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An Expeditious Synthesis of Substituted and Annelated Pyrido[2,3-*b*]indoles

Okram Barun, Pranab K. Patra, H. Ila*, H. Junjappa*

Department of Chemistry, Indian Institute of Technology, Kanpur-208016, India
E-mail:hila@iitk.ernet in; Fax:91-0512-597436, 91-0512-590260

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Abstract: An efficient and versatile synthesis of substituted and annelated pyrido[2,3-*b*]indoles (α-carboline) involving conjugate displacement on α-oxoketene dithioacetals by 1-methyl-2-oxoindole enolate anion and subsequent cyclization of the adducts in the presence of ammonium acetate has been described.

Synthesis of pyrido[2,3-*b*]indole (α-carboline) derivatives has attracted considerable interest[1,2] due to the recent discoveries of several naturally occurring compounds containing this skeleton. These compounds have displayed a wide range of important biological activities. Thus marine alkaloids Grossularine 1 and 2[3] display marked cytotoxicity towards murine and human tumor cells, whereas Mescengricin (isolated from *Streptomyces griseoflavus*) is found to protect the nervous system against L-glutamate induced excitotoxicity.[4] A few of the synthetic pyrido[2,3-*b*]indole derivatives such as **A** are shown to possess marked biological activity as potential anxiolytic agents.[5] The two best known synthetic approaches for this class of compounds involve construction of either pyridine ring from 2-amino-3-substituted indole derivatives (or its equivalent)[6] or synthesis of pyrrole (B ring) ring *via* cross coupling between an appropriately substituted pyridine and aniline derivatives.[7] Other approaches involve intramolecular Diels-Alder reaction of 2(1*H*)-pyrazinones[2] and conjugated carbodiimides.[8] However most of these methods suffer from limitations such as not easily accessible starting materials, overall poor yields or inflexibility for substituent introduction. We therefore considered it to be of interest to devise a more efficient and versatile method for construction of pyrido[2,3-*b*]indoles utilizing easily accessible α-oxoketene dithioacetals[9] and oxindole. We have successfully realized this goal involving formation of both N-1/C-2 and N-1/C-9a bonds in the final cyclization step. We herein report our preliminary results in this communication.

In a typical experiment, when **1** was treated with sodium hydride (1.5 eqv) in DMF at 0°C, and after 30 min, with ketenedithioacetal **2a**, the adduct **3a** was obtained in 89% yield. The product **3a** without further purification was cyclized with ammonium acetate in refluxing acetic acid (5h) to afford only one compound (79%) which was characterized as 9-*N*-methyl-4-methylthio-2-phenylpyrido[2,3-*b*]indole (**4a**)[10] on the basis of spectral and analytical data.[10] Dethiomethylation of **4a** in the presence of Raney Nickel in ethanol afforded 4-unsubstituted **5a** in 82% yield. The other substituted acyclic ketene dithioacetals **2b-e** similarly afforded 2-alkyl/aryl pyrido[2,3-*b*]indoles **4b-e**[10] in 61-75% overall yields (Scheme 1). Similarly the corresponding 2-heteroaryl substituted pyrido[2,3-*b*]indoles **4f-h**[10] could be synthesized from the respective oxoketene

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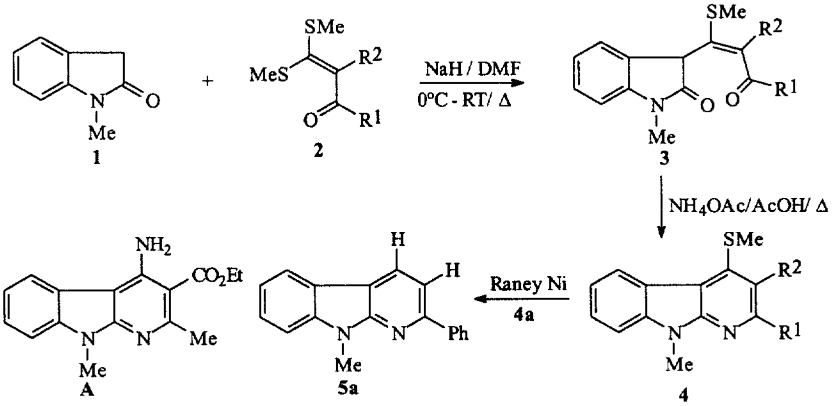
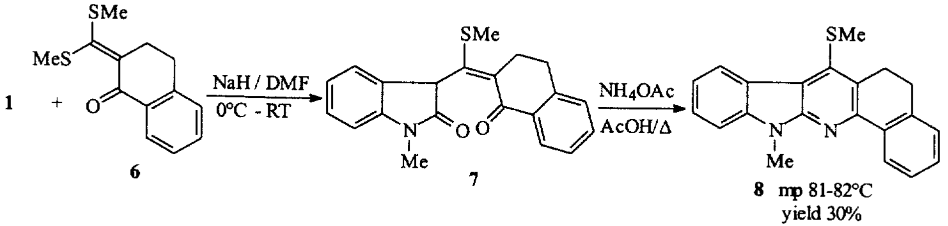
dithioacetals **2f-h** under identical conditions in overall high yields. Further, it was also possible to introduce substituents in the 3 position of pyridoindoles (**4i-j**,[10] entries 9 and 10) by employing appropriately substituted acyclic ketene dithioacetals **2i-j** respectively (Scheme 1). The methodology was also extended to doubly polarized ketene dithioacetal **1k** which afforded the corresponding 4-(methylthio)pyridoindole **4k**[10] in 59 % yield under similar conditions.



Entry	2 - 4	R^1	R^2	Mp (°C) of 4	Yield(%) of 4
1	**a**	Ph	H	119 – 120	79
2	**b**	4 – $MeOC_6H_4$	H	147 - 148	75
3	**c**	4 – ClC_6H_4	H	115 - 116	74
4	**d**	CH_3	H	126 - 127	61
5	**e**	*i*-C_3H_7	H	86 – 87	45
6	**f**	2-Furyl	H	151 - 152	73
7	**g**	2-Thienyl	H	131 - 132	71
8	**h**	2-Pyridyl	H	140 - 141	59
9	**i**	Ph	CH_3	110 - 112	59
10	**j**	CH_3	CH_3	96 - 97	60
11	**k**	CH_3	CO_2Et	97-98	51

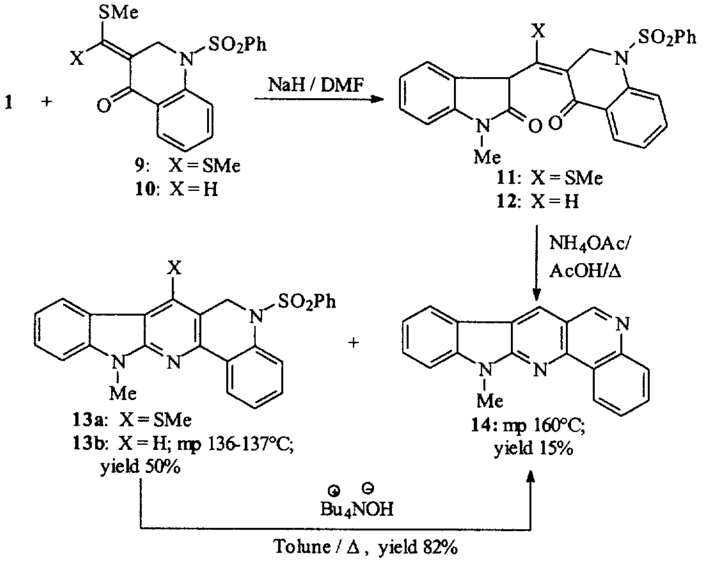
Scheme 1

To further extend the scope of this reaction, we investigated the synthesis of 3,4-annelated pyrido[2,3-*b*]indoles by employing cyclic ketene dithioacetals (Schemes 2 and 3). Thus α-oxoketene dithioacetal **6** from α-tetralone was reacted with enolate anion of **1** under the described reaction conditions to afford the corresponding adduct **7** in 79% yield. However subsequent cyclization of **7** with ammonium acetate in refluxing acetic acid gave the corresponding condensed pyridoindole **8**[10] only in 30% yield. Similarly, the



Scheme 2

adduct **11** obtained from **1** and ketenedithioacetal **9**, failed to furnish novel 2,3-heteroannelated pyridoindole **13a** (X = SMe) on treatment with ammonium acetate under the described conditions and yielded only complex product mixture. However **13b** (X = H) could be obtained in good yield from the corresponding β-methylthioenone **10** (prepared by our earlier reported procedure[9c]) following the same sequence. Thus the adduct **12** obtained by base catalyzed conjugate addition of **1** to **10** underwent facile pyridine ring annulation on treatment with ammonium acetate in refluxing acetic acid to afford **13b**[10] in 50% yield along with the small amount of **14** (15%). The product **13b** could be converted to **14**[10] in good yields (85%) by dehydrobenzenesulphonylation in the presence of phase transfer catalyst in refluxing toluene.



Scheme 3

In summary, an efficient and simple two step procedure for synthesis of a wide range of substituted and annelated α-carbolines has been described. This versatile route employs readily available α-oxoketene dithioacetals[9] as starting materials, proceeds in good overall yields and allows flexibility in introduction of a wide range of substituents. Besides, by utilizing various cyclic and heterocyclic analogs of ketene dithioacetals, access to a variety of novel heteroannulated pyrido[2,3-*b*]indoles can be envisaged. Our efforts in this direction and the application of this methodology for synthesis of naturally occuring α-carbolines are in progress which will be published later.

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References and Notes

[1] (a) Abouabdellah A, Dodd RH. Tetrahedron Lett. 1998;39:2119-2122 and references therein. (b) Papamicael C, Dupas G, Queguiner G, Bourguignon J. Heterocycles 1998;47:991-1004. (c) Papamicael C, Dupas G, Bourguignon J, Queguiner G. Tetrahedron Lett. 1994;35:4099-4102.

[2] Tahri A, Buysens KJ, van der Eycken EV, Vandenberghe DM, Hoornaert GJ. Tetrahedron 1998:13211-13226.

[3] (a) Moquen-Pattey C, Guyot M. Tetrahedron 1989;45:3445-3450. (b) Abas SA, Bilaijet Hossain M, van der Helm D, Schmitz FJ. J. Org. Chem. 1996;61:2709-2712. (c) Chosi T, Yamada S, Sugino E, Kuwada T, Hibino S. J. Org. Chem. 1995;60:5899-5904.

[4] Kin J-S, Shin-ya K, Furihata K, Hayakawa Y, Seto H. Tetrahedron Lett. 1997;38:3431-3434.

[5] Bolton D, Forbes IT, Hayward CJ, Piper DC, Thomas DR, Thompson M, Upton N. Bioorg. Med. Chem. Lett. 1993;3:1941-1946.

[6] (a) Meyer M, Guyot M. Tetrahedron Lett. 1996;37:4931-4932. (b) Forbes IT, Johnson CN. Thompson M. J. Chem. Soc. Perkin Trans I 1992:275-280. (c) Molina P, Fresneda PM, Sanz MA. Tetrahedron Lett. 1997;39:6909-6912. (d) Molina P, Fresneda PM, Sanz MA, Foces-Foces C, Carmen Ramirez de Arellano M. Tetrahedron 1998;54:9623-9638. (e) Levacher V, Boussad N, Dupas G, Bourguignon J, Queguiner G. Tetrahedron 1992;48:831-840.

[7] (a) Achab S, Guyot M, Potier P. Tetrahedron Lett. 1995;36:2615-2618. (b) Achab S, Guyot M, Potier P. Tetrahedron Lett. 1993;34:2127-2130. (c) Rocca P. Marsais F, Godard A, Queguiner G. Tetrahedron 1993;49:49-64.

[8] (a) Saito T, Ohmori H, Furuno E, Motoki S. J.C.S. Chem. Com. 1992:21-24. (b) Molina P, Alajarin M, Vidal A, Sanchez-Andrada P. J. Org. Chem. 1992;57:929-939. (c) Molina P, Fresneda PM. Synthesis 1989:878.

[9] Review: (a) Junjappa H, Ila H, Asokan CV. Tetrahedron 1990;46:5423. (b) Dieter RK. Tetrahedron 1986;42:3029. (c) Patra PK, Suresh JR, Ila H, Junjappa H. Tetrahedron 1998;54:10167-10178 and references therein.

[10] The structures of all the new compounds synthesized were established with the help of spectral and analytical data. Spectral and analytical data for a few selected compounds are given below:

4a:Colorless crystal(chloroform-hexane); mp. 119-120°C; IR (KBr): 1554, 1534, 1489 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74 (s, 3H, SCH_3), 4.00 (s, 3H, NCH_3), 7.29-7.53 (m, 7H, ArH), 8.15 (dd, J = 3, 6 Hz, 2H, ArH), 8.32 (d, J = 9 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 27.60, 96.08, 106.634, 108.5, 111.06, 119.86, 120.56, 123.39, 125.71, 127.25, 128.61, 139.99, 140.17, 145.01, 151.07, 153.50; MS (m/z): 304 (M$^+$, 100%). Anal. calcd. for $C_{19}H_{16}N_2S$ (304.42): C, 74.96; H, 5.30; N, 9.20%. Found: C, 74.71; H, 5.49; N, 9.41%.

4f: Colorless crystal (hexane-ether); mp 151-152°C; IR (KBr): 1613, 1446 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H, SCH_3), 3.84 (s, 3H, NCH_3), 6.53 (dd, J = 3Hz, 3Hz, 1H, ArH), 7.25(d, J = 3Hz, 1H, ArH), 7.22-7.29 (m, 3H, ArH), 7.39-7.44 (m, 1H, ArH), 7.51(s, 1H, ArH), 8.20(d, J = 3Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.77, 27.54, 96.07, 104.59, 108.37, 108.42, 110.95, 112.06, 119.82, 120.64, 123.15, 125.58, 139.88, 142.82, 145.12, 150.68, 154.53; MS (m/z): 294 (M$^+$, 100%). Anal. calcd. for $C_{17}H_{14}N_2OS$ (294.37): C, 69.36; H, 4.79; N, 9.52%. Found: C, 69.54; H, 4.52; N, 9.37%.

4j: Light yellow crystals (hexane-ether): mp 96-97°C; IR (KBr): 1563, 1547, 1489 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41(s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.91(s, 3H, NCH_3), 7.25-7.31 (m, 1H, ArH), 7.39 (d, J = 7.9Hz, 1H, ArH), 7.46-7.52 (m, 1H, ArH), 8.72 (d, J = 7.9 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.08, 18.25, 24.45, 27.55, 96.08, 108.52, 115.37, 119.57, 120.48, 123.48, 125.92, 139.99, 140.04, 149.00, 153.88; MS (m/z): 256 (M$^+$, 100%). Anal. calcd. for $C_{15}H_{16}N_2S$ (256.37): C, 70.28; H, 6.29; N, 10.93%. Found: C, 70.43; H, 6.42; N, 10.76%.

14: Colorless crystals (chloroform-hexane); mp. 160°C; IR (KBr): 1599, 1436 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 (s, 3H, CH_3), 7.33 – 7.39 (m, 1H, ArH), 7.43 (d, J = 8.1 Hz, 1H, ArH), 7.60 (t, J = 7.5 Hz, 1H, ArH), 7.71 (t, J = 7.3 Hz, 1H, ArH), 7.76 – 7.82 (m, 1H, ArH), 8.11 – 8.19 (m, 2H, ArH), 8.71 (s, 1H, ArH), 9.22 (dd, J = 8.0, 1.3 Hz, 1H, ArH), 9.30 (s, 1H, ArH). MS (m/z): 283 (M$^+$, 100%). Anal. calcd. for $C_{19}H_{13}N_3$ (283.33): C, 80.55; H, 4.62; N, 14.83%. Found: C, 80.34; H, 4.48; N, 14.68%.