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

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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. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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(1H)-pyrazinones² 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 dithioacetals⁹ 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-e¹⁰ in 61-75% overall yields (Scheme 1). Similarly the corresponding 2-heteroaryl substituted pyrido[2,3-b]indoles 4f-h¹⁰ could be synthesized from the respective oxoketene

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.



				Mp (°C) of	Yield(%) of
Entry	2 - 4		R ²	4	4
1	a	Ph	Н	119 - 120	79
2	b	$4 - MeOC_6H_4$	Н	147 - 148	75
3	c	$4 - ClC_6H_4$	Н	115 - 116	74
4	d	CH ₃	Н	126 - 127	61
5	e	i-C ₃ H ₇	Н	86 - 87	45
6	f	2-Furyl	Н	151 - 152	73
7	g	2-Thienyl	Н	131 - 132	71
8	h	2-Pyridyl	Н	140 - 141	59
9	i	Ph	CH ₃	110 - 112	59
10	j	CH ₃	CH3	96 - 97	60
11	k	CH ₃	CO ₂ Et	97-98	51

Scheme 1

To further extend the scope of this reaction, we investigated the synthesis of 3,4-annelated pyrido[2,3b]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



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 13b¹⁰ in 50% yield along with the small amount of 14 (15%). The product 13b could be converted to 14¹⁰ in good yields (85%) by dehydrobenzenesulphonylation in the presence of phase transfer catalyst in refluxing toluene.



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 dithioacetals⁹ 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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- [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; ¹H NMR (300 MHz, CDCl₃): δ 2.74 (s, 3H, SCH₃), 4.00 (s, 3H, NCH₃), 7.29-7.53 (m, 7H, ArH), 8.15 (dd, J = 3, 6 Hz, 2H, ArH), 8.32 (d, J = 9 Hz, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₉H₁₆N₂S (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; ¹HNMR (300 MHz, CDCl₃): δ 2.63 (s, 3H, SCH₃), 3.84 (s, 3H, NCH₃), 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₇H₁₄N₂OS (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; ¹H NMR (300 MHz, CDCl₃): δ 2.41(s, 3H, CH₃), 2.61 (s, 3H, CH₃), 2.68 (s, 3H, CH₃), 3.91(s, 3H, NCH₃), 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₆N₂S (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; ¹H NMR (300 MHz, CDCl₃): δ 4.03 (s, 3H, CH₃), 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 C₁₉H₁₃N₃ (283.33): C, 80.55; H, 4.62; N, 14.83%. Found: C, 80.34; H, 4.48; N, 14.68%.

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