Preparation of 3*H*-pyrrolo[2,3-*c*]isoquinolines and 3*H*-pyrrolo[2,3-*c*][2,6]- and 3*H*-pyrrolo[2,3-*c*][1,7]-naphthyridines

U. Narasimha Rao, Xuemei Han, and Edward R. Biehl*

Chemistry Department, Southern Methodist University, Dallas, TX 75275, U. S. A.
E-mail: ebiehl@mail.smu.edu

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Abstract

The synthesis of several 5-substituted derivatives of 3*H*-pyrrolo[2,3-*c*]isoquinolines, 3*H*-pyrrolo[2,3-*c*][2,6]naphthyridines, and 3*H*-pyrrolo[2,3-*c*][1,7]-naphthyridines is described. These compounds were prepared by the dihydroxylation of the alkenyl group of the 1-substituted 4-alkenyl-3-amino analogs of isoquinoline, [2,6]- and [1,7]naphthyridines, respectively, followed by oxidative cleavage of the resulting diols.

Keywords: Pyrroloisoquinolines, pyrrolonaphthyridines, dihydroxylation, oxidative cleavage

Introduction

It has been shown[1,2] that α-alkenyl-2-cyano-3-pyridylacetonitriles,[1] α-alkenyl-4-cyano- 3-pyridyl acetonitriles[2] and α-alkenyl-α-cyano-*o*-tolunitriles[3] serve as valuable allylating agents in the preparation of 4-alkenyl-3-amino-1,7-naphthyridines,[1] 4-alkenyl-3-amino-2,6-naphthyridines,[2] and 4-alkenyl-3-aminoisoquinolines[3] respectively. Furthermore, several of these heterocycles underwent palladium-assisted intramolecular cyclization[4] under either catalytic or stoichiometric conditions to give 3*H*-pyrrolo[2,3-*c*]isoquinolines,[1] 3*H*-pyrrolo[2,3-*c*][1,7]naphthyridines,[1] 3*H*-pyrrolo[2,3-*c*][2,6]naphthyridines,[2] 3,4-dihydrobenzo[*c*][1,8]naphthyridines,[1] and 3,4-dihydropyridino[4,3-*c*][1,8]naphthyridines.[1] However, many 4-alkenyl-3-amino derivatives gave only inextractible mixtures of palladium complexes when subjected to palladium-assisted cyclization conditions.

Recently, a new ring forming methodology for the synthesis of bioactive pyrroloquinoline derivatives was reported.[5] This synthesis involved the vicarious nucleophilic substitution of nitro quinolines and hydrogenation of the resulting *ortho* cyanomethyl nitrogen heterocycle. Since we had some difficulty in acquiring 3*H*-pyrrolo[2,3-*c*] derivatives by Hegedus coupling[4] we sought an alternate cyclization method of the 4-alkenyl-3-amino heterocycles.

Results and Discussion

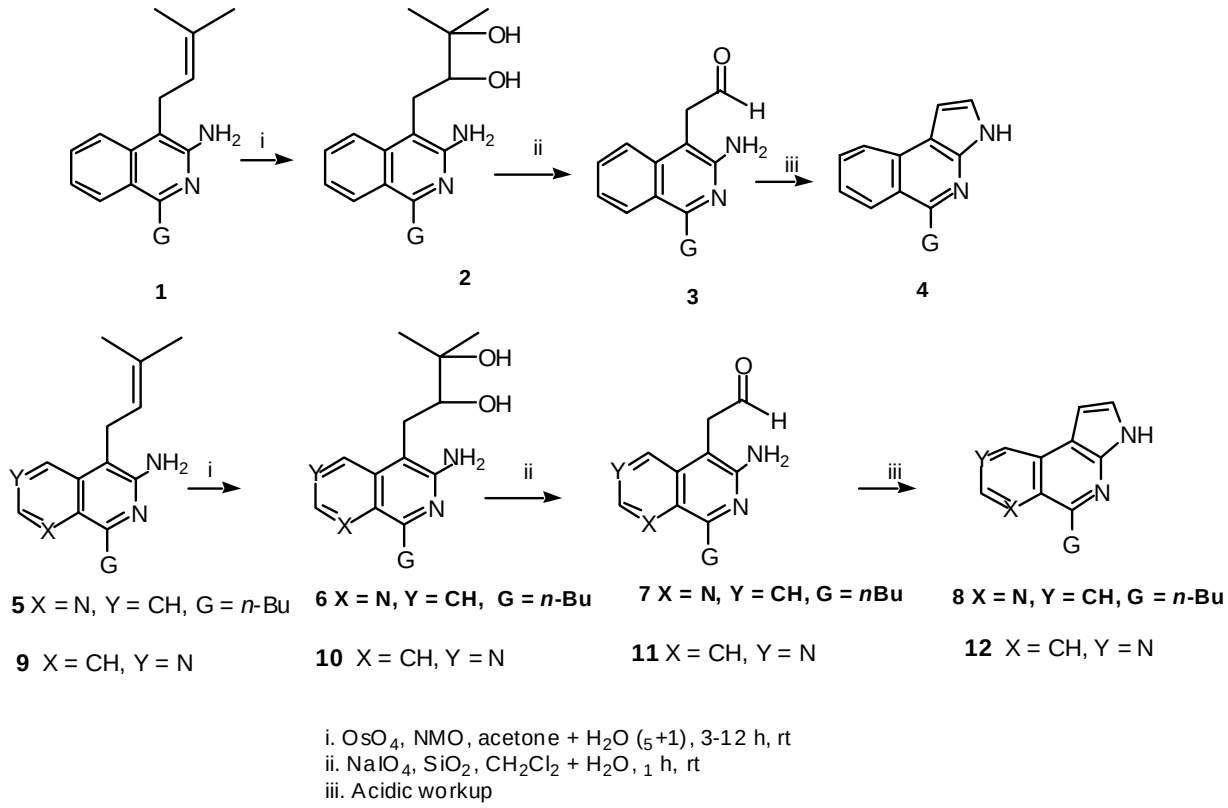
We first explored the possibility of oxidatively cleaving the 4-alkenyl group of 4-alkenyl-3-aminoisoquinolines (**1**), 4-alkenyl-3-amino-1,7-naphthyridines (**5**) and 4-alkenyl-3-amino-2,6-naphthyridines (**9**) to the corresponding aldehydes (**3, 7** and **11**) by ozonolysis. Although each 4-alkenyl analog would give the same aldehyde, we choose the 4-prenyl derivatives over the other two, [1]since they could be synthesized in high yields without any isomerization of the alkenyl double bond. The aldehyde would then be expected to react intramolecularly with the adjacent 3-amino group resulting in the construction of a pyrrole ring. We first tried the time-honored ozonolysis cleavage of carbon-carbon double bond at room temperature. However, the desired aldehyde or final cyclization products were not obtained. In most cases, inextractible tars were produced. When the ozonolysis was carried out at -78 ^{o}C, unidentifiable viscous, hygroscopic, polar substances were obtained.

Thus we used a milder synthetic method which involved the following steps. First, (**1a-e**, **5**, and **9a-c**) were converted into the diols (**2a-e, 6**, and **10a-c**) by treatment with OsO_4 under catalytic conditions[6] using *N*-methylmorpholine *N*-oxide[7] (Upjohn Process) as the cooxidant. In the second step, the crude diols in CH_2Cl_2, were treated with a solution of $NaIO_4$ (2 equiv.) in water in the presence of an appropriate amount of silica gel to give the aldehydes (**3a-e**, **7**, and **11a-c**), which were cyclized to 3*H*-pyrrolo derivatives (**4a-e**, **8**, and **12a-c**). These results are summarized in Scheme 1 and Table 1.

The spectral data for **4, 8** and **12** were consistent with the proposed structures. For example, the ^{1}H NMR spectrum of each pyrrolo product exhibited characteristic pyrrole ring proton splitting patterns in the range of 6-7 ppm.[8] These hydrogens appeared as doublet of doublets resulting from coupling with each other and with the 3-N-H group. These patterns resolved into clearly separated doublets when ^{1}H NMR spectra were obtained from solutions to which a drop of D_2O was added. The chemical shifts and splitting pattern of the hydrogen atoms in the pyridine ring of the naphthyridines were also consistent with the proposed structures. For example, the signal of 7-H, which is adjacent to the pyridine ring nitrogen, occurred downfield at 8.95 ppm whereas similar hydrogens in the isoquinolines (**4a-e**) appeared at 7-7.5 ppm. Additionally, the signal of the N-H group in all products occurred between 10-11.95 ppm. Unfortunately, the 4-alkenyl-1-(piperidin-1-yl) and 4-alkenyl-1-(pyrrolidin-1-yl) analogs were not converted into the desired diols and, of course, the desired 3*H*-pyrrole derivatives. TLC, GC/MS and ^{1}H NMR of the worked-up reaction mixtures revealed the presence of only starting materials.

In conclusion, several 5-substituted 3*H*-pyrrolo[2,3-*c*]isoquinolines and 5-substituted 1,7- and 2,6-naphthyridines have been prepared by the oxidative cleavage of the corresponding 4-alkenyl-3-aminoisoquinolines and 4-alkenyl-3-aminonaphthyridines. The major significance of this synthetic method is the ease in which primary and secondary alkyl and aryl groups are readily introduced onto these heterocyclic compounds. In addition, several pyrroloquinoline derivatives have been found to exhibit significant cytotoxicity in ovarian carcinoma cell line

panels.[5] These derivatives may provide new leads in the search for effective agents in drug resistant diseases.



Scheme 1

Table 1. Yields of 3*H*-Pyrrolo Derivatives **(4**, **8**, and **12)**

Compound	G	Y	X	Yield (%)
4a	*n*-butyl	CH	CH	86
4b	*sec*-butyl	CH	CH	81
4c	morpholin-4-yl	CH	CH	46
4d	phenyl	CH	CH	93
4e	methyl	CH	CH	42
8	*n*-butyl	CH	N	72
12a	morpholin-4-yl	N	CH	59
12b	phenyl	N	CH	42
12c	*p*-tolyl	N	CH	40

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to tetramethylsilane as internal standard. The mass spectra were run on a HP G1800C, GCD SeriesII. The amines and α-cyano-*o*-tolunitrile were distilled or recrystallized before use. The reactions were carried out in glassware, which had been heated at 125 ^{o}C overnight prior to use, under an atmosphere of dry O_2-free N_2 *via* balloon.

Stepwise cleavage procedure

To a solution of substrate (**1**) (0.5 mmol) and *N*-methylmorpholine *N*-oxide (NMO) monohydrate (81 mg, 0.6 mmol) in acetone/water (5:1, 10 mL) at 0°C was added OsO_4 (7.62 mg, 0.03 mmol). The resulting mixture was stirred for 3-12 h at rt and then concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), and solid sodium sulfite was added. The mixture was filtered through Celite, silica gel (100-200 mesh, 10 g) was added to the filtrate, and the mixture was cooled to 0°C. Sodium periodate (214 mg, 1 mmol) was added in a solution of water (2 mL). The reaction mixture was stirred at rt for 1 h followed by filtration through Celite. The filtrate was dried and concentrated, and the crude product was purified by silica gel column chromatography using hexane-ethyl acetate (1:9) as eluent. The spectral and analytical data for products are listed below.

5-Butyl-3*H*-pyrrolo[2,3-*c*]isoquinoline (4a). Pale yellow solid, mp 150-151 °C (recrystallized from 20% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.3 Hz, 3H, C-5-CH_2CH_2-CH_2CH_3), 1.55-1.63 (m, 2H, C-5-$CH_2CH_2CH_2CH_3$), 1.90-1.95 (m, 2H, C-5-$CH_2CH_2CH_2CH_3$), 3.40 (t, *J* = 7.9 Hz, 2H, C-5-$CH_2CH_2CH_2CH_3$), 6.99 (dd, *J* = 3.3, 2.2 Hz, 1H, 1-H [D_2O d, *J* = 3.3 Hz, 1 H]), 7.31 (dd, *J* = 3.3, 2.7 Hz, 1 H, 2-*H* [D_2O d, *J* = 3.3 Hz, 1 H]), 7.51 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 8-H), 7.72 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 7-H), 8.23 (d, *J* = 7.8 Hz, 1 H, 9-H), 8.25 (d, *J* = 7.7 Hz, 1 H, 6-H), 9.94 (br s, 1H, 3-NH). ^{13}C NMR ($CDCl_3$) δ 14.1, 23.2, 32.8, 35.7, 99.7, 112.7, 121.3, 122.8, 123.3, 123.6, 126.6, 129.5, 132.2, 142.9, 156.1. HRMS: Calcd for $C_{15}H_{16}N_2$: 224.1313. Found: 224.1316. Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.92; H, 7.19; N, 12.49. Found: C, 80.94; H, 7.24; N, 12.70.

5-*sec*-Butyl-3*H*-pyrrolo[2,3-*c*]isoquinoline (4b). Pale yellow solid, mp 117-118 °C (recrystallized from 20% ethyl acetate in hexane) ^{1}H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3,) 1.53 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.85-1.92 (m, 1 H, C*H* CH_3), 2.12-2.19 (m, 1 H), 3.83-3.88 (m, 1 H, *CH* CH_3), 7.00 (dd, *J* = 3.4, 2.1 Hz, 1 H, 1-H [D_2O d, *J* = 3.4 Hz, 1 H]), 7.31 (dd, *J* = 3.4, 2.7, Hz, 1 H, 2-H[D_2O d, *J* = 3.4 Hz, 1 H]), 7.52 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 8-H), 7.72 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 7-H), 8.23 (d, *J* = 7.8 Hz, 1 H, 9-H), 8.25 (d, *J* = 7.7 Hz, 1 H, 6-H), 10.29 (br s, 1 H, 3-NH). ^{13}C NMR ($CDCl_3$) δ 12.5, 20.5, 30.0, 37.7, 100.0, 112.4, 121.4, 123.0, 123.3, 123.6, 126.0, 129.3, 132.1, 142.9, 160.4. HRMS: Calcd for $C_{15}H_{16}N_2$:

224.1313. Found: 224.1316. Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.92; H, 7.19; N, 12.49. Found: C, 81.04; H, 7.29; N, 12.56.

5-Morpholino-3*H*-pyrrolo[2,3-*c*]isoquinoline (4c). Pale yellow solid, mp 205-206°C (recrystallized from 20% ethyl acetate in hexane) ^{1}H NMR (CD_3OD) δ 3.42 (t, *J* = 4.7 Hz, 4 H,N-CH_2-*CH_2*O), 4.04 (t, *J* = 4.5 Hz, 4 H, N-*CH_2*CH_2O), 6.92 (dd, *J* = 3.4, 2.2 Hz, 1 H, 1-H[D_2O d, *J* = 3.4 Hz, 1 H]), 7.21 (dd, *J* = 3.4, 2.7 Hz, 1 H, 2-H[D_2O d, *J* = 3.4 Hz, 1 H]), 7.45 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 8-H), 7.70 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 7-H), 8.16 (d, *J* = 8.1 Hz, 1 H, 9-H), 8.26 (d, *J* = 8.4 Hz, 1 H, 6-H), 9.24 (br s, 1 H, 2 -NH). ^{13}C NMR ($CDCl_3$) δ 52.5, 67.2, 100.3, 110.2, 118.7, 119.8, 123.1, 123.3, 126.6, 129.7, 133.6, 141.6, 157.9. HRMS: Calcd for $C_{15}H_{15}N_3O$: 253.1215. Found: 253.1217.5. Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.22; H, 6.03; N, 16.68.

5-Phenyl-3*H*-pyrrolo[2,3-*c*]isoquinoline (4d). Colorless solid, mp 218-219 ^{o}C (recrystallized from 20% ethyl acetate in hexane). ^{1}H NMR (CD_3OD) δ 7.06 (dd *J* = 3.4, 2.1 Hz, 1 H, 1-H), 7.43 (dd, *J* = 3.4, 2.7 Hz, 1 H, 2-H), 7.56-7.69 (m, 5 H), 7.70 (ddd, *J* = 8.3, 7.7, 1.2 Hz, 1 H, 8-H), 7.76 (ddd, *J* = 8.3, 7.8, 1.2 Hz, 1 H, 7-H), 8.02 (d, *J* = 8.9 Hz, 1 H, 9-H), 8.33 (d, *J* = 8.7 Hz, 1 H, 6-H), 10.85 (s, 1 H, 3-NH). ^{13}C NMR ($CDCl_3$) δ 99.3, 113.5, 123.0, 123.1, 123.6, 128.2, 128.3, 128.4, 128.7, 129.5, 130.2, 132.4, 140.2, 143.0, 154.2. HRMS: Calcd for $C_{17}H_{12}N_2$: 244.1000. Found: 244.1003. Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.74; H, 5.02; N, 11.55.

5-Methyl-3*H*-pyrrolo[2,3-*c*]isoquinoline (4e). Colorless solid, mp 214-215 ^{O}C (recrystallized from 20% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3 H, 5-*CH_3*), 7.00 (dd, *J* = 3.3, 2.1 Hz, 1 H, 1-H[D_2O d, *J* = 3.3 Hz, 1 H]), 7.37 (dd, *J* = 3.3, 2.7 Hz, 1 H, 2-H [D_2O d, *J* =3.3 Hz, 1 H]), 7.52 (ddd, *J* = 8.6 , 7.6, 1.2 Hz, 1 H, 8-H), 7.75 (ddd, *J* = 8.7, 7.6, 1.2 Hz, 1 H, 7-H), 8.22 (d, *J* = 7.8 Hz, 1 H, 9-H), 8.24 (d, *J* = 7.9 Hz, 1 H, 6-H), 11.35 (br s, 1 H, 3-NH). ^{13}C NMR ($CDCl_3$) δ 22.5, 99.9, 112.6, 131.0, 123.1, 123.6, 123.7, 126.7, 129.6, 131.8, 142.7, 152.2. HRMS: Calcd for $C_{12}H_{10}N_2$: 182.0844. Found: 182.0846. Anal: Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.17; H, 5.56, N, 15.18.

5-(*n*-Butyl)-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridine (8). Colorless solid, mp 155-156°C (recrystallized from 20% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J*=7.3 Hz, 3 H, C-5- $CH_2CH_2CH_2$-*CH_3*), 1.57-1.63 (m, 2 H, C-5-CH_2CH_2-*CH_2*CH_3), 1.99 (m, 2 H,C-5- CH_2-*CH_2*CH_2 - CH_3), 3.68 (t, *J* = 7.8 Hz, 2H, C-5-*CH_2*$CH_2CH_2CH_3$). 7.01 (dd, *J* = 3.3, 2.1 Hz, 1 H, 1-H), 7.45 (dd, *J* = 3.3, 2.7 Hz, 1 H, 2-H), 7.62 (dd, *J* = 8.3, 4.1Hz, 1 H, 8-H), 8.53 (dd, *J* = 8.3, 1.7 Hz, 1 H, 9-H), 8.95 (dd, *J* = 4.1, 1.7 Hz, 1 H, 7-H), 11.74 (br s, 1 H, 3-NH). ^{13}C NMR ($CDCl_3$) δ 14.2, 23.2, 32.4, 34.1, 100.3, 111.9, 122.3, 124.1, 127.1, 131.2, 139.1, 142.6, 147.0, 158.6. HRMS: Calcd for $C_{14}H_{15}N_3$: 225.1266. Found: 225.1266. Anal. Calcd for C, 74.64; H, 6.71; N, 18.65. Found: C, 74.60; H, 6.79; N, 18.69.

5-Morpholino-3*H*-pyrrolo[2,3-*c*][2,6]naphthyridine (12a). Pale yellow solid, mp 230°C (decomp, recrystallized from 20% ethyl acetate in hexane). ^{1}H NMR (CD_3OD) δ 3.38 (t, *J* = 4.7Hz, 4H, N-CH_2-*CH_2*O), 4.00 (t, *J* = 4.7 Hz, 4 H, N-*CH_2*CH_2O), 7.03 (d, *J* = 3.4 Hz, 1 H,), 7.35 (d, *J* = 3.4 Hz, 1 H), 8.10 (dd, *J* = 5.8, 0.7 Hz, 1 H), 8.47 (d, *J* = 5.8 Hz, 1 H),[8.8 (br s, 1 H,

3-NH) in $CDCl_3$], 9.57 (s, 1 H, 9-H). ^{13}C NMR ($CDCl_3$) δ 53.4, 68.1, 100.1, 109.3, 120.7, 122.6, 123.5, 129.3, 141.2, 144.2, 149.0, 157.1. HRMS: Calcd for $C_{14}H_{14}N_4O$: 254.1168. Found: 254.1167. Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.23; H, 5.63; N, 22.10.

5-Phenyl-3*H*-pyrrolo[2,3-*c*][2,6]naphthyridine (12b). Colorless solid, mp 303-304 °C (recrystallized from 20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 7.14 (m, 1 H), 7.26 (m, 1H), 7.62-7.68 (m, 3 H), 7.79 (dd, *J* = 7.8, 1.6 Hz, 2 H), 7.96 (d, *J* = 5.5 Hz, 1 H), 8.60 (d, *J* = 4.9 Hz, 1 H), 9.79 (s, 1 H), 10.88 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 99.8, 111.6, 120.3, 124.4, 126.1, 126.8, 128.2, 128.7, 128.9, 138.7, 142.1, 143.8, 148.6, 153.5. HRMS: Calcd for $C_{16}H_{11}N_3$: 245.0953. Found: 245.0955. Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.46; H, 4.62; N, 17.03.

5-(*4*-Tolyl)-3*H*-pyrrolo[2,3-*c*][2,6]naphthyridine (12c). Colorless solid, mp 282-283 °C, (recrystallized from 20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 2.58 (s, 3 H, 4-Me), 7.10 (dd,*J* = 3.3, 2.0 Hz, 1 H, 1-H [D_2O d, *J* = 3.3 Hz, 1 H]), 7.14 (dd, *J* = 3.3, 2.7 Hz, 1 H, 2-H [D_2O d, *J* = 3.3 Hz, 1 H]), 7.48 (d, *J* = 7.8 Hz, 2 H, phenyl 3-H), 7.71 (d, *J* = 7.9 Hz, 2 H, phenyl-2-H), 7.97 (d, *J* = 5.8 Hz, 1 H, 6-H), 8.59 (d, *J* = 6.8 Hz, 1 H, 7-H), 9.78 (s, 1 H, 9-H), 12.04 (br s, 1 H,3-NH). ^{13}C NMR ($CDCl_3$) δ 21.4, 99.5, 117.7, 120.4, 123.0, 124.6, 125.1, 126.0, 126.4, 129.4, 130.0, 135.8, 138.9, 142.0, 144.0, 148.6, 153.3. HRMS: Calcd for $C_{17}H_{13}N_3$: 259.1109. Found: 259.1108. Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.84; H, 5.12; N, 16.29.

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References

1. Rao, U. N.; Biehl, E. R. *Heterocycles* **2002**, *56*, 443.
2. Han, X.; Biehl, E. R. *ARKIVOC* **2002**, *(x)*.
3. Tandel, S.; Biehl, E. R. *Heterocycles* **2000**, *53*, 1183.
4. Hegedus, L.; Mckearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.
5. Viachou, M.; Tsotinis, A.; Keliand, L. R.; Thurston, D. E. *Heterocycles* **2002**, *57*, 129.
6. (a) Gadicota, R. R.; Callam C. S.; Lowry, T. L. *J. Org. Chem*. **2001**, *66*, 9046. (b) Boger, D. L.; Zarrinmayeh, H. *J. Org. Chem*. **1990**, *55*, 1379.
7. Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, 1973.
8. Pretsch, E.; Clerc, T.; Seibel J.; Simmons, W. *Tables of Spectral Data for Structure Determination of Organic Compounds,* 2nd Edn; Springer-Verlag: Berlin, 1989.