Heteroaromatic annulation studies on 2-[bis(methylthio)methylene]-1-methyl-3-oxoindole: synthesis of novel heterocyclo[b] fused indoles

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Dedicated to Professor P. T. Narasimhan on his 75th birthday
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Abstract: Heteroannulation of 2-[Bis(methylthio)methylene]-1-methyl-3-oxoindole with β-substituted β-lithioaminoacrylonitrile, malononitrile and guanidine has been reported to yield novel substituted pyrido[3,2-b]indoles and pyrimido[5,4-b]indole derivatives in varying yields.

Keywords: Oxoindole, heterocyclization, δ-carbolines, pyrimido[5,4-b]indoles

Introduction

In the earlier work from this laboratory, we have described for the first time, the synthesis of 2-[bis(methylthio)methylene]-1H-3-oxoindole 4 and the corresponding N-methyl analog 5 by careful in situ trapping of the unstable dipotassium salt 2 of the indoxyl enolate (obtained by base induced intramolecular condensation of 1) with carbon disulphide in an inert atmosphere and subsequent in situ methylation of the dithiolate salt 3 with either two or three equivalents of methyl iodide (Scheme 1).1 We have further carried out aromatic and heteroaromatic annulation studies on the N-methyl analog 5 with various allyl Grignard reagents and the anions derived from aryl/heteroaryl acetonitriles and antipyrine yielding novel benzo[c]-, naphtho[1,2-c]- and heterocyclo- fused carbazoles in good yields.1 Similarly, the heterocyclization studies on 5 with various 1,3-heterobinucleophilic species such as lithioacetonitrile, lithioaminocrotononitrile and 2- picollylithium afforded the novel heterocyclo[b]- fused indoles such as pyrido[3,4-b]- or pyrido[3,2-b]indoles and the corresponding indolo[3,2-b]- quinolizinium salts in good yields.1 In continuation of these studies and in view of the biological importance of indolo[b]- fused heterocycles,2 we have now further investigated heterocyclization of ketene dithioacetals 5 with other bifunctional heterobinucleophiles such as β-substituted-β-lithioaminoacrylonitriles,
malononitriles and guanidine yielding novel pyrido- and pyrimido fused indolo[\(b\)]-heterocycles. The results of these studies have been reported in the present paper.

\[
\begin{align*}
\text{KOH / H}_2\text{O} & \quad 280 \degree C / \text{N}_2 & \quad -\text{CO}_2 \\
\text{O} & \quad \text{K} & \quad \text{CS}_2 \\
\text{0 \degree C / H}_2\text{O} & \\
\end{align*}
\]

\[
\begin{align*}
\text{3K} & \quad \text{MeI (2 or 3 eqv)} & \quad 0 \degree C / \text{H}_2\text{O} \\
\text{R} & \quad \text{H} & \quad 4 \\
\text{R} & \quad \text{Me} & \quad 5 \\
\end{align*}
\]

Scheme 1

**Results and Discussion**

We have earlier reported the reaction of \(\beta\)-lithioaminocrotononitrile generated in situ by treatment of one equivalent of \(n\)-butyllithium with two equivalents of acetonitrile at –78 \degree C with 5 affording the corresponding 3-cyano-2,5-dimethyl-4-(methylthio)pyrido[3,2-\(b\)]indole (\(\delta\)-carboline) in good yield.\(^1\)\(^3\) To further explore the scope of this reaction, we extended this method for the synthesis of various 2-substituted \(\delta\)-carbolines by addition of the corresponding \(\beta\)-substituted \(\beta\)-lithioaminoacrylonitriles 8 generated in situ by addition of lithioacetonitrile to various aromatic and aliphatic nitriles as shown in Scheme 2.\(^3\)

\[
\begin{align*}
\text{a) MeCN (1 eqv) / RCN (1 eqv) / n-BuLi (1 eqv) / -78 \degree C} & \\
\text{b) 80 \degree C / 28 h} \\
\end{align*}
\]

6-8a, \(R = \text{Ph}, 62\%\)

\(b, R = 4-\text{MeOC}_6\text{H}_4 \), 63\%  

\(c, R = 2\)-thienyl, 58\%  

\(d, R = \text{MeOCH}_2\), 64\%

Scheme 2
Thus the 2-substituted 3-cyano-4-(methylthio)pyrido[3,2-b]-indoles 7a-d were obtained in 58-64% overall yields through initial 1,4-conjugate addition of lithioaminoacrylonitriles 8a-d followed by in situ heterocyclization of adducts 6a-d as observed earlier. The present method thus provides an efficient three component route for substituted δ-carbolines. It should be noted that the reported methods for the synthesis of δ-carbolines are scant in the literature in comparison to those for β- or γ-carboline derivatives.2g,4 The structures and regiochemistry of all newly synthesized δ-carbolines 7a-d were confirmed with the help of spectral and analytical data.

In an another approach towards functionalized pyrido[3,2-b]indole frameworks, the ketene dithioacetal 5 was reacted with malononitrile in presence of sodium methoxide in refluxing methanol, when the reaction mixture after work-up yielded the corresponding 2-methoxy-3-cyano-5-methyl-4-(methylthio)pyrido[3,2-b]indole 10 in 45% yield (Scheme 3). This is again an interesting example of three component heterocyclization leading to a substituted pyrido[3,2-b]indole through attack of methoxy group on one of the nitrile groups in the intermediate conjugate adduct 5 followed by cyclodehydration.

![Scheme 3](image)

We next investigated the heterocyclization of 1 with guanidine nitrate5 with a view to synthesize the pyrimido[5,4-b]indole framework6 as shown in Scheme 4. Thus when 5 was reacted with guanidine nitrate in the presence of sodium isopropoxide in refluxing isopropanol, the expected 2-amino-4-(methylthio)-5-methylpyrimido[5,4-b]indole 11 was obtained in 52% yield. On the other hand, when 5 was reacted with guanidine nitrate in the presence of sodium methoxide or sodium ethoxide in refluxing methanol (or ethanol), the corresponding 4-methoxy-and 4-ethoxy-pyrimido[5,4-b]indoles 12a-b were obtained in 48% and 50% yields respectively.
Apparently the ketene dithioacetal 5 undergoes thiomethyl displacement to give the corresponding O,S-acetals 13a-b which further reacted with guanidine nitrate to afford the observed fused pyrimidines 12a-b (Scheme 4). The sodium isopropoxide being a hindered base does not undergo displacement with 5 under these conditions.

Scheme 4

In summary, heterocyclization studies on 2-[bis(methylthio)methylene]-2,3-dihydro-3-oxo-1-methylindole 5 with β-substituted-β-lithioaminoacrylonitriles, malononitrile and guanidine yield novel substituted pyrido[3,2-b]indole and pyrimido[5,4-b]indole derivatives in moderate to good yields.

Experimental Section

General Procedures. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in CDCl$_3$ and TMS was used as an internal reference. Melting points are uncorrected. Chromatographic purification was conducted by column chromatography using 60-120 mesh silica gel obtained from Acme Synthetic Chemicals. THF was distilled over sodium/benzophenone prior to use. 4-Methoxybenzonitrile, 2-cyanothiophene, methoxyacetonitrile, malononitrile, guanidine nitrate, $n$-BuLi(1.6M in hexane) were purchased...
from standard firms and used directly. The 2-bis(methylthio)methylene-1-methyl-3-oxoindole (5) was prepared according to the earlier reported procedure.1

**General procedure for the generation of 2-substituted 2-lithioaminoacrylonitriles 8 and their reactions with 5: Synthesis of 2-substituted 3-cyano-4-(methylthio)pyrido[3,2-b]indoles 7a-d**

To stirred solution of acetonitrile (0.4 mL, 7.6 mmol) in dry THF (25 mL), n-BuLi (7.5 mmol, 1.6M in hexane) was added under N2 at –78 °C and the reaction mixture was stirred for 0.5 h at the same temperature. To the resulting white suspension of lithioacetonitrile, a solution of alkyl/aryl or heteroaryl nitrile (7.5 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was further stirred at the same temperature for 0.5 h to give a light reddish solution of 2-substituted 2-lithioaminoacrylonitriles. To these in situ generated 2-lithioaminoacrylonitriles, a solution of 5 (1.26 g, 5.0 mmol) in dry THF (25 mL) was added dropwise at –78 °C. The reaction mixture was brought to room temperature and refluxed with stirring for 40-48 h (monitored by TLC). It was then cooled, poured into saturated NH4Cl solution, extracted with CHCl3 (2 × 100 mL) and the combined organic layers were washed with water, dried (Na2SO4) and concentrated to give crude 7a-7d, which were purified by column chromatography over silica gel using hexane-EtOAc (19:1) as eluent.

3-Cyano-5-N-methyl-4-(methylthio)-2-phenylpyrido[3,2-b]indole (7a). Colorless crystals (ether-hexane); mp 171-172 °C Yield 62%; IR (KBr): 2210, 1546, 1460 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.71 (s, 3H, SCH3), 4.42 (s, 3H, NCH3), 7.36-7.41 (m, 1H, ArH), 7.49-7.56 (m, 4H, ArH), 7.67-7.71 (m, 1H, ArH); MS: (m/z, %): 329 (M⁺, 100), 314 (31); Anal. Calcd. for C20H15N3S (329.43): C, 72.92; H, 4.59; N, 12.76%. Found: C, 73.19; H, 4.95; N, 12.59%.

3-Cyano-2-(4-methoxyphenyl)-5-N-methyl-4-(methylthio)pyrido[3,2-b]indole (7b). Colorless crystals (ether-hexane); mp 209-210 °C Yield 63%; IR (KBr): 2210, 1596, 1460 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.66 (s, 3H, SCH3), 3.88 (s, 3H, OCH3), 4.23 (s, 3H, NCH3), 7.01 (d, J = 8.8 Hz, 2H, ArH), 7.05-7.09 (m, 1H, ArH), 7.31-7.33 (m, 2H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.95 (d, J = 8.8 Hz, 2H, ArH); 13C NMR (100 MHz, CDCl3): 12.92, 32.95, 55.47, 108.32, 109.54, 114.45, 115.21, 117.63, 118.66, 119.61, 125.70, 128.61, 128.62, 137.94, 146.57, 150.30, 151.71, 162.09; MS: (m/z, %): 359 (M⁺, 100); Anal. Calcd. for C21H17N3OS (359.45): C, 70.41; H, 4.68; N, 11.61%. Found: C, 70.41; H, 4.68; N, 11.61%.

3-Cyano-5-N-methyl-4-methylthio-2-(thienyl)pyrido[3,2-b]indole (7c). Colorless crystals (ether-hexane); mp 228-229 °C Yield 58%; IR (KBr): 2202, 1550, 1490 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 2.64 (s, 3H, SCH3), 4.18 (s, 3H, NCH3), 7.04-7.16 (m, 2H, ArH), 7.26-7.34 (m, 2H, ArH), 7.50 (d, J = 5.12 Hz, 1H, ArH), 7.68 (d, J = 5.1 Hz, 1H, ArH), 7.76 (d, J = 7.8 Hz, 1H, ArH); 13C NMR (100 MHz, CDCl3): 13.02, 32.91, 106.86, 109.54, 112.10, 113.51, 117.23, 118.66, 119.66, 125.83, 127.19, 128.47, 129.82, 138.00, 138.52, 146.64, 160.64, 183.17; MS: (m/z, %): 335 (M⁺, 100); Anal. Calcd. for C18H13N3S2 (335.45): C, 65.45; H, 3.91; N, 12.53%. Found: C, 65.69; H, 4.02; N, 12.41%. 

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3-Cyano-2-methoxymethyl-5-N-methyl-4-(methylthio)pyrido[3,2-b]indole (7d). Colorless crystals (ether-hexane); mp 180-181°C; Yield 64%; IR (KBr): 2202, 1600, 1541 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.67 (s, 3H, SCH₃), 3.62 (s, 3H, OCH₃), 4.37 (s, 3H, NCH₃), 4.91 (s, 2H, CH₂OCH₃), 7.38 (t, J = 7.9 Hz, 1H, ArH), 7.50 (d, J = 8.2 Hz, 1H, ArH), 7.65-7.69 (m, 1H, ArH), 4.91 (s, 2H, CH₂OCH₃), 7.38 (t, J = 7.9 Hz, 1H, ArH), 7.50 (d, J = 8.2 Hz, 1H, ArH), 7.65-7.69 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): 20.64, 32.21, 59.20, 74.68, 109.50, 111.80, 116.60, 121.08, 121.22, 122.24, 130.13, 132.76, 144.00, 144.45, 152.29; MS: (m/z, %): 297 (M⁺, 24), 267 (100); Anal. Calcd. for C₁₆H₁₅N₃OS (297.38): C, 64.62; H, 5.08; N, 14.13%. Found: C, 64.79; H, 5.22; N, 14.31%.

Procedure for cycloannulation of 5 with malononitrile
A solution of 5 (1.26 g, 5 mmol) in dry methanol was added to a solution of malononitrile (0.61 g, 5 mmol) and sodium methoxide (from 0.05 mole of sodium) in 50 mL of dry methanol and the reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure, the residue was diluted with cold water and extracted with CHCl₃ (2 × 50 mL). The CHCl₃ layer was dried (Na₂SO₄) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6: 1) as eluent.

3-Cyano-2-methoxy-5-N-methyl-4-(methylthio)pyrido[3,2-b]indole (10). Colorless crystals (ether-hexane); mp 228-229 °C Yield 45%; IR (KBr): 2202, 1550, 1490 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.17 (s, 3H, SCH₃), 3.87 (s, 3H, OCH₃), 3.97 (s, 3H, NCH₃), 7.06 (t, J = 7.08 Hz, 1H, ArH), 7.24 (d, J = 8.32 Hz, 1H, ArH), 7.35-7.39 (m, 1H, ArH), 7.74 (d, J = 8.0 Hz, 1H, ArH); Anal. Calcd. for C₁₅H₁₃N₃SO (283.45): C, 63.58; H, 4.62; N, 14.83%. Found: C, 63.69; H, 4.52; N, 14.74%.

Reaction of 5 with guanidine nitrate
(a) in the presence of sodium isopropoxide
A solution of 5 (1.26 g, 5.0 mmol) in dry isopropanol was added to a suspension of guanidine nitrate (0.61 g, 5.0 mmol) and sodium isopropoxide (0.05 mmol of sodium) in dry isopropanol (50 mL) and the reaction was refluxed for 12-14 h. The solvent was removed under reduced pressure, the residue diluted with cold water and extracted with CHCl₃ (2 × 50 mL). The CHCl₃ layer was dried (Na₂SO₄) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6: 1) as eluent.

2-Amino-5-N-methyl-4-(methylthio)pyrimido[5,4-b]indole (11). Light yellow crystals (methanol); mp 227-228 °C Yield 52%; IR (KBr): 3250, 3100, 1650, 1600, 1500 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.01 (s, 3H, SCH₃), 4.12 (s, 3H, NCH₃), 7.10-7.26 (m, 1H, ArH), 7.35-7.37 (m, 1H, ArH), 7.55-7.59 (m, 1H, ArH), 8.20 (d, J = 7.9 Hz, 1H, ArH); MS: (m/z, %): 244 (M⁺ 100); Anal. Calcd. for C₁₂H₁₂N₄S (244.32): C, 58.99; H, 4.95; N, 22.93%. Found: C, 58.79; H, 4.62; N, 22.81%.

(b) in methanol or ethanol
A solution of 5 (1.26 g, 5.0 mmol) in dry methanol/ethanol was added to a suspension of guanidine nitrate (0.61 g, 5.0 mmol) and sodium methoxide or ethoxide (from 0.05 mmol of
sodium) in 50 mL of the respective alcohol and the reaction mixture was refluxed for 12-14 h. The solvent was removed under reduced pressure, the residue was diluted with cold water and extracted with CHCl$_3$ (2 × 50 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6:1) as eluent.

2-Amino-5-N-methyl-4-(methoxy)pyrimido[5,4-b]indole (12a). Colorless crystals (Ether-hexane); mp 145-146 °C Yield 48%; IR (KBr): 3466, 3295, 3161, 3100, 1650, 1600, 1500 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 2.86 (s, 3H, SCH$_3$), 3.99 (s, 3H, NCH$_3$), 4.92 (brs, 2H, NH$_2$), 7.17-7.21 (m, 1H, ArH), 7.33-7.35 (m, 1H, ArH), 7.50-7.53 (m, 1H, ArH), 8.14 (d, $J = 8.0$ Hz, 1H, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): 31.64, 53.49, 109.45, 115.12, 119.18, 119.94, 121.26, 128.34, 141.85, 141.40, 156.82, 157.68; MS: ($m/z$, %): 228 (M$,^+$, 100), 213 (56); Anal. Calcd. for C$_{12}$H$_{12}$N$_4$S (228.25): C, 63.14; H, 5.30; N, 24.55%. Found: C, 63.39; H, 5.45; N, 24.32%.

2-Amino-5-N-methyl-4-(ethoxy)pyrimido[5,4-b]indole (12b). White crystals (ether-hexane); mp 225-226 °C Yield 50%; IR (KBr): 3479, 3287, 3151, 1650, 1600, 1500 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.48 (t, $J = 7.0$ Hz, 3H, CH$_3$), 4.00 (s, 3H, NCH$_3$), 4.56 (q, $J = 7.08$, 2H, CH$_2$CH$_3$), 4.83 (brs, 2H, NH$_2$), 7.17-7.21 (m, 1H, ArH), 7.35 (d, $J = 8.6$ Hz, 1H, ArH), 7.49-7.53 (m, 1H, ArH), 8.14 (d, $J = 7.8$ Hz, 1H, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): 14.57, 31.58, 62.18, 109.43, 115.23, 119.43, 120.04, 121.22, 128.26, 141.90, 146.21, 156.89, 157.43; MS: ($m/z$, %): 242 (M$,^+$, 100), 227 (50); Anal. Calcd. for C$_{13}$H$_{14}$N$_4$O (242.28): C, 64.45; H, 5.82; N, 23.13%. Found: C, 64.65; H, 5.60; N, 23.41%.

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