LITHIATION ROUTES TO OXINDOLES AND 2-INDOLINETHIONES: PRECURSORS TO 2,2′-DITHIOBISINDOLES WITH TYROSINE KINASE INHIBITORY PROPERTIES+

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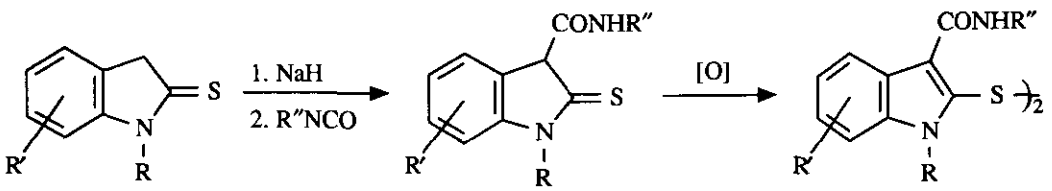
Abstract- *N*-Substituted oxindoles and 2-indolinethiones can be prepared by lithiation of carboxyl protected *N*,2-dimethylanilines followed by quenching with CO_2 or CS_2 respectively. 2-Indolinethione derivatives are also available *via* demethylation of 2-methylthioindoles, which are prepared by lithiation of *N*-substituted indoles and treatment with dimethyl disulfide.

As a continuation of our research into 2,2′-dithiobisindoles as tyrosine kinase inhibitors,[1] we required a variety of substituted 3-carboxamide derivatives (**3**). The simplest route to these compounds was found to be *via* condensation of an *N*-substituted 2-indolinethione (**1**) and an isocyanate, with facile oxidation of the initial thione products (**2**) giving rise to the desired disulfides (Scheme 1).[2]

Scheme 1



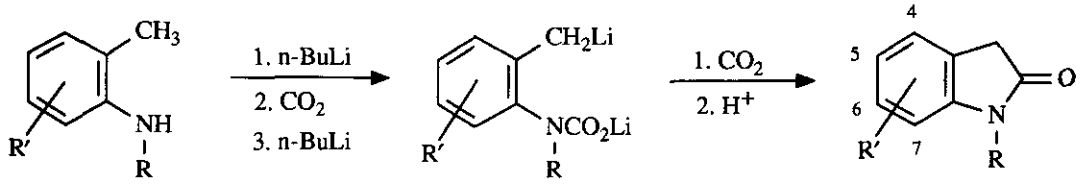
1 **2** **3**

2-Indolinethiones (**1**) are readily available by thiation of the analogous oxindoles,[1,3] so the main synthetic work involved the preparation of these latter compounds. However, although there are a number of general routes

+*This paper is dedicated to Professor Alan Katritzky on the occasion of his 65th birthday.*

available for the synthesis of *N*-unsubstituted oxindoles,[4] the synthesis of *N*-alkyl derivatives is less clear-cut, with none of the available methods being able to produce all possible ring-substituted derivatives isomerically pure. Thus, for example, the $AlCl_3$-catalyzed ring-closure of *N*-alkyl-α-haloacetanilides (Stollé synthesis) involves ring-closure onto the *ortho* position of *N*-alkylaniline derivatives,[5,6] giving rise to mixtures with *meta*-substituted anilines where two *ortho* positions are available. In addition, both dealkylation of alkoxy groups,[7] and isomerization of alkyl substituents,[8] can occur under the strongly acidic reaction conditions. To avoid all of these problems we turned our attention to lithiation routes, since we were aware that *N*-unsubstituted oxindoles had been synthesized *via* lithiation of *N*-(*tert*-butoxycarbonyl)-2-alkylanilines,[9] and that *N*-methylindoles had been prepared *via* lithiation of *N*-carboxyl derivatives of *N*,2-dimethylanilines.[10] We now report that a combination of these two methods successfully gives the desired *N*-substituted oxindoles in good yields. Thus, by using the carbon dioxide protection procedure,[10] a variety of *N*-alkyl-2-methylaniline derivatives (**4**) could be lithiated on the 2-methyl group, and successfully converted to the analogous oxindoles (**6**) after quenching with carbon dioxide and treatment with aqueous acid (Scheme 2).[11]

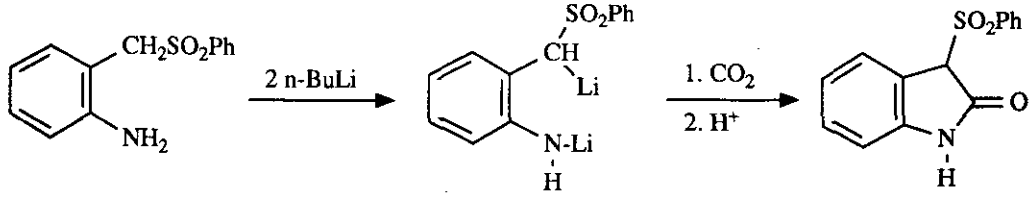
Scheme 2



4 **5** **6**

The lithiation method is not compatible with a meta-chloro group, where ring lithiation followed by benzyne formation represents a probable degradative pathway, although it can be extended to *N*-unsubstituted anilines, provided that *tert*-BuLi is used in the second lithiation step.[12] In the case of 2-phenylsulfonylmethylaniline (**7**) no nitrogen protection was necessary, due to the anion stabilizing properties of the sulfonyl group (Scheme 3).

Scheme 3



7 **8** **9**

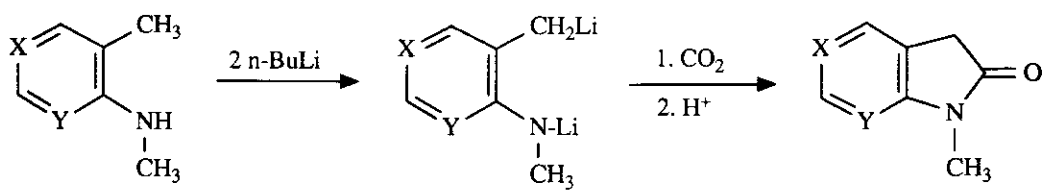
The oxindoles prepared by these routes are shown in Table 1. The substituted *N*-methylanilines required for the synthesis of the *N*-methyloxindoles were normally prepared from the appropriate *N*-(1-*H*-benzotriazol-1-yl-methyl)anilines[13] by $NaBH_4$ reduction,[10,14] although in certain cases alternative procedures were necessary.[15]

Table 1. Oxindoles prepared by methods of Schemes 2 and 3.[16]

Compound	R	R′	% Yield	Compound	R	R′	% Yield
6a	CH_3	H	55	**6b**	$(CH_2)_2N(CH_3)_2$	H	43
6c	CH_3	4-CH_3	58	**6d**	CH_3	5-CH_3	48
6e	CH_3	6-CH_3	42	**6f**	CH_3	7-CH_3	42
6g	CH_3	4-OCH_3	45	**6h**	CH_3	5-OCH_3	36
6i	CH_3	6-OCH_3	9	**6j**	CH_3	7-OCH_3	38
6k	CH_3	5-Cl	41	**9**	H	H	56

Protection of the nitrogen atom was also not necessary with 2-methylamino-3-methylpyridine (**10**) and 4-methylamino-3-methylpyridine (**11**), and both of these compounds were able to be converted directly to the analogous azaoxindoles (**14**) and (**15**) *via* C,N-dianion intermediates (**12**) and (**13**) (Scheme 4).[17] The two pyridylamines (**10**) and (**11**) are known to form resonance stabilized monoanions where the lone pair electrons of the exocyclic nitrogen are oriented towards the adjacent methyl group,[18] and these conformations would favour directed metalation of the alkyl group. 2-Methylamino-3-phenylthiomethylpyridine has previously been converted to the 3-phenylthio derivative of compound (**14**) by a similar procedure,[19] but the present work represents the first use of unsubstituted 3-alkyl substituents.

Scheme 4



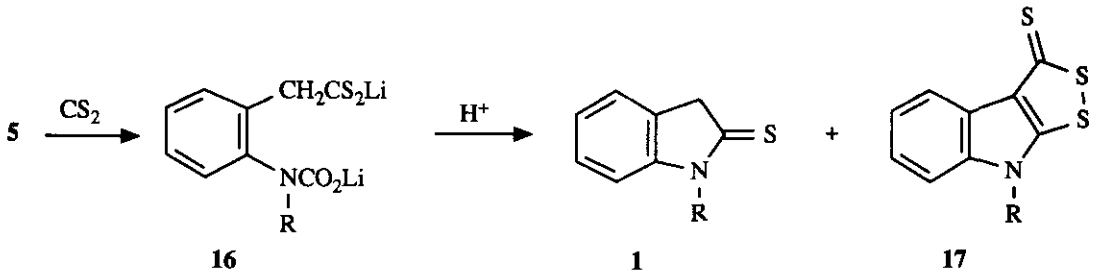
10; X = CH, Y = N
11; X = N, Y = CH

12; X = CH, Y = N
13; X = N, Y = CH

14; X = CH, Y = N
15; X = N, Y = CH

The majority of the oxindoles prepared were able to be converted to the analogous 2-indolinethiones (**1**),[2] but in certain cases direct thiation could not be achieved, so we investigated the direct synthesis of the desired 2-indolinethiones by use of CS_2 as the quenching reagent in the original lithiation procedure. However the results were not as straightforward as for the analogous CO_2 quench, and although the desired 1-methyl-2-indolinethione (**1a**) was obtained from *N*,2-dimethylaniline (Scheme 5), it was accompanied by a minor product that was identified as 1,2-dithiolo-8-methyl[3,4-*b*]indole-3-thione (**17a**).[20] This compound has been prepared previously by condensation of **1a** with CS_2 in the presence of NaH.[21] Interestingly, in the case of the *N*-(2-dimethylaminoethyl) derivative (**16b**) only starting material and the tricyclic derivative (**17b**) could be isolated.[22]

Scheme 5

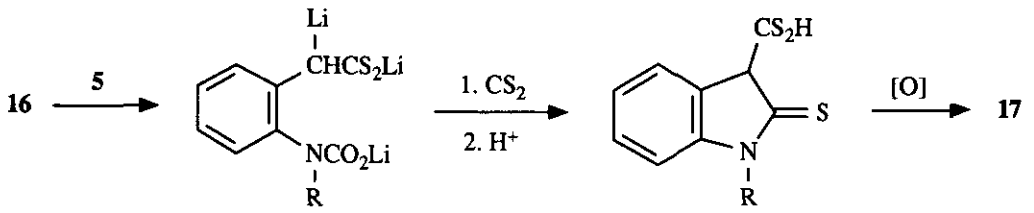


16 **1** **17**

[**a**; R = CH_3 **b**; R = $CH_2CH_2N(CH_3)_2$]

Although compound (**17a**) was previously prepared from the indolinethione (**1a**),[21] it is probable that a different mechanism is operating in the present case. Thus, deprotonation of the initial intermediate (**16**), by reaction with anion (**5**), would give the resonance stabilized anion (**18**), which would then form the thioacid (**19**) following addition of a second equivalent of CS_2 and acid-catalyzed ring-closure. *In situ* oxidation would then lead to the isolated tricyclic derivatives (**17**) (Scheme 6). The isolation from these reactions of appreciable quantities of unreacted amine (**4**), resulting from the protonation of **5**, supports this interpretation.

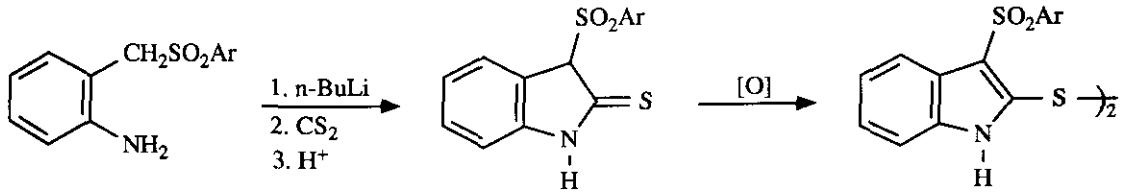
Scheme 6



18 **19**

However despite the fact that the lithiation and CS_2 quenching procedure failed to proceed cleanly to a single product, it was still possible to use the method synthetically to produce, albeit in low yield, a disulfide derivative (**22**) from **20** (Scheme 7), as a result of *in situ* oxidation of the initially formed 2-indolinethione (**21**).[23]

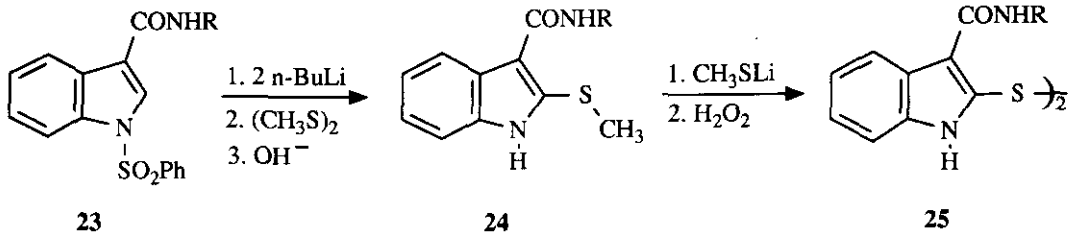
Scheme 7



(Ar = *p*-$C_6H_4CH_3$)

An alternative approach to *N*-unsubstituted 3-carboxamido disulfides (**25**) involved the lithiation of 1-phenylsulfonylindole-3-carboxamide derivatives (**23**).[24] Quenching of the dianionic intermediates with dimethyl disulfide gave the 2-methylthio derivatives (**24**)[25] which were able to be demethylated using methanethiolate ion in DMA,[26] and subsequently oxidized *in situ* to give the desired disulfides (**25**) (Scheme 8).

Scheme 8



(**a**; R = CH_3 **b**; R = CH_2Ph **c**; R = Ph)

Although tertiary derivatives of 1-phenylsulfonylindole-3-carboxamides have been previously lithiated and derivatized,[27] the present work represents the first example where secondary carboxamide derivatives have been utilized.

In summary, lithiation procedures have provided new routes to 2-indolinethiones and their oxindole precursors.

ACKNOWLEDGEMENT

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9. R.D. Clark, J.M. Muchowski, L.E. Fisher, L.A. Flippin, D.B. Repke, and M. Souchet, *Synthesis*, 1991, 871.
10. A.R. Katritzky, W.-Q. Fan, K. Akutagawa, and J. Wang, *Heterocycles*, 1990, **30**, 407.
11. *N*,2-Dimethylanilines were lithiated according to the conditions of reference 10. Dry CO_2 gas was then bubbled in at -78 °C and the mixtures were allowed to warm to room temperature. After removal of the solvent the residues were treated with 0.1 M HCl, to initiate both removal of the carboxyl protecting group and ring-closure to the oxindole.
12. A.R. Katritzky, M. Black, and W.-Q. Fan, *J. Org. Chem.*, 1991, **56**, 5045.
13. *N*-(1-*H*-Benzotriazol-1-ylmethyl)anilines were prepared by Mannich reaction of the appropriately substituted anilines with formaldehyde and benzotriazole.[10,28] All compounds gave nmr spectral data consistent with their structures, and all new compounds gave satisfactory elemental analysis results. New derivatives prepared were the 4-methyl (mp 132-134 °C), 2,3-dimethyl (mp 156-158 °C), 2,4-dimethyl (mp 147-149 °C), 2,5-dimethyl (mp 149-151 °C), 3-methoxy-2-methyl (mp 129-132 °C), 4-methoxy-2-methyl (mp 122-124 °C), and 2-aza-6-methyl (mp 175-177 °C).
14. A.R. Katritzky, S. Rachwal, and B. Rachwal, J. *Chem. Soc., Perkin Trans. 1*, 1987, 805.
15. The main alternative route employed for *N*,2-dimethylaniline synthesis was *via* methylation

(MeI/NaH) of the benzyl carbamates of the appropriate 2-methylanilines, followed by hydrogenation. New benzyl *N*-phenylcarbamates prepared were the 2,6-dimethyl (mp 126.5-129 °C), 5-methoxy-2-methyl (mp 104-105 °C), and the 6-methoxy-2-methyl (mp 132-134 °C), all of which gave satisfactory elemental analysis results. New benzyl *N*-methyl-*N*-phenylcarbamates prepared were the 2,3-dimethyl, 2,6-dimethyl, 5-methoxy-2-methyl and the 6-methoxy-2-methyl, all of which were oils that gave acceptable hrms data. *N*-(2-Dimethylaminoethyl)-2-methylaniline was prepared by acid hydrolysis (90% H_2SO_4) of the analogous *N*-tosyl derivative (mp 75.5-77.5 °C), which was prepared by alkylation of *N*-2-methylphenyltoluenesulfonamide with 2-chloro-*N,N*-dimethylethylamine. All compounds gave nmr spectral data consistent with their structures.

16. All oxindoles gave spectral data consistent with their structures, and all new compounds gave satisfactory elemental analysis or hrms (compound **6b**) results. Melting points for new compounds are: **6e**, 94.5-96 °C; and **9**, 220 °C (decomp.).

17. 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**14**): mp (hexane) 94-95 °C; ^{1}H nmr ($CDCl_3$) δ 8.18 (d, J = 5.3 Hz, 1 H, H-6), 7.48 (d, J = 7.2 Hz, 1 H, H-4), 6.94 (dd, J = 7.2, 5.3 Hz, 1 H, H-5), 3.53 (s, 2 H, CH_2), and 3.29 (s, 3 H, CH_3); ^{13}C nmr ($CDCl_3$) δ 174.1 (C=O), 158.1 (C-7a), 146.6 (C-6), 131.3 (C-4), 119.0 (C-3a), 117.8 (C-5), 34.6 (CH_2), and 25.1 (CH_3). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.4; N, 18.9. Found: C, 65.1; H, 5.7; N, 19.0. 1,3-Dihydro-2*H*-pyrrolo[3,2-*c*]pyridin-2-one (**15**): mp (hexane) 146-148.8 °C; ^{1}H nmr ($CDCl_3$) δ 8.48 (d, J = 5.2 Hz, 1 H, H-6), 8.36 (d, J = 0.9 Hz, 1 H, H-4); 6.81 (d, J = 5.2 Hz, 1 H, H-7), 3.57 (s, 2 H, CH_2), and 3.22 (s, 3 H, CH_3); ^{13}C nmr ($CDCl_3$) δ 174.6 (C=O), 152.4 and 120.2 (C), 149.8, 144.1, and 103.9 (CH), 33.4 (CH_2), and 26.2 (CH_3). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.4; N, 18.9. Found: C, 64.8; H, 5.5; N, 18.9.

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20. 1,2-Dithiolo-8-methyl[3,4-*b*]indole-3-thione (**17a**): mp (benzene) 234-236 °C (lit.,[21] 227-228 °C); ^{1}H nmr (DMSO-d^6) δ 7.64 (d, J = 7.6 Hz, 1H, H-4), 7.66 (d, J = 8.2 Hz, 1H, H-7), 7.47 (td, J = 7.8, 1.3 Hz, 1H, H-6), 7.38 (td, J = 7.6, 0.9 Hz, 1H, H-5); ^{13}C nmr (DMSO-d^6) 198.1 (C=S), 162.6, 143.8, 127.5, and 122.1 (C), 124.8, 122.7, 118.0, and 110.9 (CH), and 32.3 (CH_3); Hrms Calcd for $C_{10}H_7NS_3$: m/z 236.9741. Found: m/z 236.9743. Anal. Calcd for $C_{13}H_{14}N_2S_3$: C, 50.6; H, 3.0; N, 5.9; S, 40.5. Found: C, 50.7; H, 2.7; N, 6.1; S, 40.6.

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22. 8-(2-Dimethylaminoethyl)-1,2-dithiolo[3,4-*b*]indole-3-thione (**17b**): mp (benzene) 151.5 - 152.5 °C; ^{1}H nmr ($CDCl_3$) δ 8.64-8.58 (m, 1H, H-4), 7.33-7.19 (m, 3H, H-5,6,7); 4.14 (t, J = 5.7 Hz, 8-CH_2), 2.83 (t, J = 5.7 Hz, CH_2NMe_2), and 2.33 (s, 6H, CH_3); ^{13}C nmr ($CDCl_3$) δ 200.0 (C=S), 161.3, 143.8, and 123.0 (C), 124.8, 122.9, 119.2, and 109.2 (CH), 57.5 and 44.1 (CH_2), and 45.2 (CH_3); Hrms Calcd for $C_{13}H_{14}N_2S_3$: m/z 294.0319. Found: m/z 294.0345. Anal. Calcd for $C_{13}H_{14}N_2S_3$: C, 53.0; H, 4.8; N, 9.5; S, 32.7. Found: C, 53.3; H, 4.9; N, 9.6; S, 32.5.

23. Compound (**20**) was lithiated with 2 equivalents of n-BuLi at -78 °C and after being allowed to warm to -10 °C for 30 min, the solution was recooled to -78 °C and a slight excess of CS_2 was added. After being allowed to warm to room temperature the reaction mixture was treated with 5% HCl solution, and the solvent was removed. Aerobic oxidation, followed by chromatography on SiO_2 gave the disulfide (**22**) in 7% yield.

24. The 1-phenylsulfonylindole-3-carboxamides (**23**) were prepared by reaction of an excess of the appropriate amine with 3-chlorocarbonyl-1-phenylsulfonylindole[29] in CH_2Cl_2 at room temperature, and gave spectral and elemental analysis data in agreement with the assigned structures. Melting points (from MeOH): **23a**, (192.5-195 °C); **23b**, (188-189 °C); **23c**, (220-222.5 °C).

25. The 1-phenylsulfonylindoles (**23**) were treated with n-BuLi in THF at -78 °C, and after being allowed to warm to -20 °C for 15 min, the mixture was recooled to -78 °C and treated with dimethyl disulfide. The crude products were then reacted with K_2CO_3 in MeOH to hydrolyse the phenylsulfonyl group to give compound (**24a**) as a solid [mp (hexane-CH_2Cl_2) 138.5-139.5 °C] and compounds (**24b**) and (**24c**) as oils. These products gave spectral and elemental analysis (compound **24a**) or high resolution mass spectral data (compounds **24b** and **24c**) in accordance with the assigned structures.

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