were developed for silyl ethers to afford the 4-substituted silanols. Both alkyl and aryl substituents at the 3- and 5-positions of the isoxazole were selectively incorporated based on the choices of the dipole and dipolarophile. The subsequent transformation of the silanol through a cross-coupling reaction provided a wide array of 3,4,5-trisubstituted isoxazoles. In the development of the cross-coupling reaction conditions, the use of $Cu(OAc)_2$ effected the rate of the cross-coupling reaction; however, in some cases, $Cu(OAc)_2$ also promoted the protodesilylation of the silanol. Investigations into the role of $Cu(OAc)_2$ in the silicon-based cross-coupling reaction as well as application of the sequential cycloaddition/silicon-based cross-coupling to other families of five-membered heterocycles are ongoing.

Experimental Section

General Experimental Procedures. See the Supporting Information.

3-Ethyl-4-(dimethylhydroxysilyl)-5-phenylisoxazole (4). In a 50-mL oven-dried round-bottom flask containing a magnetic stir bar and equipped with a reflux condenser and a nitrogen inlet adapter capped with a rubber septum were combined **1** (2.19 g, 11.5 mmol), toluene (8.75 mL), phenyl isocyanate (6.25 mL, 57.5 mmol, 5.0 equiv), and triethylamine (0.32 mL, 2.3 mmol, 0.2 equiv). This solution was heated to reflux under an atmosphere of N_2. A solution of 1-nitropropane (2.56 mL, 28.75 mmol, 2.5 equiv) and triethylamine (0.32 mL, 2.3 mmol, 0.2 equiv) in toluene (8.75 mL) was added via syringe pump over 5.5 h. After 6 h, the mixture was cooled to room temperature. Diethyl ether (20 mL) was added to the yellow reaction mixture, and the slurry was filtered and eluted with Et_2O (3 × 20 mL). The filtrate was concentrated *in vacuo* to afford a yellow oil that was dissolved in CH_3CN (115 mL) and treated with a 1.0 M aqueous HOAc solution (46 mL). The yellow solution was stirred at room temperature for 2 h. The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (50 mL). After addition of H_2O (50 mL) and brine (50 mL), the aqueous layer was back extracted with CH_2Cl_2 (25 mL). Concentration of the combined organic layers *in vacuo* afforded the crude silanol. Purification by column chromatography (SiO_2, 60 mm × 15 cm, Florisil, 60 mm × 1 cm, CH_2Cl_2/acetone 97/3) and then a second column chromatography (SiO_2, 50 mm × 20 cm, Florisil, 60 mm × 1 cm, pentane/Et_2O 2/1) followed by trituration of the resulting light yellow solid using pentane/Et_2O (15/1) afforded 1.40 g (49%) of **4** as a white solid. Data for **4**: mp 63−64 °C (pentane/ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.7, 1.6, 2 H, HC(7)), 7.44 (m, 3 H, HC(8), HC(9)), 2.81 (q, J = 7.6, 2 H, HC(11)), 2.60 (s, 1 H, H(OSi)), 1.33 (t, J = 7.6, 3 H, H(C12)), 0.29 (s, 6 H, HC(10)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4 C(5), 168.6 C(3), 130.1 C(7), 129.5 C(6), 128.8 C(8) or C(9), 128.4 C(8) or C(9), 107.8 C(4), 20.9 C(11), 12.9 C(12), 1.8 C(10); IR (film) 3369 (br s), 2976 (m), 1612 (w), 1558 (m), 1499 (w), 1460 (m), 1445 (m), 1388 (m), 1257 (s), 1073 (w), 879 (s), 825 (s), 770 (s); MS (EI, 70 eV) 247 (49, M^+), 233 (20), 232 (100), 214 (27), 186 (13), 137 (19), 128 (21), 105 (12), 77 (47), 75 (29); R_f 0.26 (pentane/Et_2O, 2/1) [silica gel, UV]. Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.93; N, 5.66. Found: C, 63.12; H, 6.98; N, 5.77.

3-Ethyl-4-(4-nitrophenyl)-5-phenylisoxazole (12). In an oven-dried 5-mL, round-bottom flask containing a magnetic stir bar were placed NaO-*t*-Bu (0.240 g, 2.5 mmol, 2.5 equiv) and $Cu(OAc)_2$ (0.181 g, 1.0 mmol, 1.0 equiv) in a drybox. After removal of the flask from the drybox, 4-iodonitrobenzene (0.249 g, 1.0 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.052 g, 0.05 mmol, 0.05 equiv) were added. The flask was fitted with an argon inlet adaptor capped with a septum. Toluene (1.5 mL) was added. The reaction mixture was heated to 40 °C for 10 min followed by addition of **4** (0.272 g, 1.1 mmol, 1.1 equiv). After being heated 3 h at 40 °C, the mixture was cooled to room temperature and was diluted with EtOAc (3 mL). The resulting mixture was filtered through a SiO_2 plug (2 cm × 2 cm) and eluted with EtOAc (30 mL), and the filtrate was concentrated *in vacuo* to afford a yellow oil. Purification of the oil by column chromatography (SiO_2, 40 mm × 20 cm, CH_2Cl_2) then (SiO_2, 20 mm × 25 cm, hexanes/EtOAc, 5/1) afforded a yellow solid that was further purified by recrystallization from hexanes to afford 0.228 g (78%) of **12** as light yellow needles. Data for **12**: mp 96−97 °C (hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, J = 9.0, 2 H, HC(12)), 7.49 (d, J = 9.0, 2 H, HC(11)), 7.46 (dt, J = 6.9, 1.5, 2 H, HC(7)), 7.40 (tt, J = 7.5, 1.5, 1 H, HC(9)), 7.35 (tt, J = 7.5, 0.9, 2 H, HC(8)), 2.68 (q, J = 7.6, 2 H, HC(14)), 1.22 (t, J = 7.6, 3 H, HC(15)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6 C(5), 164.0 C(3), 147.6 C(13), 138.0 C(10), 130.8 C(12), 130.3 C(9), 128.9 C(7), 127.12 C(8), 127.09 C(6), 124.3 C(11), 113.7 C(4), 18.9 C(14), 12.0 C(15); IR (KBr) 2977 (w), 1624 (w), 1601 (m), 1519 (s), 1460 (m), 1447 (m), 1425 (w), 854 (s); MS (EI, 70 eV) 295 (20), 294 (98 M^+), 251 (13), 165 (28), 164 (14), 117 (18), 105 (100), 103 (17), 78 (10), 77 (89), 62 (35); R_f 0.73 (CH_2Cl_2). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.12; H, 4.78; N, 9.42.

Acknowledgment. We are grateful to the National Institutes of Health (GM 63167) for generous financial support. J.M.K. thanks the University of Illinois for a graduate fellowship.

Supporting Information Available: Detailed synthetic procedures as well as full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO047755Z