Pergamon

Tetrahedron Letters 39 (1998) 2029–2032

TETRAHEDRON LETTERS

Benzoannelation of 2-methylindole via 1-N-Carboxy-2-methylindole Dianion: A Direct Regiospecific Route to Substituted and Annelated Carbazoles

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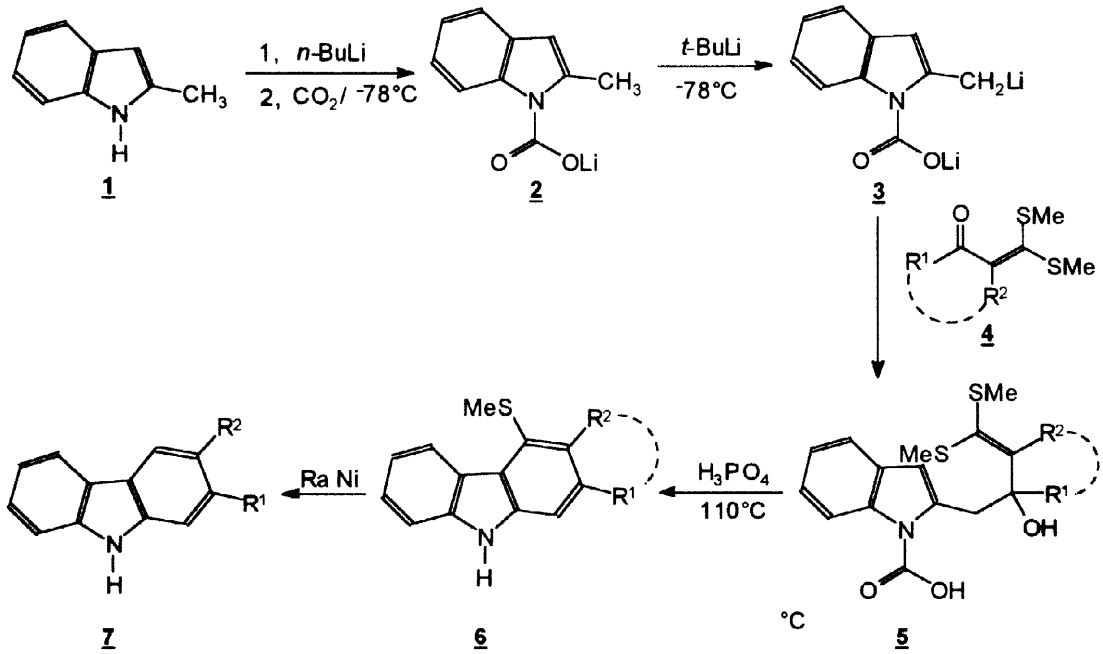
Received 27 November 1997; accepted 16 January 1998

Abstract: A facile general route for substituted and annelated N-H-carbazoles **6** has been developed by regiospecific 1,2-addition of 1-N-carboxy-2-methylindole dianion **3** to acyclic and cyclic α-oxoketene dithioacetals **4** followed by cycloaromatization in the presence of H_3PO_4.

Katritzky and Akutagawa[1] have successfully demonstrated that the 2-methylindole **1**, when protected as its lithium carbamate **2**, undergoes a facile deprotonation of the α-methyl protons to afford the corresponding 1-N-carboxy-2-lithiomethylindole **3** in high yield. This dianion **3** was subsequently reacted with various electrophiles such as alkyl halides, ketones and isocyanates to afford the corresponding 2-(substituted alkyl)indoles with simultaneous loss of carbon dioxide during workup in acid medium. Thus, carbon dioxide was used efficiently both to temporarily block the N-H position and to activate the 2-alkyl group towards proton loss. We therefore considered **3** as an important allyl anion, which should react with α-oxoketene dithioacetals **4** to yield carbazoles following our heteroaromatic annelation protocol.[2,3] There have been many methods described in the literature for the synthesis of carbazoles and most of them use indole as the starting material with a reactive N-H group, generally blocked by conventional protecting groups.[2f,4,8a,b] However, the protecting groups such as alkyl and benzyl functionalities require more rigorous reaction conditions for their removal.[5] The other labile groups such as phenylsulfonyl, methoxymethyl *etc.* display their own directing and activating effect and interfere with the regiospecific anion formation process.[6,7] Thus, the C,O-dianion **3** with its temporarily blocked nitrogen is an attractive allyl anion component and should react with various α-oxoketene dithioacetals **4** to yield the corresponding carbinolacetals **5**, which should undergo a facile acid assisted ring closure with simultaneous loss of carbon dioxide to afford the corresponding regioselectively substituted N-H-carbazoles **6** in one pot reaction. These expectations have been fully realised, which to our knowledge is the first report of regiospecific [*b*]-annulation of N-unsubstituted indole to N-unsubstituted carbazoles under anionic conditions.[8] Our preliminary results are presented in this communication.

0040-4039/98/$19.00
PII: S0040-4039(98)00164-6

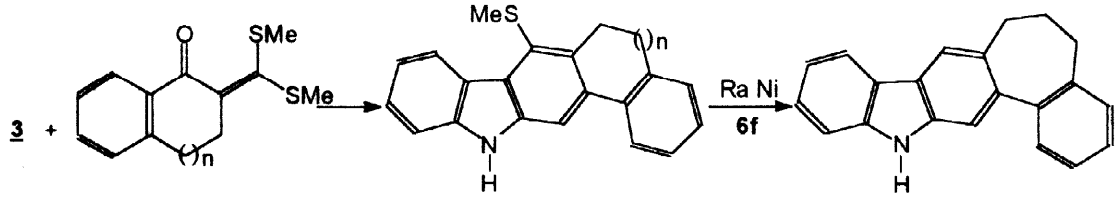


7a, R^1 = Me, R^2 = H (mp 264-266°C)
c, R^1 = Ph, R^2 = Me (mp 147-149°C)

4, 5, 6a, R^1 = Me, R^2 = H (mp 107°C)
b, R^1 = Ph, R^2 = H (mp 131°C)
c, R^1 = Ph, R^2 = Me (mp 141°C)
d, R^1 = $-(CH_2)_5-$ = R^2 (mp 179°C)

Scheme 1

In a typical experiment, the dianion **3** was generated as reported and reacted with α-oxoketene dithioacetal **4a** at -78°C to afford the corresponding carbinolacetal **5a** in good yield (TLC). The R_f of **5a** was corresponding to the formation of carbinolacetal involving exclusive 1,2-addition mode. The carbinolacetal, thus obtained was cycloaromatized in the presence of H_3PO_4 at 110°C to afford the corresponding 2-methyl-4-(methylthio)carbazole (**6a**) in 62% yield (Scheme 1). The carbazole **6a** was then desulfurized in the presence of Raney Ni to afford the known 2-methylcarbazole (**7a**)[8b] in 56% yield. The formation of **7a** further confirms the regiospecific reaction of **3** with **4a**. In subsequent reactions, the anion **3** was reacted with oxoketene dithioacetals **4b** and **4c** under the described reaction conditions to afford the corresponding carbazoles **6b** and **6c**[10] in 63% and 70% yields respectively. Similarly, the reaction of cyclic oxoketene dithioacetals with **3** was examined. When **3** was reacted with oxoketene dithioacetal derived from cyclohexanone, the corresponding carbinolacetal was however not formed and the reaction mixture resulted into an intractable tar. However, when **3** was reacted with **4d** derived from cycloheptanone, the



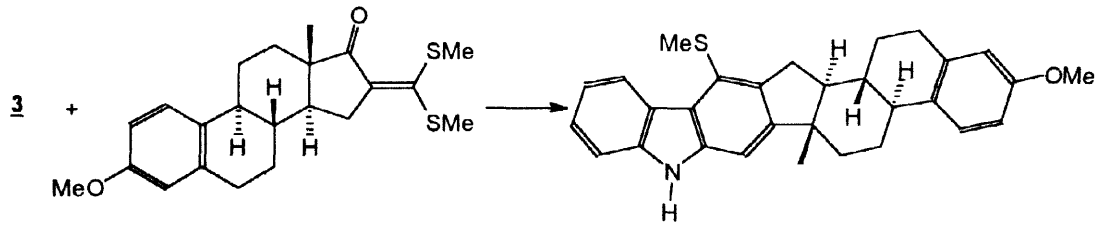
4e, n = 1
f, n = 2

6e, n = 1 (mp 196°C)
f, n = 2 (mp 179°C)

7f (mp 203°C)

Scheme 2

corresponding carbinolacetal **5d** was formed, which was cyclized as described to yield **6d**[10] in 66% yield (Scheme 1). The oxoketene dithioacetals **4e, f** derived from tetralone and benzsuberone could also be reacted with **3** to afford the corresponding carbazoles **6e**[10] and **6f** in 64% and 68% yields respectively (Scheme 2). The carbazoles **6c** and **6f** were desulfurized in the presence of Raney Ni to afford the corresponding dethiomethylated carbazoles **7c** and **7f** in 61% and 58% yields respectively. As an extension of this method for the synthesis of optically active carbazole, **3** was reacted with oxoketene dithioacetal **4g** derived from estrone-3-methylether to afford the corresponding carbazole **6g**[10] in 70% yield under similar reaction conditions (Scheme 3). The optical rotation of **6g** was found to be $[\alpha]^{25}_{D}$ +47° (c = 1, dioxane).



4g **6g** (mp 183°C)

Scheme 3

In conclusion, the dianion **3** has been successfully used for the synthesis of carbazoles using our heteroaromatic annelation methodology. Our attempts to extend this method for the synthesis of 1-alkylcarbazole from 1-N-carboxy-2-ethylindole dianion[11] was not successful as no well defined product could be isolated. Also, the dianion as generated by Inagaki and co-workers[9] by treating 2-methylindole with *n*-BuLi in the presence of potassium-*t*-butoxide, did not give satisfactory yields of carbazoles. Thus, the C,O-dianion **3** is unique for the synthesis of N-H-carbazoles through a variety of α-oxoketene dithioacetals in one pot reaction. We are currently pursuing this approach for the synthesis of more functionalized carbazoles of biological interest and apply to other N-H-heteroallyl systems

Acknowledgement: Financial assistance by CSIR, DST is gratefully acknowledged. UKS and PKP thank CSIR for Junior Research Fellowship and Research Associateship respectively.

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10. Structure of all compounds prepared were confirmed with the help of spectral and analytical data. Representative spectral and analytical data for compounds **6c-e** and **6g** are given below.

6c: Colourless crystals (ether); mp 141°C; yield 70%; IR (KBr): 3409, 2911, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 7.08 (s, 1H, ArH), 7.23-7.39 (m, 8H, ArH), 7.78 (brs, 1H, NH, exchanges with D_2O), 8.97 (d, J = 9 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.33, 18.38, 110.32, 112.30, 119.51, 123.07, 123.83, 124.34, 125.81, 126.75, 128.00, 129.38, 130.30, 131.44, 137.74, 140.03, 140.85, 143.09; MS (*m/z*, %): 303 (M^+, 100), 255 (89). Anal. Calcd for $C_{20}H_{17}NS$ (303.427): C, 79.09; H, 5.65; N, 4.62%. Found: C, 78.88; H, 5.69; N, 4.65%.

6d: Colourless crystals (ether); mp 179°C; yield 66%; IR (KBr): 3391, 2924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.68-1.85 (m, 6H, CH_2), 2.35 (s, 3H, SCH_3), 2.92-2.96 (m, 2H, CH_2), 3.43-3.47 (m, 2H, CH_2), 7.09 (s, 1H, ArH-1), 7.23-7.39 (m, 3H, ArH), 7.85 (brs, 1H, NH, exchanges with D_2O), 8.96 (d, J = 7.8 Hz, 1H, ArH-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.46, 28.71, 28.80, 30.66, 32.26, 37.63, 110.21, 110.45, 111.64, 119.35, 120.10, 123.51, 123.63, 125.26, 128.89, 137.98, 139.64, 142.65; MS (*m/z*, %): 281 (M^+, 100), 235 (53.8). Anal. Calcd for $C_{18}H_{19}NS$ (281.419): C, 76.82; H, 6.80; N, 4.97%. Found: C, 76.67; H, 6.72; N, 4.92%.

6e: Colourless crystals (ether); mp 196°C; yield 64%; IR (KBr): 3385, 2923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, SCH_3), 2.84-2.89 (m, 2H, CH_2), 3.35-3.40 (m, 2H, CH_2), 7.21-7.28 (m, 5H, ArH), 7.35-7.42 (m, 1H, ArH), 7.61 (s, 1H, ArH), 7.62-7.67 (m, 1H, ArH), 7.82 (brs, 1H, NH, exchanges with D_2O), 8.96 (dd, J = 1.2, 8.7 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.73, 26.01, 29.59, 106.76, 110.36, 119.62, 123.32, 123.85, 124.22, 124.51, 125.98, 126.95, 127.38, 127.93, 129.01, 133.43, 133.92, 135.40, 138.08, 138.83, 140.25; MS (*m/z*, %): 315 (M^+, 35.7), 267 (85.8). Anal. Calcd for $C_{21}H_{17}NS$ (315.438): C, 79.96; H, 5.43; N, 4.44%. Found: C, 79.82, H, 5.48; N, 4.38%.

6g: Colourless crystals (ether-chloroform); mp 183°C; yield 70%; $[\alpha]^{25}_D$ +47°C (c = 1, dioxane); IR (KBr): 3381, 2952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 3H, CH_3), 1.23-1.31 (m, 2H), 1.49-1.59 (m, 2H), 1.71-1.90 (m, 3H), 2.09-2.15 (m, 1H), 2.25-2.45 (m, 2H), 2.46 (s, 3H, SCH_3), 2.76 (dd, J = 12, 15 Hz, 1H), 2.93-2.99 (m, 1H), 3.30 (dd, J = 6, 10 Hz, 1H), 3.79 (s, 3H, OCH_3), 6.67 (d, J = 3 Hz, 1H, ArH), 6.74 (dd, J = 3, 6 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 7.22-7.27 (m, 2H, ArH), 7.37-7.38 (m, 2H, ArH), 8.00 (brs, 1H, NH, exchanges with D_2O), 8.80 (d, J = 6 Hz, 1H, ArH); MS (*m/z*, %): 455 (100), 440 (19.7). Anal. Calcd for $C_{30}H_{31}NOS$ (453.642): C, 79.43; H, 6.88; N, 3.08%. Found: C, 79.21; H, 6.79; N, 2.90%.

11. Katritzky and Akutagawa have shown that 1-N-carboxy-2-ethylindole dianion reacts regiospecifically with methyliodide to give 2-*n*-propylindole in 95% yield; Ref. 1.