Ring Annulation with Tetrahydroisoquinoline-Derived Enaminones: Highly Convergent Routes to Functionalized Pyrrolo[2,1-*a*]- and Indolo[2,1-*a*]isoquinolines

Okram Barun, Sriparna Chakrabarti, H. Ila,* and H. Junjappa*

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016

hila@iitk.ac.in

Received March 12, 2001

Enaminoketones and enaminonitriles have proven to be versatile building blocks for the synthesis of various heterocycles such as pyridine, pyrimidine, and pyrrole derivatives.[1] However the corresponding heterocyclic enaminones/esters and nitriles derived from 1,2,3,4-tetrahydroisoquinoline, despite their considerable potential, have been scarcely investigated[2] though their dihydro derivatives have been prepared and employed in the synthesis of azasteroids and other nitrogenous compounds.[3] During the course of our studies, aimed at utilizing these potentially useful heterocyclic enamines/esters of the general structure **1** (X = H or aryl or EWG) for the construction of polycyclic *N*-heterocycles containing 1,2-fused tetrahydroisoquinoline structural framework, we have recently described an efficient general synthetic route to this class of compounds.[4] The overall methodology involves Bischler−Napieralski type cyclization of newly synthesized ketene N,S-acetals derived from 3,4-dimethoxyphenylethylamine and polarized ketene dithioacetals. In continuation of these studies, we now report, in the present paper, synthetic elaboration of few of these enaminones **1**, **2**, and **9** to pyrrolo[2,1-*a*]isoquinoline and indolo[2,1-*a*]isoquinoline analogues via ring annulation.

Several routes are described in the literature for the construction of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline skeleton involving 1,5-electrocyclization of vinyl and iminyl azomethine ylides,[5] 1,3-dipolar cycloaddition of isoquinolinium benzotriazolylmethylide,[6] Reissert compounds,[7] reaction of isoquinolinium ketene dithioacetals with active methylene compounds,[8] reaction of acetylenic tricarbonyls with phenylethylamine,[9] *N*-acyliminium ion cyclization of appropriate precursors,[10] and base-induced ring transformation of 1-furyl-3,4-dihydroisoquinolines.[11] Recently pyrrolo[2,1-*a*]isoquinolines have been reported to be formed in base catalyzed [3 + 2] cyclization of 1-chloromethyl-3,4-dihydroisoquinoline with aliphatic ketones via a postulated 1,3-dipolar cycloaddition of iminocarbene intermediate.[12] Padwa and co-workers[13] have described assembling of pyrrolo[2,1-*a*]isoquinoline skeleton via a domino thionium/*N*-acyliminium ion cyclization of α-sulfinylenamide precursors. A few of the pyrrolo[2,1-*a*]isoquinoline derivatives display valuable pharmacological activity, e.g., antileukemic,[7] muscarinic agonistic,[14] and antidepressant properties.[10d] Besides, the pyrrolo[2,1-*a*]isoquinoline ring constitutes the basic structural framework of recently discovered Lamellarins,[15] a class of marine natural products, a few showing cytotoxic and immunomodulatory activity that may prove highly effective in the treatment of multidrug resistant tumors. Therefore, the development of efficient new methods leading to this class of heterocyclic framework is highly desirable.

The enaminones **1** and **2** were initially investigated for their enamine reactivity in [3 + 2] cyclocondensation with various 1,2-electrophilic species leading to pyrrolo[2,1-*a*]isoquinoline ring systems. Thus, when **1** was reacted with bromoacetaldehyde diethylacetal in refluxing dimethylformamide, workup of the reaction mixture furnished only one product (67%), which was characterized as 1-benzoyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline **3** on the basis of its spectral and analytical data. The corresponding acetylenamine **2** similarly gave 1-acetylpyrroloisoquinoline **4** (65%) under the identical conditions (Scheme 1).

Cyclization of **1** or **2** with ethyl bromoacetate in refluxing DMF did not yield either of the pyrrolo[2,1-*a*]-

* To whom correspondence should be addressed. Fax: 91-0512-597436, 91-0512-590260.

(1) Lue, P.; Greenhill, J. V. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1997; vol. 67, pp 207−343.

(2) (a) Osbond, J. M. *J. Chem. Soc.* **1951**, 3464−3475. (b) Openshaw, H. T.; Whittaker, N *J. Chem. Soc.* **1961**, 4939−4944. (c) Akiyama, Y.; Abe, J.; Takano, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1984**, *32*, 2821−2824. (d) Meyer, H. *Liebigs Ann. Chem.* **1981**, 1534−1544 (e) Sano, T.; Toda, J.; Maehara, N.; Tsuda, Y. *Can. J. Chem.* **1987**, *65*, 94−98. (f) Benovsky, P.; Stille, J. R. *Tetrahedron Lett.* **1997**, *38*, 8475−8478. (g) Nemes, P.; Balazs, B.; Toth, G.; Schieber, P. *Synlett* **1999**, 222−224.

(3) (a) Meyers, A. I.; Reine, A. H.; Sircar, J. C.; Rao, K. B.; Singh, S.; Weidmann, H. Fitzpatrick, M. *J. Heterocycl. Chem.* **1968**, *5*, 151−159. (b) Sobotka, W.; Beverung, W. N.; Munoz, G. G.; Sircar, J. C.; Meyers, A. I. *J. Org. Chem.* **1965**, *30*, 3667−3670. (c) Meyers, A. I.; Munoz, G. G.; Sobotka, W.; Baburao, K. *Tetrahedron Lett.* **1965**, *4*, 255−260. (d) Fulop, F.; Wamhoff, H.; Sohar, P. *Synthesis* **1995**, 863−867.

(4) Barun, O.; Mohanta, P. K.; Ila, H.; Junjappa, H. *Synlett* **2000**, 653−657.

(5) (a) Grigg, R.; Gunaratne, H. Q. N.; Henderson, D.; Sridharan, V. *Tetrahedron* **1990**, *46*, 1599−1610. (b) Grigg, R.; Myers, P.; Somasunderam, A.; Sridharan, V. *Ibid.* **1992**, *48*, 9735−9744. (c) Grigg, R.; Kennewell, P.; Savic, V.; Sridharan, V. *Ibid.* **1992**, *48*, 10423−10430. (d) Grigg, R.; Montgomery, J.; Somasunderam, A. *Ibid.* **1992**, *48*, 10431−10442.

(6) Katritzky, A. R.; Qui, G.; Yang, B.; He, H.-Y. *J. Org. Chem.* **1999**, *64*, 7618−7621.

(7) Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1998**, *31*, 2097−2102.

(8) Tominaga, Y.; Shiroshita, Y.; Kurokawa, T.; Gotou, H.; Matsuda, Y.; Hosomi, A. *J. Heterocycl. Chem.* **1989**, *26*, 477−487.

(9) Wasserman, H. H.; Frechette, R.; Oida, T.; van Duzer, J. H. *J. Org. Chem.* **1989**, *54*, 6012−6014.

(10) (a) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149−7152. (b) Lee, Y. S.; Kang, D. W.; Lee, S. J. Park, H. *Synth. Commun.* **1995**, *25*, 1947−1956. (c) Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron* **1998**, *54*, 12361−12378. (d) Elwan, N. M.; Abdelhadi, H. A.; Abdallah, T. A.; Hassaneen, H. M. *Tetrahedron* **1996**, *52*, 3451−3456.

(11) Loesel, W. *Chem. Ber.* **1988**, *121*, 547−550.

(12) Nemes, P.; Kajtar-Peredy, M.; Schieber, P. *Synlett* **1996**, 623−624.

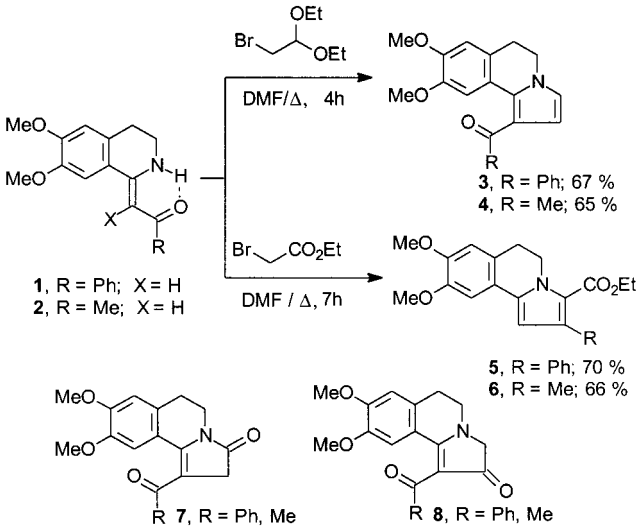
(13) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. *J. Org. Chem.* **1998**, *63*, 6778−6779.

(14) Loesel, W.; Roos, O.; Schnorrenberger, G. U. S. Patent 4694085, 1987, *Chem. Abstr.* **1988**, *108*, 204513.

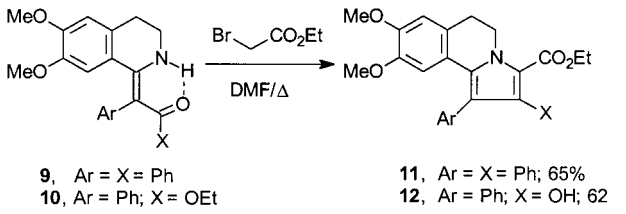
(15) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155−156. (b) Banwell, M.. Flynn, B.; Hockless, D. *J. Chem. Soc., Chem Commun.* **1997**, 2259−2260. (c) Lindquist, N.. Fenical, W. *J. Org. Chem.* **1988**, *53*, 4570−4574. (d) Andersen, R. J.. Faulkner, D. J.; Cun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492−5495.

10.1021/jo010273s CCC: $20.00
Published on Web 05/22/2001

Scheme 1



Scheme 2

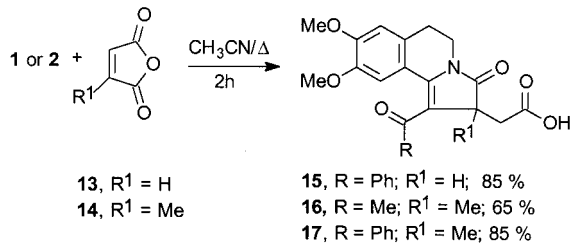


isoquinolines **7** or **8** expected from [3 + 2] cyclocondensation;[16] the products isolated were found to be 2-phenyl- (**5**) and 2-methyl- (**6**) 3-carbethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolines apparently derived by intramolecular Aldol type condensation of the initially N-alkylated enaminone intermediates. The methodology could also be extended for the synthesis of 1,2-diaryl-3-carbethoxypyrrolo[2,1-*a*]isoquinoline (**11**) which constitutes the basic structural framework of various Lamellarins (Scheme 2). Thus, the enaminone **9** derived from desoxybenzoin underwent smooth N-alkylation−intramolecular cyclization with ethyl bromoacetate under refluxing DMF to afford 1,2-diaryl-3-carbethoxypyrrolo[2,1-*a*]isoquinoline (**11**) in 65% yield. Similarly the enamino ester **10** obtained from ethyl phenylacetate also yielded the corresponding 1-phenyl-2-hydroxy derivative **12** in 62% yield under the identical conditions.

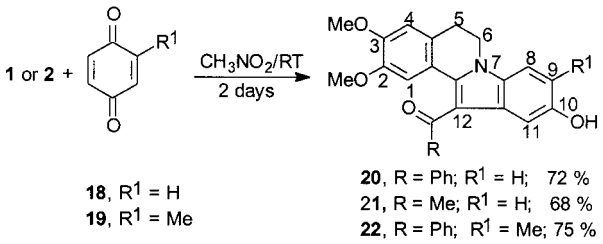
To further explore the synthetic scope and reactivity of these enaminones for obtention of highly functionalized pyrrolo[2,1-*a*]isoquinolines, cyclization of **1** and **2** with maleic and citraconic anhydride was investigated. Thus, when **1** was subjected to reaction with maleic anhydride **13** in refluxing acetonitrile, the corresponding benzoyl-substituted pyrrolo[2,1-*a*]isoquinolin-3-one-2-acetic acid **15** was obtained in 85% yield via Michael addition and intramolecular *N*-acylation process (Scheme 3). Interestingly, the cyclization of the enaminones **1** and 2 with citraconic anhydride **14** turned out to be highly regioselective under identical reaction conditions yielding only pyrrolo[2,1-*a*]isoquinoline-3-one derivatives **16** and **17**, respectively, with a quaternary C-3 center (Scheme 3).

Attention was next turned to cycloannulation of **1** and **2** with *p*-benzoquinone in Nenitzescu type reaction[17] to

Scheme 3



Scheme 4



furnish indolo[2,1-*a*]isoquinolines which have structural features of dibenzopyrrocoline alkaloids such as cryptaustoline and cryptowoline isolated from the bark of *Cryptocarya bowiei*.[18] A few of these compounds are reported to display antileukemic, antitumor,[19] and tubulin polymerization inhibitor[20] activity. Synthesis of these unique tetracyclic structures have been accomplished by several methods,[21] such as benzyne reaction[22] of 1-(2-bromobenzyl)isoquinolines,[23] enamine photocyclization,[24] addition of benzyl anion to 3,4-dihydroisoquinoline,[25] and radical and Bischler−Napieralski cyclization.[26] In a recent paper, Orito and co-workers have reported[27] facile synthesis of alkoxy-substituted 5,6-dihydroindolo[2,1-*a*]isoquinolines in a one-pot cyclization of the *erythro*-1-(2′-bromo-α-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines in refluxing dimethylformamide containing potassium carbonate. Despite several of these elegant routes for indolo[2,1-*a*]isoquinolines,

(16) Pinnick, H. W.; Chang, Y. H. *J. Org. Chem*. **1978**, *43*, 4662−4663.

(17) (a) Patrick, J. B.; Saunders, E. K. *Tetrahedron Lett*. **1979**, 4009−4012. (b) Coates, R. M.; MacMann, P. A. *J. Org. Chem*. **1982**, *47*, 4822−4824. (c) Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem*. **1996**, *61*, 9055−9059.

(18) Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618−619; *Aust. J. Chem*. **1953**, *6*, 78−85.

(19) (a) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 481−486. (b) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 743−747.

(20) Goldbrunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; von Angerer, E. *J. Med. Chem*. **1997**, *40*, 3524−3533.

(21) Elliott, I. W. *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1987; vol. 31, pp 101−116.

(22) (a) Meyers, A. I.; Sielecki, T. M. *J. Am. Chem. Soc*. **1991**, *113*, 2789−2790. (b) Kametani, T.; Ogasawara, K. *J. Chem. Soc*. **1967**, 2208−2212. (c) Kametani, T.; Shibuya, S.; Kano, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1212−1214. (d) Ahmad, I.; Gibson, M. *Can. J. Chem*. **1975**, *53*, 3660−3664.

(23) (a) Harley-Mason, J. *J. Chem. Soc*. **1953**, 1465−1466. (b) Hess, U.; Hiller, K.; Schroeder, R. S. *J. Prakt. Chem*. **1977**, *319*, 568−572.

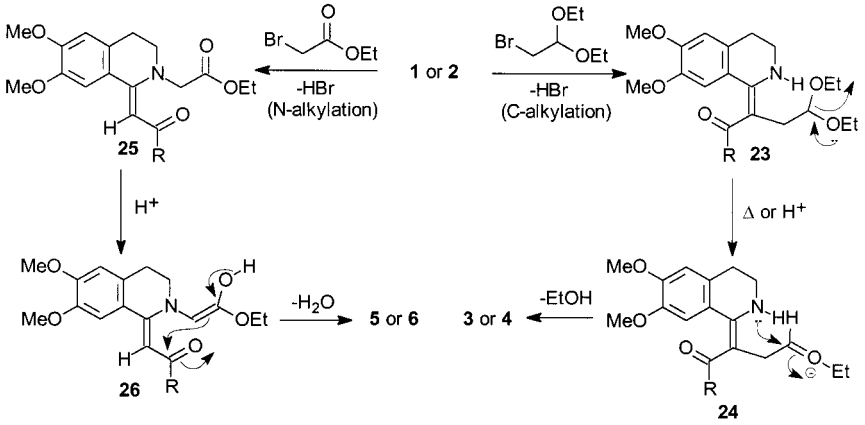
(24) Ninomiya, I.; Yasui, J.; Kiguchi, T. *Heterocycles* **1977**, *6*, 1855−1860.

(25) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1987**, *26*, 1483−1485.

(26) (a) Mathew, K. K.; Menon, K. N. *Proc. Indian. Acad. Sci*. **1949**, *29A*, 361−363. (b) Yasuda, S.; Hirasawa, T.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull*. **1989**, *37*, 1682−1683. (c) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett*. **2000**, *2*, 307−310.

(27) (a) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem*. **1999**, *64*, 6583−6596. (b) Orito, K.; Miyazawa, M.; Suginome, H. *Heterocycle Commun*. **1995**, *1*, 239−240. (c) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett*. **2000**, *2*, 1799−1801.

Scheme 5



a direct convergent approach involving Nenitzescu reaction between tetrahydroisoquinoline-derived enaminones/ester and *p*-benzoquinone has not been reported. In a typical reaction, when the equimolar quantities of enaminone **1** and *p*-benzoquinone **18** were stirred at room temperature in nitromethane, workup and column chromatography of the reaction mixture yielded exclusively one product identified as 12-benzoyl-2,3-dimethoxy-10-hydroxy-5,6-dihydroindolo[2,1-*a*]isoquinoline **20** (72%) based on its spectral and analytical data (Scheme 4). Similarly, the acetylenaminone **2** was smoothly transformed into the respective 12-acetylindolo[2,1-*a*]isoquinoline analogue **21** when reacted with *p*-benzoquinone under identical conditions. Unexpectedly, the reaction of **1** with toluquinone **19** yielded only one regioisomer characterized as 9-methyl-10-hydroxyindoloisoquinoline **22**, thus showing that initial Michael addition of **1** to **19** occurs only *para* to the methyl group.

In summary, study of annulation reactions of enaminones **1**, **2**, and **9** with various one- and two-carbon electrophilic synthons has yielded direct one-pot novel convergent routes to a variety of functionalized pyrrolo-[2,1-*a*]isoquinolines and indolo[2,1-*a*]isoquinolines, and some of them may prove useful precursors for biologically important natural products possessing these structural frameworks. Our efforts in this direction are in progress and will be published later. It should be noted that the enaminones **1** or **2** display typical enamine reactivity in their reactions with either maleic anhydride or *p*-benzoquinone as observed earlier in the reactions of enaminoesters with these species.[17,28] Similarly the cyclocondensation of **1** or **2** with bromoacetaldehyde diethylacetal also appears to follow the enamine reactivity pattern via initial C-alkylation to form **23** followed by intramolecular ring closure with elimination of ethanol to afford the corresponding **3** or **4** (Scheme 5). However, the reaction takes different course with more reactive ethyl bromoacetate involving N-alkylation of enaminones **1** or **2** followed by acid-assisted (HBr generated in the reaction) intramolecular Aldol condensation of the aminoacetate intermediate **25**. The ambident reactivity of enaminones **1** or **2** toward bromoacetaldehyde diethylacetal and ethyl bromoacetate can be rationalized in terms of soft and hard electrophilic character of their bromine-bearing carbon atoms resulting in the attack by respective softer (C) and harder (N) nucleophilic terminus of **1** or **2** as depicted in Scheme 5.

(28) (a) Blanton, C. D., Jr.; Whidby, J. F.; Briggs, F. H. *J. Org. Chem.* **1971**, *36*, 3929−3931. (b) Gupta, A. K.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 284−286. (c) Blanton, C. D., Jr; Shah, K. R. *J. Org. Chem.* **1982**, *47*, 502−508. (d) Nagasaka, T.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848−850. (e) Cave, C.; Abdoulaye, G.; Mahuteau, J.; d'Angelo, J.; Riche, C. *Tetrahedron Lett.* **1997**, *38*, 4773−4776.

Experimental Section

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$, and TMS was used as internal reference. Melting points are uncorrected. Chromatographic purification was conducted by column chromatography using 60−120 mesh silica gel obtained from Acme Synthetic Chemicals. Bromoacetaldehyde diethylacetal, ethyl bromoacetate, citraconic anhydride, *p*-benzoquinone, and toluquinone were purchased from Lancaster. Maleic anhydride and mercuric chloride were purchased from E-Merk India Ltd. DMF and acetonitrile were distilled over CaH_2 and stored over molecular sieves. Nitromethane (AR grade) was purchased from Spectrochem and used directly. All reagents were purchased commercially and used as such unless stated otherwise.

All the enaminones **1**, **2**, **9** and enaminoester **10** were prepared accordingly to our earlier reported method[4] by $HgCl_2$-induced cyclization of respective N,S-acetals.

1-(Benzoylbenzylidene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9). Yield 64 %. Yellow crystals, mp 136−137 °C; R_f 0.25 (9.5:0.5 hexane−EtOAc); IR (KBr): 3091, 2935, 1697, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (t, J = 6.6 Hz, 2H, CH_2), 3.06 (s, 3H, OCH_3), 3.52 (t, J = 6.6 Hz, 2H, OCH_3), 3.87 (s, 3H, OCH), 6.28 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.93−7.11 (m, 10H, ArH), 13.29 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 39.2, 55.1, 55.7, 106.3, 109.82, 114.3, 121.2, 125.5, 127.1, 127.6, 127.7, 128.0, 132.1, 133.9, 141.3, 143.4, 145.9, 150.0, 159.3, 192.9; MS (*m*/*z*, %): 385 (M^+, 100). Anal. Calcd for $C_{25}H_{23}NO_3$ (385.46): C, 77.90; H, 6.01; N, 3.63%. Found: C, 77.79; H, 6.28; N, 3.81%.

General Procedure for the Preparation of 1-Substituted 5,6-Dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolines (3 and 4). To a stirred solution of **1** (1.3 mmol) in dry DMF (15 mL) was added bromoacetaldehyde diethylacetal (0.24 mL, 1.6 mmol) under nitrogen atmosphere, and the reaction mixture was refluxed for 4 h (monitored by TLC). It was cooled and poured into ice-cold water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through silica gel column using hexane/ethyl acetate (9:1) as eluent.

1-Benzoyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (3). Yield 67% (0.29 g). Brown crystals, mp 105−106 °C; R_f 0.7 (9:1 hexane−EtOAc); IR(KBr): 3091, 2935, 1637, 1526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (t, J = 6.6 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.06 (t, J = 6.6 Hz, 2H, CH_2), 6.39 (d, J = 2.9 Hz, 1H, ArH), 6.60 (d, J = 2.9 Hz, 1H, ArH), 6.71 (s, 1H, ArH), 7.39−7.43 (m, 2H, ArH), 7.47−7.51 (m, 1H, ArH), 7.83−7.85 (m, 2H, ArH), 7.97 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 44.9, 55.8, 56.0, 110.5, 110.9, 114.3, 119.1, 119.7, 121.0, 125.4, 127.9, 129.5, 131.3, 133.2, 140.7, 147.5, 148.3, 192.6; MS (*m*/*z*, %): 334 ($M + 1^+$, 15.9), 333

(M^+, 59.5), 105 (100). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.38): C, 75.66; H, 5.74; N, 4.20%. Found: C, 75.49; H, 5.88; N, 4.11%.

1-Acetyl-5,6-dihydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinoline (4). Yield 65% (0.23 g). Viscous liquid; R_f 0.68 (9:1 hexane−EtOAc); IR (KBr): 2986, 1652, 1549, 1422, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H, $COCH_3$), 2.98 (t, J = 6.6 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.03 (t, J = 6.6 Hz, 2H, CH_2), 6.61 (d, J = 2.9 Hz, 1H, ArH), 6.64 (d, J = 2.9 Hz, 1H, ArH), 6.70 (s, 1H, ArH), 8.60 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.4, 29.7, 45.0, 55.9, 56.1, 110.5, 111.6, 112.6, 120.0, 120.2, 121.2, 125.8, 132.0, 147.5, 148.5, 194.5; MS (*m*/*z*, %): 272 ($M + 1^+$, 20.9), 271 (M^+, 100). Anal. Calcd for $C_{16}H_{17}NO_3$ (271.31): C, 70.83; H, 6.32; N, 5.16%. Found: C, 70.71; H, 6.52; N, 5.22%.

General Procedure for the Preparation of 5, 6, 11, and 12. To a stirred solution of **1** (2.2 mmol) in dry DMF (18 mL) was added ethyl bromoacetate (0.24 mL, 2.2 mmol) under nitrogen atmosphere, and the reaction mixture was refluxed for 8 h (monitored by TLC). After being cooled to room temperature, the reaction mixture was poured into ice-cold water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through silica gel column using hexane/ethyl acetate (9.5:0.5) as eluent.

Ethyl5,6-Dihydro-8,9-dimethoxy-2-phenylpyrrolo[2,1-*a*]-isoquinoline-3-carboxylate (5). Yield 70% (0.58 g). Yellow crystals, mp 126−127 °C; R_f 0.65 (9:1 hexane−EtOAc); IR (CH_2Cl_2): 2922, 1630, 1528, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.97 (t, J = 6.6 Hz, 2H, 6-CH_2), 3.71 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.93 (t, J = 6.6 Hz, 2H, 5-CH_2), 4.05 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.52 (s, 1H, vinylic H), 6.69 (s, 1H, ArH), 7.37−7.41 (m, 2H, ArH), 7.46−7.49 (m, 1H, ArH), 7.74 (s, 1H, ArH), 7.82−7.84 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 28.8, 38.9, 55.9, 55.9, 66.4, 89.1, 110.6, 110.9, 116.5, 121.2, 125.1, 126.2, 127.9, 129.5, 131.2, 140.9, 145.2, 147.4, 147.9, 192.4; MS (*m*/*z*, %): 377 (M^+, 4.5), 348 (12.4), 271 (26.3). Anal. Calcd for $C_{23}H_{23}NO_4$ (377.43): C, 73.19; H, 6.14; N, 3.71%. Found: C, 73.33; H, 6.29; N, 3.59%.

Ethyl 5,6-Dihydro-8,9-dimethoxy-2-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (6). Yield 66% (0.46 g). Pale yellow crystals, mp 127−128 °C; R_f 0.65 (9:1 hexane−EtOAc); IR (KBr): 1647, 1574, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.49 (s, 3H, CH_3), 2.91 (t, J = 6.6 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.91 (t, J = 6.6 Hz, 2H, CH_2), 3.99 (s, 3H, OCH_3), 4.11 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.67 (s, 1H, ArH), 6.68 (s, 1H, ArH), 8.58 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 28.9, 29.5, 38.8, 55.8, 56.0, 66.4, 87.3, 110.5, 111.3, 111.4, 117.5, 121.3, 125.5, 145.1, 147.5, 148.1, 194.1; MS (*m*/*z*, %): 316 ($M + 1^+$, 9.3), 315 (M^+, 31.2), 286 (100). Anal. Calcd for $C_{18}H_{21}NO_4$ (315.37): C, 68.55; H, 6.71; N, 4.44%. Found: C, 68.34; H, 6.53; N, 4.28%.

Ethyl 5,6-Dihydro-8,9-dimethoxy-1,2-diphenylpyrrolo-[2,1-*a*]isoquinoline-3-carbo xylate (11). Yield 62% (0.62 g). Yellow crystals, mp 131−132 °C; R_f 0.63 (9:1 hexane−EtOAc); IR (KBr): 2936 (br), 1684, 1546, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.92 (t, J = 7.1 Hz, 3H, CH_2CH_3), 3.07 (t, J = 6.7 Hz, 2H, CH_2), 3.26 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.05 (q, J = 7.1 Hz, 2H, CH_2CH_3), 4.64 (t, J = 6.7 Hz, 2H, CH_2), 6.49 (s, 1H, ArH), 6.72 (s, 1H, ArH), 7.11−7.24 (m, 10 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.6, 29.1, 42.8, 55.0, 55.9, 59.7, 108.7, 110.6, 118.4, 120.8, 121.8, 125.9, 126.1, 126.5, 126.9, 128.2, 129.8, 130.6, 131.1, 131.3, 132.9, 135.5, 147.2, 148.0, 162.0; MS (*m*/*z*, %): 453 (M^+, 100). Anal. Calcd for $C_{29}H_{27}NO_4$ (453.54): C, 76.80; H, 6.0; N, 3.09%. Found: C, 76.62; H, 6.18; N, 3.20%.

Ethyl 5,6-Dihydro-8,9-dimethoxy-2-hydroxy-1-phenylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12). Yield 65% (0.56 g). Green crystals, mp 124−125 °C; R_f 0.62 (9:1 hexane−EtOAc); IR (KBr): 2949, 1630, 1565, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H, CH_2CH_3), 3.01 (t, J = 6.6 Hz, 2H, CH_2), 3.33 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.36−4.43 (m, 4H, NCH_2 and CH_2CH_3), 6.69 (s, 1H, ArH), 6.72 (s, 1H, ArH), 7.26−7.30 (m, 2H, ArH), 7.38−7.42 (m, 1H, ArH), 7.46−7.48 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 28.8, 42.4, 55.2, 55.9, 60.1, 104.8, 108.6, 109.0, 110.8, 120.2, 126.1, 126.9, 128.5, 130.6, 131.3, 133.1, 147.2, 148.5, 165.2; MS (*m*/*z*, %): 393 (M^+, 100). Anal. Calcd for $C_{23}H_{23}NO_5$ (393.44): C, 70.22; H, 5.89; N, 3.56%. Found: C, 70.33; H, 5.71; N, 3.68%.

General Procedure for the Reaction of Maleic Anhydride or Citraconic Anhydride with Enaminone 1 or 2: Synthesis of 15−17. A mixture of enaminone (1.3 mmol) and maleic anhydride or citraconic anhydride (1.3 mmol) in acetonitrile (15 mL) was refluxed for 2 h (monitored by TLC). It was then cooled, concentrated under reduced pressure, poured into ice-cold water, and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through neutral alumina column using hexane:ethyl acetate (9:1) as eluent.

(1-Benzoyl-5,6-dihydro-8,9-dimethoxy-3-oxopyrrolo[2,1-*a*]isoquinolin-2-yl)acetic Acid (15). Yield 85% (0.45 g). Brown solid, mp 180−181 °C; R_f 0.01 (EtOAc); IR (KBr): 3428 (br), 1702, 1662,1505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.83−3.06 (m, 2H, CH_2CO_2H), 3.11 (t, J = 4.6 Hz, 2H, CH_2), 3.19 (s, 3H, OCH_3), 3.26−3.33 (m, 1H, $CHCH_2COOH$), 3.86 (s, 3H, OCH_3), 4.01 (t, J = 4.6 Hz, 1H, NC*H*H), 4.19−4.22 (m, 1H, NCH*H*), 6.37 (s, 1H, ArH), 6.66 (s, 1H, ArH), 7.17−7.21 (m, 2H, ArH), 7.33−7.36 (m, 1H, ArH), 7.62−7.63 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 32.4, 37.4, 46.0, 55.5, 55.9, 110.4, 113.3, 113.9, 117.7, 128.5, 129.5, 130.9, 132.5, 138.8, 146.7, 146.9, 151.1, 175.1, 176.9, 191.4; MS (*m*/*z*, %): 407 (M^+, 30), 363 (25.6), 258 (95.1). Anal. Calcd For $C_{23}H_{21}NO_6$ (407.42): C, 67.81; H, 5.20; N, 3.44%. Found: C, 67.69; H, 5.08; N, 3.58%.

(1-Acetyl-5,6-dihydro-8,9-dimethoxy-2-methyl-3-oxopyrrolo[2,1-*a*]-isoquinolin-2-yl)acetic Acid (16). Yield 65% (0.30 g). Off-white crystals, mp 200−201 °C; R_f 0.01 (EtOAc); IR (KBr); 3434 (br), 1734, 1675, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 2.87−2.91 (m, 3H, CH_2-COOH and NCH_2CHH), 3.19−3.22 (m, 1H, NCH_2CHH), 3.44−3.46 (m, 1H, NC*H*H), 3.88 (s, 3H, OCH_3), 3.93−3.96 (m, 1H, NCH*H*), 3.97 (s, 3H, OCH_3), 6.80 (s, 1H, ArH), 7.05 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 29.0, 30.0, 37.2, 39.8, 50.1, 56.1, 56.2, 110.8, 113.5, 118.0, 119.6, 132.0, 147.4, 147.6, 151.8, 175.2, 180.2, 195.1; MS (*m*/*z*, %): 360 ($M + 1^+$, 7.3), 359 (M^+, 65.3), 300 (100). Anal. Calcd for $C_{19}H_{21}NO_6$ (359.37): C, 63.50; H, 5.89; N, 3.90%. Found: C, 63.32, H, 6.11, N, 3.81%.

(1-Benzoyl-5,6-dihydro-8,9-dimethoxy-2-methyl-3-oxopyrrolo[2,1-*a*]isoquinolin-2-yl)acetic Acid (17). Yield 85% (0.46 g). Light yellow solid, mp 204−205 °C; R_f 0.01 (EtOAc); IR (KBr): 3447 (br), 1730, 1677, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 2.81−2.99 (m, 3H, CH_2COOH and NCH_2CHH), 3.22 (s, 3H, OCH_3), 3.18−3.25 (m, 1H, NCH_2CHH), 3.41−3.52 (m, 1H, NC*H*H), 3.86 (s, 3H, OCH_3), 4.00−4.06 (m, 1H, NCH*H*), 6.28 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.11−7.15 (m, 2H, ArH), 7.27−7.31 (m, 1H, ArH), 7.52−7.54 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 28.9, 37.3, 39.4, 50.8, 55.5, 55.9, 110.3, 113.9, 116.5, 117.9, 128.3, 129.4, 130.8, 132.3, 139.4, 146.9, 147.0, 150.9, 175.4, 180.37, 192.2; MS (*m*/*z*, %): 421 (M^+, 23.8), 362 (100). Anal. Calcd for $C_{24}H_{23}NO_6$ (421.45): C, 68.40; H. 5.50; N, 3.32%. Found: C, 68.62; H, 5.39; N, 3.41%.

General Procedure for Nenitzescu Reaction with Enaminone 1 or 2: Synthesis of Indolo[2,1-*a*]isoquinoline Derivatives 20−22. To a stirred solution of enaminone **1** or **2** (1.6 mmol) in dry nitromethane (15 mL) was added *p*-benzoquinone or toluquinone (2.2 mmol) under nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 2 days (monitored by TLC). It was then concentrated under reduced pressure, poured into ice-cold water, and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give crude products which were purified by passing through silica gel column using hexane/ethyl acetate (9:1) as eluent.

12-Benzoyl-2,3-dimethoxy-10-hydroxy-5,6-dihydroindolo-[2,1-*a*]isoquinoline (20). Yield 72% (0.46 g). Yellow crystals, mp 235 °C; R_f 0.35 (9:1 hexane−EtOAc); IR (KBr): 3410 (br), 1724, 1560, 1526 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.17 (t, J = 6.6 Hz, 2H, CH_2), 3.32 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.21 (t, J = 6.6 Hz, 2H, CH_2), 6.74 (s, 1H, ArH), 6.79 (dd, J = 8.8, 2.2 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 7.17 (d, J = 2.2 Hz, 1H, ArH), 7.28 (d, J = 8.8 Hz, 1H, ArH), 7.32−7.36 (m, 2H, ArH), 7.45−7.48 (m, 1H, ArH), 7.76−7.78 (m, 2H, ArH) and 7.96 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.5, 39.6, 55.3, 55.6, 105.1, 109.3, 109.8, 110.9, 112.8, 113.0, 119.6, 127.4, 128.2, 129.4, 129.6, 129.9, 131.8, 138.8, 140.1, 146.7, 148.9, 153.0, 191.6; EIMS (*m*/*z*, %): 400 (M +1, 17.3), 385 (13.2), 323 (100). Anal. Calcd

For $C_{25}H_{21}NO_4$ (399.44): C, 75.17; H, 5.30; N, 3.51%. Found: C, 75.33; H, 5.21; N, 3.70%.

12-Acetyl-2,3-dimethoxy-10-hydroxy-5,6-dihydroindolo-[2,1-*a*]isoquinoline (21). Yield 68% (0.37 g). Green crystals, mp 228−229 °C; R_f 0.35 (9:1 hexane- EtOAc); IR (CH_2Cl_2): 3405 (br), 1603, 1559 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, $COCH_3$), 3.08 (t, J = 6.6 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.15 (t, J = 6.6 Hz, 2H, CH_2), 6.78 (d, J = 8.8 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 7.27 (d, J = 8.8 Hz, 1H, ArH), 7.38 (s, 1H, ArH), 7.82 (s, 1H, ArH), 8.88 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.6, 31.4, 39.6, 55.7, 55.8, 105.5, 110.0, 111.1, 112.0, 112.4, 113.2, 120.0, 128.13, 128.3, 129.7, 139.2, 147.0, 149.5, 153.2, 194.0; MS (m/z, %): 338 (M + 1^+, 23.6), 337 (M^+, 84.9), 322 (100). Anal. Calcd For $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15%. Found: C, 71.38; H, 5.85; N, 4.01%.

12-Benzoyl-2,3-dimethoxy-10-hydroxy-9-methyl-5,6-dihydroindolo[2,1-*a*]isoquinoline (22). Yield 75% (0.50 g). Yellow crystals, mp 224−225 °C; R_f 0.38 (9:1 hexane−EtOAc); IR(KBr): 3440 (br), 1748, 1564 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 3.15 (t, J = 6.6 Hz, 2H, CH_2), 3.36 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.18 (t, J = 6.6 Hz, 2H, CH_2), 6.79 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.30−7.34 (m, 2H, ArH), 7.43−7.44 (m, 1H, ArH), 7.63 (s, 1H, ArH), 7.79−7.81 (m, 2H, ArH), 8.61 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.1, 28.8, 39.7, 55.5, 55.7, 104.9, 109.6, 110.3, 110.8, 113.0, 120.1, 122.3, 127.1, 127.6, 128.2, 129.8, 130.1, 131.8, 138.2, 140.2, 146.9, 148.8, 151.7, 192.1; MS (m/z, %): 414 (M + 1^+, 30.3), 413 (M^+, 100). Anal. Calcd for $C_{26}H_{23}NO_4$ (413.47): C, 75.53; H, 5.61; N, 3.39%. Found: C, 75.36; H, 5.77; N, 3.29%.

Acknowledgment. O.B. and S.C. thank CSIR, New Delhi, for Senior research fellowships. Financial assistance under DST sponsored research project is also acknowledged.

JO010273S