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

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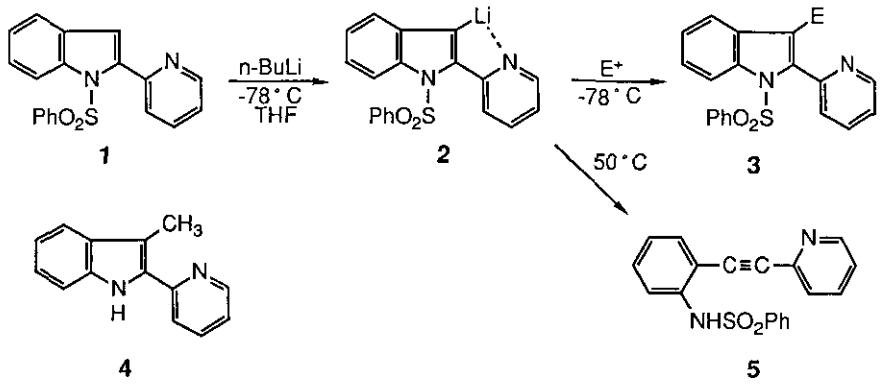
Abstract - Treatment of several N-protected 2-substituted indoles with n-butyllithium at -78°C leads to C-3 lithiation, presumably via coordination with the C-2 substituent. Depending on the exact system, the 3-lithioindole can either be trapped with electrophiles or suffer ring-opening to an alkyne.

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" route[2] 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 101.5-102°C (lit.[7] mp 100-101°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).



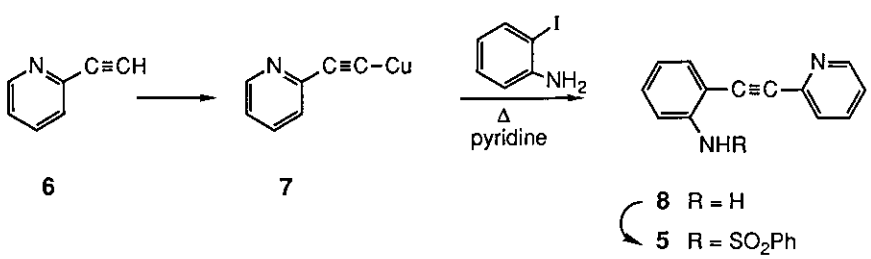
1 **2** **3** **4** **5**

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

Electrophile	Product[b]	E	mp,°C	%Yield[c]
CH_3I	**3a**	CH_3	148.5-150.5[d]	74
CO_2	**3b**	CO_2H	234-235 (dec)[e]	58
Me_3SiCl	**3c**	Me_3Si	170-172.5[d]	51
CH_3CHO	**3d**	$CH(CH_3)OH$	157.5-158[d]	68
$ClCO_2Et$	**3e**	CO_2Et	93-95[d]	55
$CH_3CONCH_3OCH_3$	**3f**[f]	$COCH_3$	136-137[g]	52

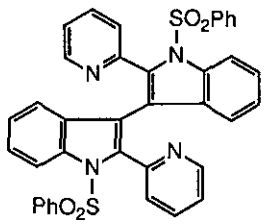
[a]To a THF solution of **2**, prepared by the addition over 5 min of n-BuLi to **1** at -78°C, was added after 1 h of stirring at -78°C the appropriate electrophile. The mixture was stirred overnight while being allowed to warm slowly to room temperature, and then worked up. [b]All products gave satisfactory elemental analyses[9] and spectral data (IR, ^1H and ^{13}C NMR) consistent with their assigned structures. [c]Isolated and recrystallized material. [d]From ethyl acetate-hexane. [e]From chloroform-hexane. [f]HMPA (1.2 equiv) was added just prior to the addition of N-methoxy-N-methylacetamide. [g]From benzene-petroleum ether.

Surprisingly, and in contrast to 2,3-dilithio-1-(phenylsulfonyl)indole and related heterocycles[8], **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 procedure[12] to give 2-aminophenyl-2-pyridinylacetylene (**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, ^{13}C NMR, ms) with that obtained from **2**.



6 **7** **8** R = H; **5** R = SO_2Ph

The lithiated indole **2**, as well as the corresponding Grignard reagent (prepared by transmetalation of **2** with $MgBr_2{\cdot}Et_2O$), failed to react with several other electrophiles (EtI, ICH_2CH_2OTMS, allyl bromide, ethylene oxide) including several enolizable carbonyl compounds. Likewise, the organocopper species, generated from **2** with $CuBr{\cdot}Me_2S$, 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).



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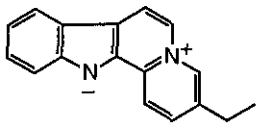

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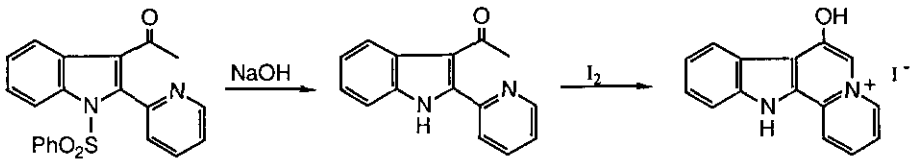
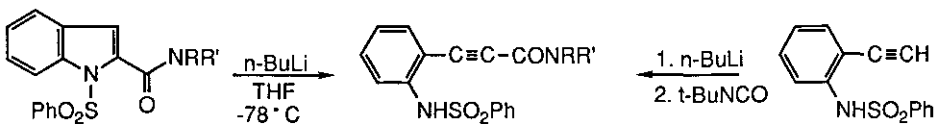
We have also examined this methodology as a route to the indolo[2,3-*a*]quinolizine ring system, several examples of which are zwitterionic alkaloids[14], including the antitumor alkaloid flavopereirine (**10**)[15]. Accordingly, deprotection of **3f** (aqueous NaOH, MeOH) gives ketone **11**[9,16] (mp 174-176°C) (97% yield). This same material can also be prepared from alcohol **3d** by oxidation with MnO_2 ($CHCl_3$, reflux, 72 h) (70% yield) and base hydrolysis. Treatment of **11** with iodine in the presence of cyclohexene oxide (CCl_4, reflux, 2 h) affords **12**[9,17] (mp 292-295°C dec) in 72% yield.



3f **11** **12**

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-(phenylsulfonamido)phenyl - acetylene (**17**)[8] by treatment with n-BuLi (2.1 equiv, THF, -78°C) and quenching with t-butylisocyanate.

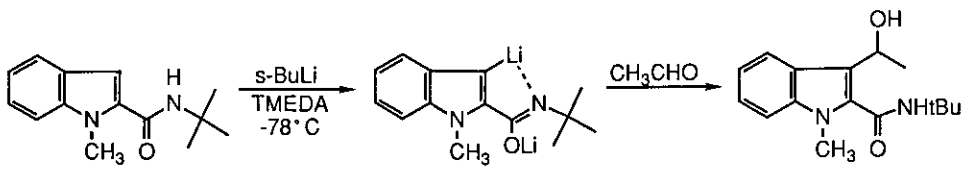


13 R = R' = Et
14 R = H, R' = t-Bu

15 R = R' = Et
16 R = H, R' = t-Bu

17

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 synergis - tic 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.



18 **19** **20**

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 fragmentations[25], 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

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REFERENCES AND NOTES

1. (a) M.G. Saulnier and G.W. Gribble, *J. Org. Chem.*, 1982, *47*, 757. (b) M.G. Saulnier and G.W. Gribble, *J. Org. Chem.*, 1983, *48*, 2690. (c) G.W. Gribble and T.C. Barden, *J. Org. Chem.*, 1985, *50*, 5900.
2. For a leading reference, see P. Beak and V. Snieckus, *Accts. Chem. Research*, 1982, *15*, 306.
3. Prepared from 2-(2-pyridinyl)indole[4] (NaH; $PhSO_2Cl$) 73% yield: mp 114-115.5°C (lit.[5] mp 117-119°C).
4. S. Sugasawa, M. Terashima and Y. Kanaoka, *Pharm. Bull. Japan*, 1956, *4*, 16.
5. J. Caixach, R. Capell, C. Galvez, A. Gonzalez and N. Roca, *J. Heterocycl. Chem.*, 1979, *16*, 1631.
6. For a leading reference, see F. Marsais and G. Queguiner, *Tetrahedron*, 1983, *39*, 2009.
7. C.K. Bradsher and E.F. Litzinger, Jr., *J. Org. Chem.*, 1964, *29*, 3584.
8. G.W. Gribble and M.G. Saulnier, *J. Org. Chem.* 1983, *48*, 607, and references therein.
9. This new compound gave an elemental analysis within the following limits: C, ± 0.24%; H, ± 0.08% N, ± 0.07%; S, ± 0.10%. Exceptions were **3e**, **9** and **12**, which showed C, ± 0.38%; H, ± 0.30%; N, ± 0.16%; S, ± 0.24%; I, ± 0.05, with **12** as the hemihydrate.
10. **5**: IR (KBr) 3400, 2210, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (m, 1H), 8.0-6.7 (m, 13H); ^{13}C NMR ($CDCl_3$) 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.
11. D. Leaver, W.K. Gibson and J.D. Vass, *J. Chem. Soc.*, 1963, 6053.
12. C.E. Castro, E.J. Gaughan and D.C. Owsley, *J. Org. Chem.*, 1966, *31*, 4071.
13. **9**: IR (KBr) 1590, 1455, 1375, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.7-6.7 (m); ^{13}C NMR ($CDCl_3$) 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^+-$PhSO_2$), 386, 385, 308 (100%), 306.

14. (a) R. Kaschnitz and G. Spiteller, *Monatsh Chem.*, 1965, *96*, 909. (b) G. Büchi, R.E. Manning and F.A. Hochstein, *J. Am. Chem. Soc.*, 1962, *84*, 3393.

15. M. Beljanski and M.S. Beljanski, *Exp. Cell. Biol.*, 1982, *50*, 79.

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 (DMSO-d_6) δ 9.38 (d, 1H, J=6Hz), 8.82 (d, 1H, J=8Hz), 8.47 (s, 1H), 8.39 (d, 1H, J=8Hz), 8.18 (m, 1H), 7.9-7.4 (m, 4H); ^{13}C NMR (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 (M^+-HI, 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=7Hz), 1.13 (t, 3H, J=7Hz); ^{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=7.5Hz), 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 (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-BuLi and t-butylisocyanate (59% yield) according to the general method of Shirley [23]: 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.

23. D.A. Shirley and P.A. Roussel, *J. Am. Chem. Soc.*, 1953, *75*, 375.

24. **20**: IR (KBr) 3240, 1625 cm^{-1}; ^1H NMR (acetone -d_6) δ 8.68 (br s, 1H), 7.72 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz), 7.25 (m, 1H), 7.07 (m, 1H), 5.47 (q, 1H, J=7Hz), 3.8 (s, 3H), 2.08 (s, 1H), 1.64 (d, 3H, J=7Hz), 1.43 (s, 9H); ^{13}C NMR (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.

25. (a) T. Frejd, *J. Heterocycl. Chem.*, 1977, *14*, 1085. (b) E.G. Doadt and V. Snieckus, *Tetrahedron Lett.*, 1985, *26*, 1149.

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