Preparation of 4,5-Disubstituted Pyrimidines: Ring Substitution of 5-Mesyloxymethylpyrimidines

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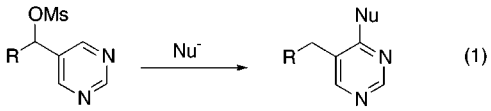
Introduction

Pyrimidine derivatives are widespread in medicinal and natural products chemistry. A number of commercially important drugs incorporate this heterocycle.[1] Specifically substituted pyrimidines are valuable intermediates for drug discovery. In particular, the preparation of 4,5-disubstituted pyrimidines can be difficult via the reported methods. Several synthetic routes to these compounds are known starting from the corresponding 5-substituted derivatives. Strekowski[2] has reported that treatment of 5-methylpyrimidine with methyllithium, followed by oxidation of the intermediate dihydropyrimidine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), affords 4,5-dimethylpyrimidine. Similarly, Wilson and Strekowski[3] have described the preparation of a 4-aryl-5-methylpyrimidine upon exposure of 5-methylpyrimidine to an aryllithium, followed by DDQ oxidation. Davis[4] has reported that deprotonation of 5-methylpyrimidine with lithium diisopropylamide (LDA), followed by treatment with a nitrile and more LDA gave, after workup, 4,5-fused pyrrolopyrimidines. Hara[5] and van der Plas have prepared 4-amino-5-phenylpyrimidine from 5-phenylpyrimidine by use of potassium amide and potassium permanganate in liquid ammonia. Synthesis of 4,5-disubstituted pyrimidines from acyclic precursors has also been reported. For example, Bredereck[6] has described a general method to this class of compounds from trisformaminomethane and active methylene compounds.

During a project to prepare a series of functionalized nitrogen heterocycles, we became aware of the possibility of carrying out a transformation of the type shown in eq 1, where the nucleophile is the sodium salt of a nitrogen heterocycle (Ms = SO_2CH_3).

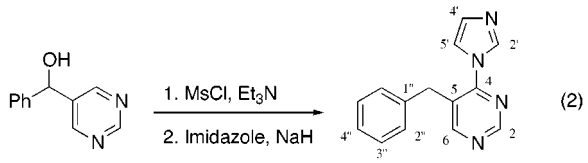


(1)

Simple aminopyrimidines can be prepared via the Chichibabin reaction[7] using alkali-metal amides in an intermolecular reaction. Also, several intramolecular versions of eq 1 using substituted pyridines have been reported.[8,9] However, we were not aware of any methods that could provide heteroaromatic-substituted pyrimidines according to eq 1. We felt that there might be considerable interest in ready access to such derivatives and therefore embarked upon a preliminary investigation of this new reaction.

Results and Discussion

The reaction of pyrimidine **1** with imidazole to afford **2** was examined initially (eq 2).



(2)

1 **2**

The known compound **1** was prepared according to the published procedure from 5-bromopyrimidine and benzaldehyde.[11] Treatment of **1** with methanesulfonyl chloride (1.1 equiv) and triethylamine (1.2 equiv) in methylene chloride at −40 °C for 1 h afforded the corresponding mesylate of **1**. At the same time, imidazole (1.5 equiv) was treated with sodium hydride (2.6 equiv) in DMF for 1 h at 5−10 °C and then chilled to −40 °C. The mesylate solution was then added to the flask containing the imidazole sodium salt at −40 °C, and the resulting mixture was allowed to warm to 25 °C and stirred at that temperature for 18 h. Workup afforded a crude mixture, which by ^{1}H NMR analysis suggested that the 4,5-disubstituted pyrimidine **2** was the major product. Purification by flash chromatography provided **2** in 64% yield. The ^{1}H NMR spectrum clearly supported the assigned structure. Singlets at 9.09 ppm (1H) and 8.71 ppm (1H) could be assigned to H_2 and H_6 of the pyrimidine ring, respectively, while a singlet at 4.19 ppm (2H) could be assigned to the benzyl methylene.

A second, less polar product, 2,5-disubstituted pyrimidine **3**, was also readily separated by chromatography from this mixture (17%). Compound **3** displayed singlets at 8.51 ppm (2H) and 3.99 ppm (2H), which could be assigned to $H_{4,6}$ of the pyrimidine ring and the benzyl

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(10) Examination of the ^{1}H NMR spectrum of our sample of **1** revealed that all of the chemical shift data were about 0.1−0.15 ppm downfield as compared to those reported.[11]

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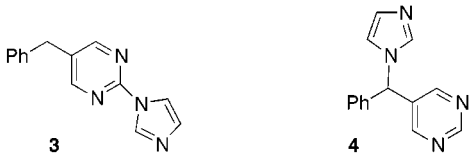
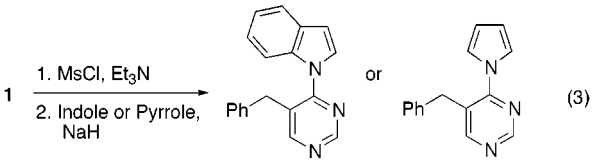
methylene, respectively. Analysis of the ^{13}C, ^{1}H COSY, HMBC, and HMQC spectra obtained for **2** and **3** confirmed these structural assignments. Monosubstituted



3 **4**

pyrimidine **4**, which would arise from direct displacement on the mesylate of **1**, could not be isolated from the reaction mixture. Inspection of the crude product by ^{1}H NMR suggested that **4** was not present to any appreciable amount.

We then attempted to determine whether other heterocycles could be induced to undergo a similar transformation with pyrimidine **1** (eq 3). When indole was used

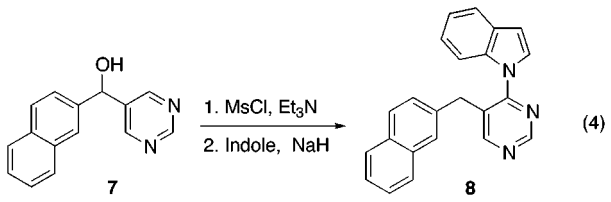


5 **6** (3)

as the nucleophile under the same reaction conditions, the 4,5-disubstituted pyrimidine **5** was obtained in 61% yield after purification. We also examined the use of a less stable heterocycle, pyrrole, in this new method. We were gratified to find that the 4,5-disubstituted pyrrolylpyrimidine **6** was obtained in 35% yield after purification. The NMR spectral assignments for **5** and **6** followed from those determined for compound **2**.

In these two reactions, none of the 2,5-disubstituted isomers corresponding to **3** were isolated. However, the ratio of 4,5- to 2,5-disubstituted compounds appears to be ca. 10:1 as shown by ^{1}H NMR analysis of the crude reaction mixtures. Singlets are present 0.1−0.2 ppm upfield from the corresponding benzyl methylene absorbances for the 4,5-disubstituted products. These absorbances are tentatively assigned to the 2,5-disubstituted compounds. This is consistent with the ^{1}H NMR chemical shift data observed for the benzyl methylenes of **2** and **3** (see Experimental Section).

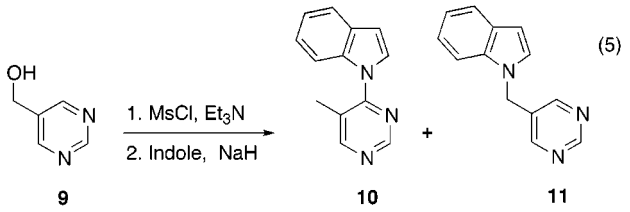
We next examined the effect of changing the substitution at C_5 of the pyrimidine. The reaction of the substituted pyrimidine **7** with indole was investigated (eq 4).



7 **8** (4)

Compound **7** was prepared following the published method.[11] The reaction of **7** according to the general procedure afforded 47% of pyrimidine **8** after purification. Once again, the ratio of **8** to the corresponding 2,5-disubstituted isomer was ca. 10:1.

To probe when direct benzylic displacement might intervene in preference to ring substitution, the use of the substituted pyrimidine **9** was investigated (eq 5).

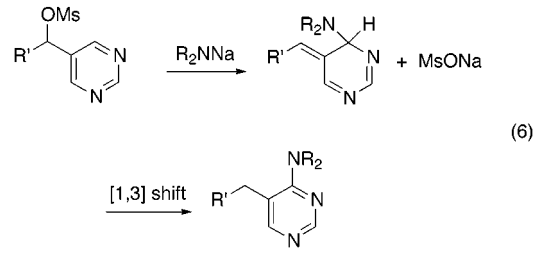


9 **10** **11** (5)

The known compound **9**, prepared according to published procedures,[13,14] was exposed to the standard reaction conditions. Remarkably, a preponderance of 4,5-disubstituted pyrimidine **10** (26%) was isolated as compared to the normal direct substitution product **11** (24%). The ^{1}H NMR spectrum for **10** reveals singlets at 9.06 ppm (1H) and 8.71 ppm (1H) that are assigned to H_2 and H_6 of the pyrimidine ring, respectively, while the singlet at 2.38 ppm (3H) is due to the methyl group. Compound **11**, on the other hand, displays singlets at 9.14 ppm (1H) and 8.51 ppm (2H) that are assigned to H_2 and H_4 of the pyrimidine ring, respectively, while the singlet at 5.34 ppm (2H) arises from the diaryl methylene group.

We also attempted to determine whether other nucleophiles might be induced to undergo this ring displacement. Unfortunately, the reaction of benzylamine, aniline, or 4-methoxyaniline with the mesylate of **1** gave a complex mixture from which no products could be isolated. Also, when the mesylate of **1** was treated with phenylmagnesium bromide, a similar result was obtained.

We propose that the 4,5-disubstituted pyrimidine products are formed via the mechanism shown below (eq 6, R_2NNa = the sodium salt of a nitrogen heterocycle).



(6)

Initial attack of the nucleophile on C_4 of the pyrimidine ring should be promoted by the highly electron-deficient nature of this heterocycle. A [1,3]-sigmatropic shift would then provide the rearomatized products. 2,5-Disubstituted pyrimidines such as **3** are envisioned to arise from a similar nucleophilic attack at C_2 of the pyrimidine ring, followed by a [1,5]-sigmatropic shift. However, a stepwise mechanism, involving initial dissociation of the mesylate, is also possible.

Conclusion

Herein we report a novel and efficient method for the synthesis of a variety of 4,5-disubstituted pyrimidines. The sodium salts of nitrogen heterocycles react preferentially with 5-mesyloxymethylpyrimidines at C_4 of the pyrimidine ring. Other minor products observed are a

(12) In our experience, use of mechanical stirring for lithiation reactions of 5-bromopyrimidine, as reported by Rho,[13] is important to obtain good yields.

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ring substitution at C_2, and in the case of **9**, direct mesylate displacement at the benzylic position. This new method affords quick access to highly functionalized pyrimidines in reasonable overall yields. Starting from commercially available 5-bromopyrimidine, 4,5-disubstituted pyrimidines can be obtained in only two separate reactions. The synthesis of these interesting polycyclic nitrogen heterocycles by existing methods would likely require a lengthy synthetic sequence. More highly substituted mesyloxymethylpyrimidines or even pyridine derivatives may react in a similar fashion. In fact, we have prepared a tetrasubstituted pyrimidine (albeit in low yield) by the reaction of the 2,4-dimethoxy derivative of **1**[15] with an indole derivative.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a JEOL Eclipse 300 Spectrometer. NMR assignments are based on a combination of the ^{1}H, ^{13}C, ^{1}H COSY, HMBC, and HMQC spectra. Mass spectra were run at the Department of Chemistry, Harvard University. Elemental analyses were performed at Atlantic Microlab. Thin-layer chromatography was carried out on Baker Si 250F plates. Visualization was accomplished with ultraviolet exposure or with phosphomolybdic acid. Flash chromatography was carried out on ICN SiliTech silica gel (60 μM). Anhydrous methylene chloride, tetrahydrofuran, and dimethylformamide were Aldrich Sure/Seal, and triethylamine was dried over potassium hydroxide. Other materials were reagent grade.

General Procedure for the Preparation of 4,5-Disubstituted Pyrimidines. A solution of the alcohol **1**[10,11] (93 mg, 0.50 mmol) was dissolved in methylene chloride (4 mL) and then cooled to −40 °C. Triethylamine (85 μL, 62 mg, 0.61 mmol) was added, followed by methanesulfonyl chloride (43 μL, 64 mg, 0.56 mmol). The reaction mixture was stirred for 1 h at −35 to −45 °C. At the same time, the heterocyclic compound (0.75 mmol) was dissolved in 4 mL of DMF in a separate flask and cooled to 0 °C. Sodium hydride (54 mg of a 60% oil dispersion, 1.35 mmol) was added, and the resulting suspension was stirred at 5−10 °C for 1 h and then cooled to −40 °C. The mesylate solution was then added via cannula to the sodium salt of the heterocycle over 15 min. The reaction mixture was allowed to warm to 25 °C and stirred at that temperature for 18 h. Water and ethyl acetate were added, and the layers were separated. The organic phase was dried (sodium sulfate), filtered, and concentrated. The crude product obtained was purified by flash chromatography with the indicated eluents to afford the pyrimidine products.

5-Benzyl-4-imidazol-1-ylpyrimidine (2) and 5-Benzyl-2-imidazol-1-ylpyrimidine (3). The use of imidazole as heterocycle following the general procedure (elution with 30% to 60% ethyl acetate/hexanes) afforded 76 mg (64%) of **2** as a yellow oil, R_f = 0.35 (ethyl acetate). ^{1}H NMR (chloroform-*d*): δ 9.09 (s, 1H, H_2); 8.71 (s, 1H, H_6); 8.26 (s, 1H, $H_{2'}$); 7.47 (br s, 1H, $H_{5'}$); 7.26−7.38 (m, 3H, $H_{3''}$, $H_{4''}$); 7.23 (br s, 1H, $H_{4'}$); 7.07 (d, 2H, J = 7.1, $H_{2''}$); 4.19 (s, 2H, benzyl). ^{13}C NMR (chloroform-*d*): δ 162.06 (C_6); 157.46 (C_2); 154.65 (C_4); 136.96 (overlapping $C_{1''}$ and $C_{2'}$); 130.39 ($C_{4'}$); 129.37 ($C_{3''}$); 128.35 ($C_{2''}$); 127.50 ($C_{4''}$); 124.00 (C_5); 118.62 ($C_{5'}$); 35.10 (benzyl). Exact mass calcd for $C_{14}H_{12}N_4$ *m/e* 236.1062, found *m/e* 236.1056. Anal. Calcd for $C_{14}H_{12}N_4 \cdot 0.5\ H_2O$: C, 68.56; H, 5.34; N, 22.84. Found: C, 68.33; H, 5.10; N, 22.84. Also isolated were 20 mg (17%) of **3** as a white solid, mp 112−114 °C, R_f = 0.55 (ethyl acetate). ^{1}H NMR (chloroform-*d*): δ 8.58 (s, 1H, $H_{2'}$); 8.51 (s, 2H, H_4); 7.85 (br s, 1H, $H_{5'}$); 7.26−7.36 (m, 3H, $H_{3''}$, $H_{4''}$); 7.19 (d, 2H, J = 7.1, $H_{2''}$); 7.15 (br s, 1H, $H_{4'}$); 3.99 (s, 2H, benzyl). ^{13}C NMR (chloroform-*d*): δ 158.71 (C_4); 153.49 (C_2); 138.28 ($C_{1''}$); 136.18 ($C_{2'}$); 131.89 (C_5); 130.71 ($C_{4'}$); 129.12 ($C_{3''}$); 128.77 ($C_{2''}$); 127.15 ($C_{4''}$); 116.57 ($C_{5'}$); 36.01 (benzyl). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 70.93; H, 5.14; N, 23.49.

(15) Unpublished results.

1-(5-Benzylpyrimidin-4-yl)-1*H*-indole (5). The use of indole as heterocycle following the general procedure (elution with 10% to 20% ethyl acetate/hexanes) afforded 76 mg (61%) of **5** as an orange oil, R_f = 0.50 (50% ethyl acetate/hexanes). ^{1}H NMR (chloroform-*d*): δ 9.09 (s, 1H, H_2); 8.67 (s, 1H, H_6); 7.67 (d, 2H, J = 8.8, $H_{4',7'}$); 7.18−7.33 (m, 6H); 6.96 (d, 2H, J = 8.0, $H_{2''}$); 6.69 (d, 1H, J = 3.6, $H_{3'}$); 4.07 (s, 2H, benzyl). ^{13}C NMR (chloroform-*d*): δ 161.36 (C_6); 157.39 (C_4); 157.27 (C_2); 137.92; 135.78; 129.68; 129.01 ($C_{3''}$); 128.61 ($C_{2''}$); 127.06; 126.93; 126.89 (C_5); 123.46; 121.82; 121.30; 112.43; 106.17 ($C_{3'}$); 35.22 (benzyl). Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73. Found: C, 79.40; H, 5.40; N, 15.10.

5-Benzyl-4-pyrrol-1-ylpyrimidine (6). The use of pyrrole as heterocycle following the general procedure (elution with 10% to 20% ethyl acetate/hexanes) afforded 41 mg (35%) of **6** as a yellow oil, R_f = 0.50 (50% ethyl acetate/hexanes). ^{1}H NMR (chloroform-*d*): δ 8.98 (s, 1H, H_2); 8.53 (s, 1H, H_6); 7.25−7.38 (m, 5H, phenyl); 7.10 (br d, 2H, $H_{2''}$); 6.34 (t, 2H, J = 2, $H_{3'}$); 4.21 (s, 2H, benzyl). ^{13}C NMR (chloroform-*d*): δ 161.53 (C_6); 157.00 (C_2); 156.69 (C_4); 137.81 ($C_{1''}$); 129.06 ($C_{3''}$); 128.44 ($C_{2''}$); 127.05 ($C_{4''}$); 122.82 (C_5); 120.85 ($C_{2'}$); 111.71 ($C_{3'}$); 35.37 (benzyl). Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.35; H, 5.58; N, 17.64.

Naphthalen-2-ylpyrimidin-5-ylmethanol (7). 5-Bromopyrimidine (2.00 g, 12.6 mmol) was dissolved in 15 mL of ether and 25 mL of THF and cooled to −105 °C (internal) with mechanical stirring.[12] A 2.5 M solution of *n*-butyllithium in hexanes (6.50 mL, 16.2 mmol) was then added dropwise, over 15 min, at a rate that maintained the temperature between −100 and −105 °C. After 30 min at this temperature, a solution of 2-naphthaldehyde (2.77 g, 17.7 mmol) in 5 mL of THF was then added via cannula over 15 min, again maintaining the temperature between −100 and −105 °C. The resulting yellow solution was allowed to warm to 25 °C over 1−2 h and stirred for 18 h at 25 °C. Water and ethyl acetate were added, and the layers were separated. The organic phase was washed with water, dried (sodium sulfate), filtered, and concentrated. The crude product obtained was purified by flash chromatography (elution with 40% to 60% ethyl acetate/hexanes) to give 2.47 g (83%) of **7** as a white solid, mp 100−102 °C, R_f = 0.07 (50% ethyl acetate/hexanes). ^{1}H NMR (chloroform-*d*): δ 9.14 (s, 1H, H_2); 8.79 (s, 2H, H_4); 7.83−7.88 (m, 4H); 7.51−7.54 (m, 2H); 7.41 (dd, 1H, J = 8.5, 1.9, $H_{1''}$); 6.07 (d, 1H, J = 3, C*H*OH); 2.62 (d, 1H. J = 3, O*H*). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.97; H, 5.14; N, 11.93.

1-(5-Naphthalen-2-ylmethylpyrimidin-4-yl)-1*H*-indole (8). The use of indole as heterocycle and alcohol **7** (118 mg, 0.50 mmol) following the general procedure (elution with 10% to 20% ethyl acetate/hexanes) afforded 78 mg (47%) of **8** as a yellow solid, mp 86.5−87.5 °C, R_f = 0.50 (50% ethyl acetate/hexanes). ^{1}H NMR (chloroform-*d*): δ 9.12 (s, 1H, H_2); 8.72 (s, 1H, H_6); 7.65−7.80 (m, 4H); 7.74 (d, 1H, J = 8.3, $H_{4''}$); 7.41−7.49 (m, 2H); 7.34 (d, 1H, J = 0.8, $H_{1''}$); 7.20−7.34 (m, 3H); 7.09 (dd, 1H, J = 8.4, 1.8, $H_{3''}$); 6.66 (d, 1H, J = 3.6, $H_{3'}$); 4.22 (s, 2H, benzyl). ^{13}C NMR (chloroform-*d*): δ 161.34 (C_6); 157.39 (C_4); 157.24 (C_2); 135.69; 135.31; 133.43, 132.25; 129.62; 128.76; 127.60; 127.53; 127.08; 126.86; 126.58; 126.50 (C_5); 126.40; 125.95; 123.40; 121.77; 121.21; 112.40; 106.14 ($C_{3'}$); 35.29 (benzyl). Anal. Calcd for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.12; H, 5.20; N, 12.34.

5-Hydroxymethylpyrimidine (9). The published procedure[13] to prepare pyrimidine-5-carboxaldehyde was followed, starting from 5-bromopyrimidine. The ^{1}H NMR spectrum obtained for our sample of pyrimidine-5-carboxaldehyde matches the reported data.[13] The aldehyde was then treated with lithium aluminum hydride as described previously[14] to afford pure **9**, mp 51−52 °C, lit[14] mp 58−60 °C. ^{1}H NMR (chloroform-*d*): δ 9.17 (s, 1H, H_2); 8.77 (s, 2H, H_4); 4.79 (s, 2H, CH_2); 2.11 (br s, 1H, OH).

1-(5-Methylpyrimidin-4-yl)-1*H*-indole (10) and 1-Pyrimidin-5-ylmethyl-1*H*-indole (11). The use of indole as heterocycle and alcohol **9** (72 mg, 0.65 mmol) following the general procedure (elution with 30% to 50% ethyl acetate/hexanes) afforded 36 mg (26%) of **10** as an off-white solid, mp 120−122 °C, R_f = 0.38 (50% ethyl acetate/hexanes). ^{1}H NMR (chloroform-*d*): δ 9.06 (s, 1H, H_2); 8.71 (s, 1H, H_6); 7.67−7.72 (m, 2H, $H_{4',7'}$); 7.42 (d, 1H, J = 3.3 Hz, $H_{2'}$); 7.20−7.32 (m, 2H, $H_{5',6'}$); 6.75 (d,

1H, $J = 3.6$, $H_{3'}$); 2.38 (s, 3H, CH_3). ^{13}C NMR (chloroform-*d*): δ 160.86 (C_6); 157.41 (C_4); 156.76 (C_2); 135.64; 129.50; 126.53 ($C_{2'}$); 123.32 ($C_{5' \text{ or } 6'}$); 123.23; 121.72 ($C_{5' \text{ or } 6'}$); 121.14 ($C_{4' \text{ or } 7'}$); 112.73 ($C_{4' \text{ or } 7'}$); 105.99 ($C_{3'}$); 16.13 (CH_3). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.74; H, 5.37; N, 19.89. Also isolated were 33 mg (24%) of **11** as a light green solid, mp 55−60 °C, $R_f = 0.14$ (50% ethyl acetate/hexanes). ^1H NMR (chloroform-*d*): δ 9.14 (s, 1H, H_2); 8.51 (s, 2H, H_4); 7.67 (br d, 1H, $J =$ 7.7, $H_{4' \text{ or } 7'}$); 7.12−7.23 (m, 3H); 7.13 (d, 1H, $J = 3.3$ Hz, $H_{2'}$); 6.61 (br d, 1H, $J = 3.3$ Hz, $H_{3'}$); 5.34 (s, 2H, CH_2). ^{13}C NMR (chloroform-*d*): δ 158.28 (C_2); 155.46 (C_4); 135.87; 130.98; 128.91; 127.56 ($C_{2'}$); 122.36; 121.40 ($C_{4' \text{ or } 7'}$); 120.14; 109.11; 103.05 ($C_{3'}$); 45.50 (CH_2). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.37; H, 5.37; N, 19.83.

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Supporting Information Available: ^1H and ^{13}C spectra of **2**, **3**, **5**−**8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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