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Regioselective Quinazolinone-Directed Ortho Lithiation of Quinazolinoylquinoline: Practical Synthesis of Naturally Occurring Human DNA Topoisomerase I Poison Luotonin A and Luotonins B and E[†]

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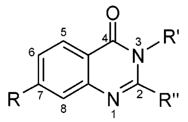
Received March 16, 2004

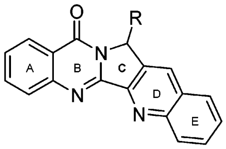
Abstract: A regioselective quinazolinone-directed ortho lithiation on an adjacent quinoline moiety has been used as a key step for a short, efficient, and practical synthesis of the human DNA topoisomerase I poison luotonin A and luotonins B and E. The quinazolinoylquinoline **5** on treatment with in situ-generated nonnucleophilic mesityllithium furnished the desired dilithiated intermediate **6**, which on treatment with formaldehyde followed by Mitsunobu ring closure reaction gave luotonin A (**1a**) in very good yield. The reaction of dilithiated intermediate **6** with DMF directly furnished luotonin B (**1b**) in 81% yield. Luotonin B (**1b**) on methylation with *p*-TSA/methanol gave luotonin E (**1c**) in 82% yield.

The use of directing groups to facilitate lithiation, followed by reaction of the organolithium reagents thus obtained with electrophiles, has found a wide range of applications in a variety of synthetic transformations.[1] The process of directed ortho metalation using carboxamides, carbamates, carboxylic acids, hydrazides, and oxazolines as directing groups is one of the better known methods for introducing various ortho substituents to the aromatic nucleus.[2] Although the great majority of studies on ortho metalation have been carried out on benzene rings,[3] there are relatively few examples of the use of group-directed lithiation of more complex heterocyclic systems.[3,4] Quinazolinones are known to undergo selective lithiation at the 2- and 8-positions[5] (Figure 1), and the 2-methyl-/alkyl-substituted quinazolinones are known to undergo lithiation at the 2-alkyl position.[6] However, to the best of our knowledge, ortho lithiation of aryl and heteroaryl substituents on quinazolinones have not been reported in the literature and will be highly useful for the introduction of ortho substituents for the facile synthesis of several complex bioactive natural and unnatural quinazolinones and related compounds (Figures 2 and 3).



R = Cl, R' = R'' = H (lithiation at 8-position)
R = R'' = H, R' = aryl (lithiation at 2-position)
R = R' = H, R'' = methyl, alkyl (lithiation on methyl group)
R = R' = H, R'' = phenyl, aryl, heteroaryl (lithiation unknown)

FIGURE 1. Lithiations on substituted quinazolinones.



Luotonin A (1a): R = H
Luotonin B (1b): R = OH
Luotonin E (1c): R = OMe

FIGURE 2. Naturally occurring luotonin alkaloids.

Recently, Nomura and co-workers[7] isolated six new alkaloids, luotonins A−F, from aerial parts of the Chinese medicinal plant *Peganum nigellastrum* (Figure 2). Luotonin A is cytotoxic toward the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL).[7] Very recently, Hecht et al.[8a] have demonstrated that despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I−DNA covalent binary complex and mediates topoisomerase I-dependent cytotoxicity in intact cells (IC_{50} 5.7−12.6 μm/mL), like camptothecin and its analogues[8,9] (Figure 3). In a very short span of time (6 years), 11 syntheses of luotonin A have been reported from different laboratories using a variety of elegant

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[†] NCL Communication No. 6661.

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10.1021/jo040153v CCC: $27.50 © 2004 American Chemical Society
Published on Web 06/02/2004

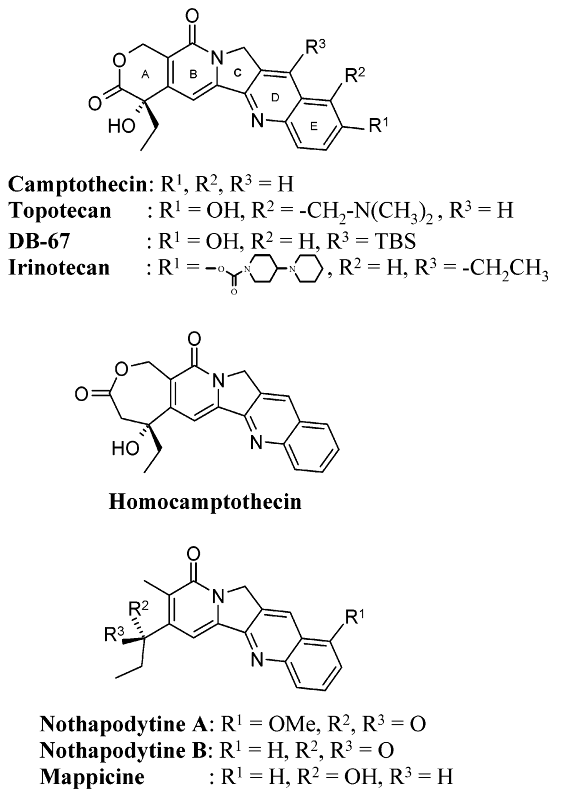

FIGURE 3. Camptothecin and its analogs.

synthetic strategies.[7,10] Out of 11 known syntheses, 10 multistep syntheses of linear pentacyclic luotonin A have been completed using two suitable building blocks with construction of ring B or D. Recently, Harayama et al.[10k] completed the synthesis of luotonin A with construction of middle ring C using a Pd-assisted biaryl coupling reaction. To date, two syntheses of each luotonin C−E and three syntheses of luotonins B and F are known.[7,10] In continuation of our studies[10f,11] on total synthesis of bioactive quinazolinone alkaloids, we herein report the first regioselective quinazolinone-directed ortho lithiation of quinazolinoylquinoline **5** to provide a direct and easy access to naturally occurring luotonins A, B, and E (Scheme 1).

Acylation of anthranilamide (**2**) with quinaldic acid chloride[12] in the presence of triethylamine furnished the corresponding diamide **4** in 96% yield. The aqueous potassium hydroxide-catalyzed dehydrative cyclization[13] of diamide **4** in ethanol gave the 2-quinolinoquinazolinone **5** in quantitative yield. The 2-quinolinoquinazolinone **5** can undergo lithiation at carbons 8, 3′, and 8′.[1] The key issue of our present approach lies in the dilithiation of the quinoline-quinazolinone skeleton with high specificity. We reasoned that like carboxamide,[14] the amide unit in quinazolinones will be useful for performing directed metalation reactions on adjacent 2-aryl/heteroaryl groups. As expected, the first lithiation of compound **5** would take place at the 3-position nitrogen atom of quinazolinone ring, and the monolithiated species formed may direct the second lithiation at the proximal 3′-position of the quinoline ring. To perform the quinazolinone-directed ortho lithiation at the 3′-position of the adjacent quinoline nucleus with the assistance of the amide moiety in the quinazolinone skeleton, we tried several reaction conditions. The reaction of **5** with *n*-BuLi, *s*-BuLi, and *t*-BuLi with or without TMEDA at 0 to −78 °C always led to the formation of a complex mixture, which was probably arising from the addition of alkyllithium to the carbon−nitrogen double bonds[1] in **5**. The use of LDA also led to the formation of complex mixtures. Finally, use of 2.2 equiv of in situ-generated nonnucleophilic mesityllithium[15] at −20 °C furnished the desired dilithiated species **6** via lithiation of the quinazolinone nitrogen at the 3-position as a first step followed by directed ortho lithiation at the 3′-position. The reaction of dilithiated intermediate **6** with formaldehyde exclusively yielded the desired *o*-hydroxymethylquinolinoquinazolinone **7** in 86% yield.[16] The Mitsunobu cyclization of **7** furnished the bioactive natural product luotonin A in 95% yield with an overall insertion of a methylene group between the 3- and 3′-positions of **5**. The reaction of dilithiated species **6** with *N*,*N*-dimethylformamide directly furnished luotonin B in 81% yield via intermediate **8** with insertion of a hydroxymethine group. The PCC oxidation of **7** in DCM also furnished luotonin B in 61% yield. Luotonin B on treatment with *p*-TSA/methanol provided luotonin E in 82% yield. The analytical and spectral data obtained for all the luotonins were in complete agreement with the reported data.[7,10] We feel that dilithiated species such as **6** can be reacted with several types of electrophiles for generation of a library of quinazolinone alkaloids.

In conclusion, we have demonstrated a facile quinazolinone-directed regioselective ortho lithiation of quinazolinoylquinoline and applied it for the short, efficient, and practical synthesis of naturally occurring promising anticancer agents, luotonins A, B, and E. We feel that our present approach is general in nature and that such a regioselective, directed lithiation of aryl- and heteroaryl-substituted quinazolinone systems will be highly useful for the synthesis of a large number of desired complex quinazolinone alkaloids, luotonin, and camptothecin-like analogues for structure activity relationship studies.

Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60−120 mesh). Commercially available anthranilamide, quinolin-2-carboxylic

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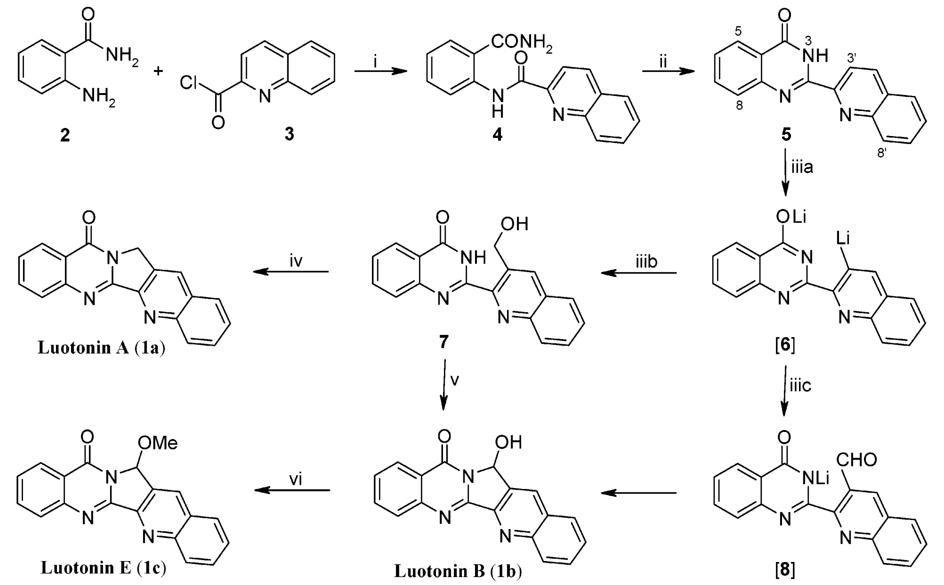
[16] In both the natural and unnatural quinazolinones, the hydrogen atom is present on the 3-position nitrogen atom and there is no noticeable existence of the corresponding tautomeric structure with the hydrogen atom on the 1-position nitrogen atom.[10f,11,13]

SCHEME 1[a]



[a] Key: (i) TEA (2 equiv), THF, rt, 3 h (96%). (ii) 5% aq KOH, EtOH, reflux, 5 min (98%). (iiia) mesityllithium (2.2 equiv), −78 °C, 30 min to −20 °C (gradually); (iiib) THF solution of HCHO (5 equiv), − 30 °C, 20 min, saturated aq solution of NH_4Cl (86%); (iiic) DMF (5 equiv), − 20 °C, 30 min, saturated aq solution of NH_4Cl (81%). (iv) PPh_3 (1.3 equiv), DEAD (1.2 equiv), THF, rt, 1 h (95%). (v) PCC (1.2 equiv), powdered 4 Å molecular sieves, DCM, rt, 1 h (61%). (vi) *p*-TSA (5 equiv), MeOH, reflux, 3 h (82%).

acid, *tert*-butyllithium, 2-bromomesitylene, PCC, triphenylphosphine (TPP), and diethyl azodicarboxylate (DEAD) were used.

2-(2′-Aminocarbonylquinolinyl)benzamide (4). 2-Quinolinecarboxylic acid (2.08 g, 12.00 mmol) and potassium hydroxide (692 mg, 12.36 mmol) were dissolved in distilled water (20 mL). The water was removed in vacuo and the resulting white solid residue was dried under high vacuum. To the resulting potassium salt suspended in benzene (30 mL) was added oxalyl chloride (1.26 mL, 14.40 mmol) dropwise at 5−10 °C. The reaction mixture was allowed to warm to room temperature and slowly heated to a gentle reflux. The resulting wine-red/black solution was allowed to cool to room temperature and added dropwise to a solution of anthranilamide (**2**) (1.63 g, 12.00 mmol) and triethylamine (3.34 mL, 24.00 mmol) in chloroform (20 mL) and stirred at room temperature for 3 h. The precipitated solid was filtered, washed with ethanol to obtain compound **4**, and used for the next step without any further purification. The analytically pure sample was obtained by recrystalization from methanol.

4: 3.35 g (96% yield); mp 269−271 °C (methanol); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.21 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.82−7.95 (m, 3H), 8.12 (d, J = 8 Hz, 2H), 8.28 (d, J = 8 Hz, 1H), 8.33 (bs, 1H), 8.64 (d, J = 8 Hz, 1H), 8.82 (d, J = 8 Hz, 1H), 13.55 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 118.7, 120.3, 121.4, 123.0, 128.2, 128.5, 128.8, 129.1, 129.4, 130.7, 132.1, 138.3, 138.9, 146.0, 150.0, 162.9, 170.6; IR (Nujol) ν_{max} 3360, 3290, 3192, 1688, 1649, 1616 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 69.89; H, 4.62; N, 14.39.

2-(2′-Quinolinyl)-3*H*-quinazolin-4-one (5). A mixture of benzamide **4** (2.91 g, 10.00 mmol) in 5% aqueous NaOH (50 mL) and EtOH (25 mL) was heated to reflux for 5 min. Ethanol was removed in vacuo, and the aqueous layer was extracted with chloroform (50 mL x 3). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using ethyl acetate as an eluant gave pure **5**.

5: 2.68 g (98% yield); mp 229−231 °C (ethyl acetate); ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.45−7.65 (m, 2H), 7.65−7.90 (m, 4H), 8.12 (d, J = 8 Hz, 1H), 8.34 (t, J = 8 Hz, 2H), 8.61 (d, J = 8 Hz, 1H), 11.19 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 118.4, 122.6, 126.7, 127.4, 127.6, 128.2 (2 carbons), 129.2, 129.6, 130.4, 134.4, 137.5, 146.7, 148.0, 148.9, 149.1, 161.3; IR (Nujol) ν_{max} 3319, 1682, 1605 cm^{-1}. Anal. Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.83; H, 4.17; N, 15.42.

2-(3′-Hydroxymethyl-2′-quinolinyl)-3*H*-quinazolin-4-one (7). To a solution of *t*-BuLi (1.5 M in pentane, 2.69 mL, 4.03 mmol) in THF (10 mL) at −78 °C was added a solution of 2-bromomesitylene (0.62 mL, 4.03 mmol) in THF (5 mL) over a period of 10 min, and the reaction mixture was stirred for 1 h. To the above reaction mixture was added a solution of quinazolinone **5** (500 mg, 1.83 mmol) in THF (30 mL), and then the mixture was stirred for 30 min at −78 °C. The reaction mixture turned deep brown in color on gradually warming to −20 °C. A solution of HCHO (9.16 mmol) in THF (1 mL) (formaldehyde solution in THF was prepared by thermal cracking of paraformaldehyde) was added to the reaction mixture, and stirring was continued for an additional 20 min at − 20 °C. The reaction was quenched with a saturated solution of NH_4Cl, and the reaction mixture was extracted with $CHCl_3$ (25 mL x 3). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/methanol (9:1) as an eluant furnished compound **7**.

7: 477 mg (86% yield); mp 212−214 °C (benzene); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.07 (d, J = 6 Hz, 2H), 6.33 (t, J = 6 Hz, 1H), 7.54−7.70 (m, 2H), 7.75−7.79 (m, 4H), 8.15 (d, J = 6 Hz, 1H), 8.28 (s, 1H), 8.39 (d, J = 6 Hz, 1H), 11.45 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 63.9, 122.5, 126.9, 127.5, 127.7, 128.2, 128.9, 129.0, 129.4, 130.7, 134.1, 134.8, 139.1, 145.9, 146.5, 147.9, 150.1, 160.9; IR (CHCl$_3$) ν_{max} 3747, 3304, 1682, 1638, 1605 cm^{-1}. Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.17; H, 4.43; N, 13.96.

Quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (Luotonin A, 1a). To the solution of compound **7** (200 mg, 0.66 mmol) and TPP (225 mg, 0.86 mmol) in THF (10 mL) was added solution of DEAD (0.144 mL, 0.79 mmol) in THF (5 mL) dropwise over a period of 10 min at room temperature and further stirred for 1 h. The reaction mixture was concentrated in vacuo. The column chromatographic purification of the residue using ethyl acetate as an eluant furnished luotonin A (**1a**).

1a: 179 mg (95% yield); mp 284−285 °C (ethyl acetate) (lit.[10k] mp 283−285 °C); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.34 (s, 2H), 7.58 (t, J = 10 Hz, 1H), 7.68 (t, J = 10 Hz, 1H), 7.84 (t, J = 10 Hz, 1H), 7.86 (t, J = 10 Hz, 1H), 7.94 (d, J = 10 Hz, 1H), 8.12 (d, J = 10 Hz, 1H), 8.43 (d, J = 10 Hz, 1H), 8.44 (s, 1H), 8.47 (d, J = 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3, 121.3, 126.4, 127.4, 127.9, 128.5, 128.8 (2 carbons), 129.4, 130.68, 130.71, 131.5, 134.6, 149.35, 149.42, 151.2, 152.5, 160.7; IR (Nujol) ν_{max} 1672, 1628, 1607, 1466 cm^{-1}. Anal. Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.89; H, 3.98; N, 14.61.

Quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-13-hydroxy-11-one (Luotonin B, 1b). (A) To a solution of *t*-BuLi (1.5 M in pentane, 2.69 mL, 4.03 mmol) in THF (10 mL) at −78 °C was added a solution of 2-bromomesitylene (0.62 mL, 4.03 mmol) in THF (5 mL) over a period of 10 min, and the reaction mixture was stirred for 1 h. To the above reaction mixture was added a solution of quinazolinone **5** (500 mg, 1.83 mmol) in THF (30 mL), and then the mixture was stirred for 30 min at −78 °C. The reaction mixture turned deep brown in color on gradually warming −20 °C. A solution of DMF (0.71 mL, 9.16 mmol) in THF (1 mL) was added to the reaction mixture, and stirring was continued for an additional 30 min at −20 °C. The reaction was quenched with a saturated solution of NH_4Cl, and the reaction mixture was extracted with $CHCl_3$ (25 mL x 3). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/methanol (9:1) as an eluant furnished luotonin B (**1b**) (447 mg, 81% yield).

(B) To the reaction mixture containing powdered 4 Å molecular sieves (200 mg) and compound **7** (100 mg, 0.33 mmol) in DCM (20 mL) was added PCC (85 mg, 0.40 mmol) in two portions, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with ether (20 mL) and stirred for another 15 min. The reaction mixture was then filtered through a bed of celite and silica gel and washed with ether (15 mL x 3). The filtrate was concentrated under vacuum, and the residue was purified by using a mixture of ethyl acetate/methanol (9:1) as an eluant to furnish luotonin B (**1b**) (61 mg, 61% yield).

1b: mp 274−276 °C (ethyl acetate) (lit.[10k] mp 271−274 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (bs, 1H), 7.14 (s, 1H), 7.61 (t, J = 10 Hz, 1H), 7.73 (t, J = 10 Hz, 1H), 7.88 (t, J = 10 Hz, 1H), 7.90 (d, J = 10 Hz, 1H), 8.02 (d, J = 10 Hz, 1H), 8.11 (d, J = 10 Hz, 1H), 8.41 (d, J = 10 Hz, 1H), 8.49 (d, J = 10 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 80.9, 121.9, 126.5, 127.9, 128.6, 128.8, 128.9, 129.2, 130.9, 131.0, 131.4, 133.3, 135.1, 149.5, 150.3, 150.4, 150.9, 161.6; IR ($CHCl_3$) ν_{max} 3238, 1686, 1636, 1609 cm^{-1}. Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.66; H, 3.51; N, 14.01.

Quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-13-methoxy-11-one (Luotonin E, 1c). The solution of Luotonin B (**1b**) (350 mg, 1.16 mmol) and *p*-toluenesulfonic acid (1.11 g, 5.81 mmol) in methanol (20 mL) was refluxed for 3 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in ethyl acetate (50 mL) and washed with an aqueous solution of $NaHCO_3$, water, and brine. The ethyl acetate layer was dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate/petroleum ether (1:1) as an eluant furnished luotonin E (**1c**).

1c: 300 mg (82% yield); mp 225−227 °C (benzene) (lit.[7b] mp 222−225 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.60 (s, 3H), 6.94 (s, 1H), 7.59 (t, J = 10 Hz, 1H), 7.71 (t, J = 10 Hz, 1H), 7.85 (t, J = 10 Hz, 1H), 7.88 (t, J = 10 Hz, 1H), 7.99 (d, J = 10 Hz, 1H), 8.09 (d, J = 10 Hz, 1H), 8.43 (d, J = 10 Hz, 1H), 8.48 (d, J = 10 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.3, 87.0, 122.3, 126.9, 127.9, 128.5, 128.7, 128.88, 128.94, 130.1, 130.8, 131.4, 133.2, 134.9, 149.0, 150.37, 150.43, 151.4, 160.8; IR ($CHCl_3$) ν_{max} 1686, 1638, 1607 cm^{-1}. Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.15; N, 13.33. Found: C, 72.43; H, 4.19; N, 13.51.

Acknowledgment. S.B.M. thanks CSIR, New Delhi, for the award of a research fellowship. N.P.A. thanks Department of Science and Technology, New Delhi, for financial support. We thank Dr. K. N. Ganesh, Head, Division of Organic Chemistry (Synthesis), for constant encouragement.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **4**, **5**, **7**, and **1a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040153V