

DIRECTED BETA-LITHIATION OF 2-SUBSTITUTED INDOLES –
A NEW SYNTHETIC ROUTE TO 2,3-DISUBSTITUTED INDOLES

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Abstract - Treatment of several N-protected 2-substituted indoles with *n*-butyllithium at -78°C leads to C-3 lithiation, presumably via coordination with the C-2 substituent. Depending on the exact system, the 3-lithioindole can either be trapped with electrophiles or suffer ring-opening to an alkyne.

Nitrogen-protected 3-lithioindoles, generated by metal-halogen exchange at low temperatures with *t*-butyllithium, have proven to be useful intermediates in alkaloid synthesis.¹ To complement and extend this methodology, we have studied the "directed-metalation" route² to these intermediates and now report our findings.

Treatment of 1-(phenylsulfonyl)-2-(2-pyridinyl)indole (**1**)³ with *n*-butyllithium (*n*-BuLi) at -78°C in tetrahydrofuran (THF) affords the relatively stable 3-lithio-1-(phenylsulfonyl)-2-(2-pyridinyl)indole (**2**). Quenching **2** at -78°C with various electrophiles and workup (NH_4Cl) gives the expected 3-substituted pyridinyl indoles **3** in fair to good recrystallized yields (Table). Despite the general propensity of pyridines to undergo nucleophilic attack,⁶ no addition of *n*-BuLi to the pyridine ring was observed. Hydrolysis of the protecting group in **3a** (aqueous NaOH, MeOH) affords the known 3-methyl-2-(2-pyridinyl)indole (**4**) (96% yield), mp $101.5\text{--}102^{\circ}\text{C}$ (lit.⁷ mp $100\text{--}101^{\circ}\text{C}$). As expected, the isomeric 1-(phenylsulfonyl)-2-(4-pyridinyl)indole did not undergo metalation under these conditions and was recovered essentially unchanged after quenching with acetaldehyde (35% deprotection).

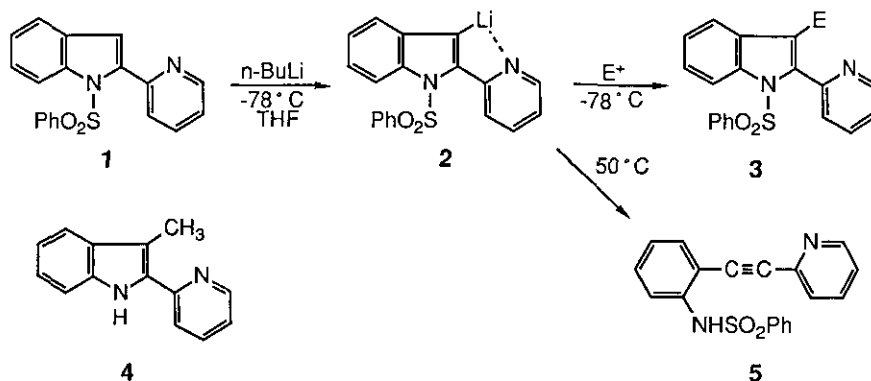


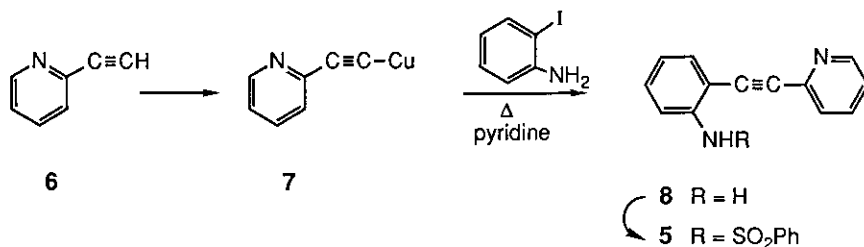
TABLE. Reaction of 3-Lithio-2-(2-pyridinyl)-1-(phenylsulfonyl)indole (**2**) with Electrophiles^a

Electrophile	Product ^b	E	mp, °C	%Yield ^c
CH ₃ I	3a	CH ₃	148.5-150.5 ^d	74
CO ₂	3b	CO ₂ H	234-235 (dec) ^e	58
Me ₃ SiCl	3c	Me ₃ Si	170-172.5 ^d	51
CH ₃ CHO	3d	CH(CH ₃)OH	157.5-158 ^d	68
ClCO ₂ Et	3e	CO ₂ Et	93-95 ^d	55
CH ₃ CONCH ₃ OCH ₃	3f ^f	COCH ₃	136-137 ^g	52

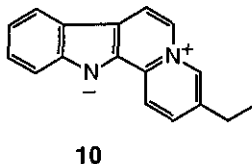
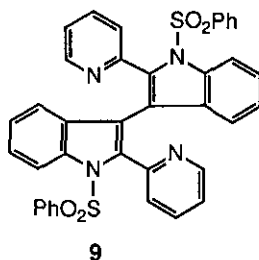
^aTo a THF solution of **2**, prepared by the addition over 5 min of n-BuLi to **1** at -78°C, was added after 1 h of stirring at -78°C the appropriate electrophile. The mixture was stirred overnight while being allowed to warm slowly to room temperature, and then worked up. ^bAll products gave satisfactory elemental analyses⁹ and spectral data (IR, ¹H and ¹³C NMR) consistent with their assigned structures.

^cIsolated and recrystallized material. ^dFrom ethyl acetate-hexane. ^eFrom chloroform-hexane. ^fHMPA (1.2 equiv) was added just prior to the addition of N-methoxy-N-methylacetamide. ^gFrom benzene-petroleum ether.

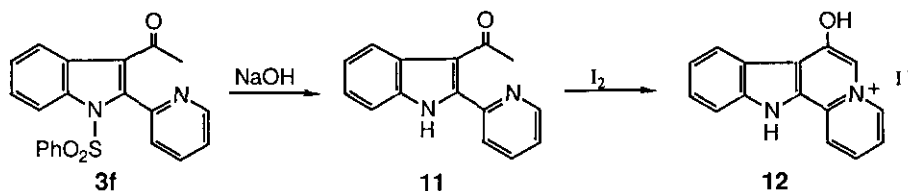
Surprisingly, and in contrast to 2,3-dilithio-1-(phenylsulfonyl)indole and related heterocycles⁸, **2** shows an aversion to ring opening, even at room temperature, and had to be heated to ~50°C to form **5**^{9,10} (mp 130.5-132°C) at a convenient rate (65% yield). The structure of **5** was confirmed by independent synthesis. Thus, 2-ethynylpyridine (**6**)¹¹ is converted to the cuprous acetylenide **7** and then coupled with 2-iodoaniline according to Castro's procedure¹² to give 2-aminophenyl-2-pyridylacetylene (**8**) (27% yield), mp 108-109°C (lit.¹² mp 104-105°C). Subsequent reaction of **8** with benzenesulfonyl chloride (pyridine, 0° → 25°C, 8h) affords **5** (93% yield), identical (mp, IR, ¹H NMR, ¹³C NMR, ms) with that obtained from **2**.



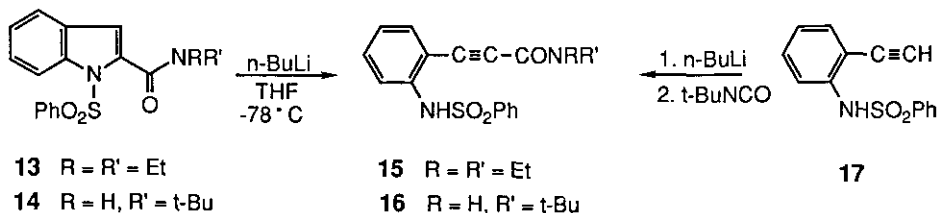
The lithiated indole **2**, as well as the corresponding Grignard reagent (prepared by transmetalation of **2** with MgBr₂·Et₂O), failed to react with several other electrophiles (EtI, ICH₂CH₂OTMS, allyl bromide, ethylene oxide) including several enolizable carbonyl compounds. Likewise, the organocopper species, generated from **2** with CuBr·Me₂S, showed a lack of reactivity and, not unexpectedly, produced small amounts (<20%) of the 3,3'-bisindole **9**^{9,13} mp 243-245°C (dec).



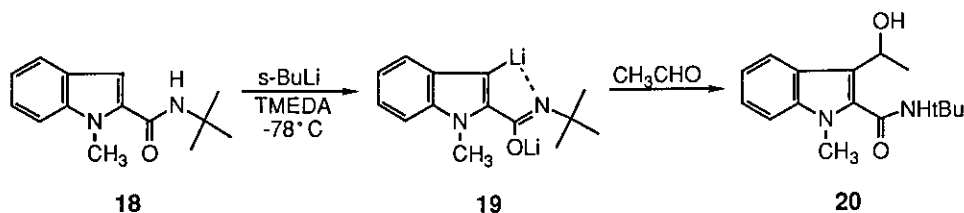
We have also examined this methodology as a route to the indolo[2,3-*a*]quinolizine ring system, several examples of which are zwitterionic alkaloids¹⁴, including the antitumor alkaloid flavopereirine (**10**)¹⁵. Accordingly, deprotection of **3f** (aqueous NaOH, MeOH) gives ketone **11**^{9,16} (mp 174-176°C) (97% yield). This same material can also be prepared from alcohol **3d** by oxidation with MnO₂ (CHCl₃, reflux, 72 h) (70% yield) and base hydrolysis. Treatment of **11** with iodine in the presence of cyclohexene oxide (CCl₄, reflux, 2 h) affords **12**^{9,17} (mp 292-295°C dec) in 72% yield.



We have also examined the metalation of indole amides **13**^{9,18} and **14**^{9,19}. In stark contrast to the behavior of **1**, both amides **13** and **14** fragment to alkynes **15**^{9,20} (mp 90-92°C) (25%) and **16**^{9,21} (mp 178-180°C) (30%), respectively, upon treatment with *n*-BuLi (THF, -78°C). Alkyne **16** could be prepared independently in 62% yield from 2-(phenylsulfonylamido)phenyl - acetylene (**17**)⁸ by treatment with *n*-BuLi (2.1 equiv, THF, -78°C) and quenching with *t*-butylisocyanate.



However, by replacing the *N*-phenylsulfonyl group with the *N*-methyl group, and thereby circumventing the formation of a highly stabilized phenylsulfonanilide anion, we were able to lithiate indole amide **18**^{9,22}. Interestingly, it is necessary to employ *sec*-butyllithium/tetramethylethylenediamine (TMEDA) to generate dilithio species **19**, perhaps indicating a synergistic acidifying effect of the *N*-phenylsulfonyl group in **14**. Quenching **19** with acetaldehyde at -78°C gives the acid-sensitive alcohol **20**^{9,24} (mp 145.5-147°C) in 60% yield.



In summary, we have demonstrated for the first time that 3-lithioindoles can be generated via a directed-metalation protocol. On the basis of related metalation-induced ring fragmentations²⁵, the remarkable stability of **2** *vis-à-vis* the anions derived from **13** and **14** can be ascribed to the superior chelating properties of the pyridine ring in **2**.

ACKNOWLEDGEMENT

This investigation was supported by PHS Grant GM-30761 awarded by the National Institutes of Health and by Merck Sharp & Dohme Research Laboratories.

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- Prepared from 2-(2-pyridinyl)indole⁴ (NaH; PhSO₂Cl) 73% yield: mp 114-115.5°C (lit.⁵ mp 117-119°C).
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- This new compound gave an elemental analysis within the following limits: C, $\pm 0.24\%$; H, $\pm 0.08\%$; N, $\pm 0.07\%$; S, $\pm 0.10\%$. Exceptions were **3e**, **9** and **12**, which showed C, $\pm 0.38\%$; H, $\pm 0.30\%$; N, $\pm 0.16\%$; S, $\pm 0.24\%$; I, ± 0.05 , with **12** as the hemihydrate.
- 5**: IR (KBr) 3400, 2210, 1580 cm⁻¹; ¹H NMR (CDCl₃) δ 8.6 (m, 1H), 8.0-6.7 (m, 13H); ¹³C NMR (CDCl₃) δ 149.9, 142.1, 138.9, 137.8, 136.2, 132.9, 132.4, 130.1, 128.7, 127.1, 124.7, 123.2, 121.2, 114.1, 94.6, 83.6; ms *m/e* 334 (M⁺), 269, 193 (100%), 166.
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- 9**: IR (KBr) 1590, 1455, 1375, 1190 cm⁻¹; ¹H NMR (CDCl₃) δ 8.7-6.7 (m); ¹³C NMR (CDCl₃) δ 150.2, 148.7, 138.0, 137.5, 137.1, 135.1, 133.5, 130.7, 128.6, 127.2, 126.0, 125.6, 124.3, 122.5, 120.4, 117.8, 116.1; ms *m/e* 525 (M⁺-PhSO₂), 386, 385, 308 (100%), 306.

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16. 11: IR (KBr) 3140, 1615 cm^{-1} ; ^1H NMR (CDCl_3) δ 10.5 (br s, 1H), 8.9-7.2 (m, 8H), 2.74 (s, 3H); ^{13}C NMR (CDCl_3) δ 195.4, 151.6, 150.3, 137.4, 136.6, 136.5, 128.4, 126.1, 124.6, 124.2, 122.6, 116.4, 112.8, 31.3; ms m/e 236 (M^+), 235, 221 (100%), 193, 192.
17. 12: IR (KBr) 3350 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 9.38 (d, 1H, $J=6\text{Hz}$), 8.82 (d, 1H, $J=8\text{Hz}$), 8.47 (s, 1H), 8.39 (d, 1H, $J=8\text{Hz}$), 8.18 (m, 1H), 7.9-7.4 (m, 4H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 150.1, 140.3, 135.3, 132.2, 131.5, 128.5, 127.8, 123.1, 121.9, 121.6, 121.1, 119.6, 115.5, 112.3, 111.5, ms m/e 234 ($\text{M}^+ - \text{H}$, 100%), 206, 128, 103; UV (MeOH) λ_{max} 222, 251, 295 (sh), 318, 379 nm.
18. Prepared from 2-lithio-1-(phenylsulfonyl)indole^{1a} and N,N -diethylcarbamoyl chloride (14% yield) or, better, from 1-(phenylsulfonyl)indole-2-carboxylic acid with thionyl chloride and diethylamine (67% yield): mp 87-90°C; IR (KBr) 1645 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.4-7.9 (m, 3H), 7.7-7.1 (m, 6H), 6.63 (s, 1H), 3.50 (m, 4H), 1.25 (m, 6H); ^{13}C NMR (CDCl_3) δ 162.9, 137.5, 134.9, 134.1, 133.9, 129.1, 128.9, 127.7, 125.2, 123.7, 121.5, 114.0, 108.3, 43.1, 39.3, 13.7, 11.9; ms m/e 356 (M^+), 284, 144 (100%), 115.
19. Prepared from 2-lithio-1-(phenylsulfonyl)indole^{1a} and t -butylisocyanate (83% yield): mp 163-165°C; IR (KBr) 1660 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.4-7.0 (m, 9H), 6.87 (s, 1H), 6.1 (br s, 1H), 1.58 (s, 9H); ^{13}C NMR (CDCl_3) δ 137.3, 136.74, 136.70, 133.9, 129.0, 128.9, 127.5, 126.0, 124.2, 121.9, 115.2, 113.2, 52.3, 28.5; ms m/e 356 (M^+), 144, 143, 142 (100%), 77, 57.
20. 15: IR (KBr) 3570, 2210 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.0-6.9 (m, 9H), 3.4 (m, 4H), 1.20 (t, 3H, $J=7\text{Hz}$), 1.13 (t, 3H, $J=7\text{Hz}$); ^{13}C NMR (CDCl_3) δ 153.3, 139.1, 138.9, 132.9, 131.2, 128.9, 127.1, 124.5, 121.2, 112.3, 87.3, 84.6, 43.6, 39.4, 14.3, 12.7; ms m/e 356 (M^+), 284, 144 (100%), 115.
21. 16: IR (KBr) 3210, 1605 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.75 (d, 2H, $J=7.5\text{Hz}$), 7.55-7.20 (m, 6H), 7.05-7.00 (m, 1H), 6.22 (s, 1H), 6.06 (br s, 1H), 1.37 (s, 9H); ^{13}C NMR ($\text{acet}-d_6$) δ 182.7, 140.7, 139.6, 134.1, 133.8, 131.6, 129.9, 127.9, 126.3, 124.6, 115.3, 105.7, 52.4, 28.7; ms m/e 356 (M^+), 284, 77 (100%).
22. Prepared from 1-methylindole with $n\text{-BuLi}$ and t -butylisocyanate (59% yield) according to the general method of Shirley²³: mp 143-146°C; IR (KBr) 3300, 1630 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.8-6.9 (m, 4H), 6.28 (s, 1H), 6.12 (br s, 1H), 4.05 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (CDCl_3) δ 162.1, 138.8, 133.2, 125.9, 123.7, 121.5, 120.3, 110.0, 103.0, 51.6, 31.4, 28.9; ms m/e 230 (M^+), 174, 158 (100%), 130, 89.
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24. 20: IR (KBr) 3240, 1625 cm^{-1} ; ^1H NMR ($\text{acetone}-d_6$) δ 8.68 (br s, 1H), 7.72 (d, 1H, $J=8\text{Hz}$), 7.42 (d, 1H, $J=8\text{Hz}$), 7.25 (m, 1H), 7.07 (m, 1H), 5.47 (q, 1H, $J=7\text{Hz}$), 3.8 (s, 3H), 2.08 (s, 1H), 1.64 (d, 3H, $J=7\text{Hz}$), 1.43 (s, 9H); ^{13}C NMR ($\text{acetone}-d_6$) δ 162.8, 137.9, 132.8, 126.1, 124.0, 120.5, 120.4, 120.2, 110.7, 62.8, 51.9, 31.6, 28.9, 24.0; ms m/e 274 (M^+), 256, 199 (100%), 184.
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Received, 6th May, 1986