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A new approach for the *ortho*-substitution of anilines and for the synthesis of indolines

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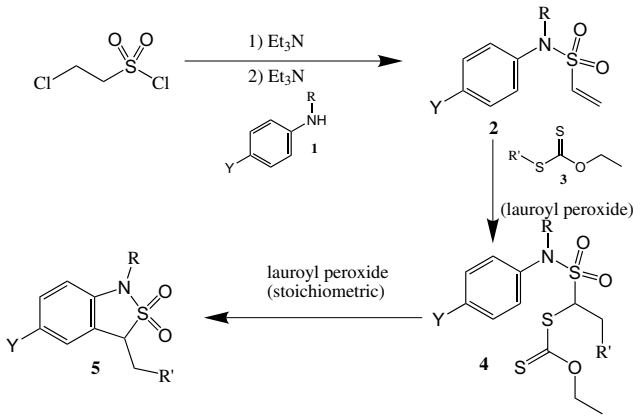
Abstract—Intermolecular radical addition of a xanthate to a vinyl sulfanilide is followed by ring closure to the aromatic ring to give a dihydrobenzoisothiazole dioxide structure, which upon heating loses sulfur dioxide to give a 2-substituted aniline; in some examples, the presence of DBU during heating induces the formation of an indoline.

The functionalisation of anilines in the *ortho* position is often a key transformation in the synthesis of medicinally important compounds. For this task, the powerful *ortho*-directed metallation is complemented by a number of less general but nevertheless quite useful reactions. Some indirect methods have also been occasionally applied to this problem. These include the addition of organometallic reagents to nitroarenes or the vicarious substitution reactions explored extensively by Makosza et al.[1] and his collaborators, both followed by reduction of the nitro group. Radical based approaches have received in contrast scant attention. One reason is the relative sluggishness of the radical addition to the aromatic ring, in comparison with other reaction pathways open to the radical. Furthermore, the intermolecular variant suffers from generally low yields and an essentially complete lack of regioselectivity.[2] We have attempted to remedy this situation by combining an intermolecular radical addition with the use of a temporary sulfonyl tether to force a second, intermolecular addition to occur at the *ortho* position on the aromatic ring.

Our conception is outlined in Scheme 1. A peroxide initiated xanthate transfer radical addition[3] to vinylsulfanilide **2** would lead to adduct **4**, which could then be subjected to a stoichiometric amount of peroxide causing the formation of **5** by ring-closure onto the aromatic ring. The required starting sulfanilides **2** are easily obtained by reaction of the commercially available 2-chloroethylsulfonyl chloride with a base to induce β-elimination of the chloride anion followed by reaction with an aniline.[4]



Scheme 1.

In the event, we found that the radical addition to the vinyl sulfanilide **2a** derived from *N*-methylaniline could indeed be accomplished using a number of different xanthates. The reaction is carried out by simply refluxing a solution of the xanthate and **2a** in 1,2-dichloromethane in the presence of lauroyl peroxide as initiator.[5] Although it was possible to isolate the expected adduct **4**

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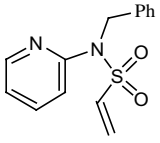
Table 1

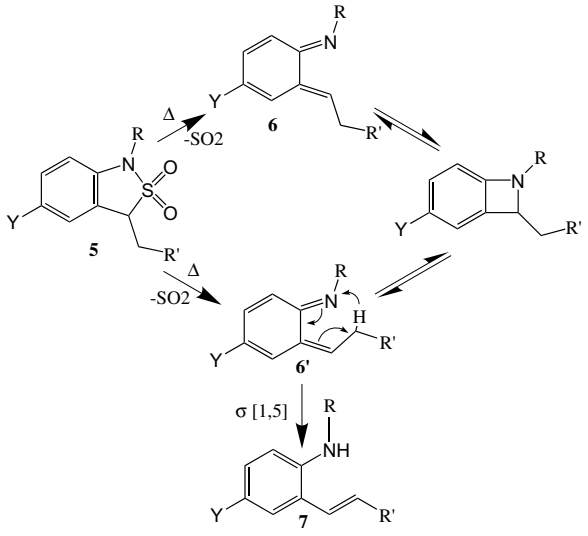
	2		3	4	5 (%)
	R	Y	R′		
a	CH_3	H	CH_2CN		70
b	CH_3	H	$CH_2COCH_2CO_2Et$		40
c	CH_3	H	$(CH_3)_2CH_2COCH_3$		34
d	CH_3	H	$CH_2(3,4,5\text{-}OCH_3)C_6H_2$	48%	63
e	CH_3	H	CH_2CO*t*-Bu		45
f	CH_3	H	CH_2COPh		45
g	H	H	CH_2CN	50 (66)%	44
h	$COCH_3$	H	CH_2CN	52 (62)%	24
i	CH_3	F	CH_2CN	38 (69)%	44
j	CH_2–Ph	H	CH_2CN		50
k			$CH_2CO(4\text{-}OCH_3)C_6H_4$		20

in some cases, it was better to add directly a stoichiometric amount of the peroxide to induce cyclisation to the aromatic ring. This gave the corresponding dihydrobenzoisothiazole dioxide **5** in moderate to good, but still unoptimised, yields. The results are compiled in Table 1 (the yields in parentheses are based on recovered starting material).

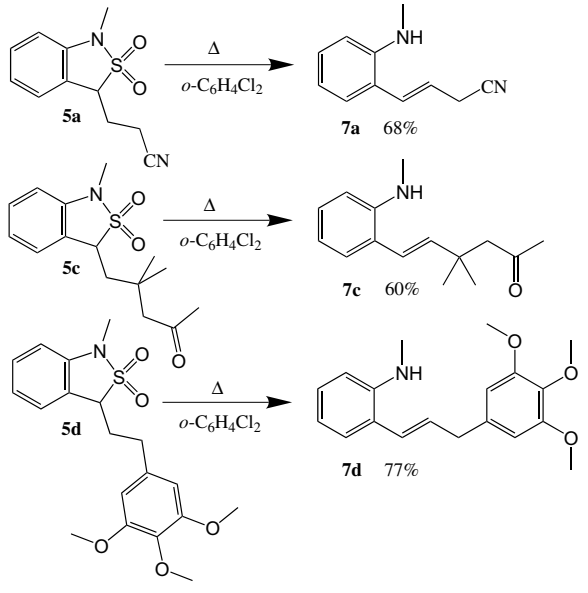
Various types of radicals could be added: benzylic (entry d), tertiary (entry c), or radicals substituted with an electrophilic group such as a nitrile (entry a), a ketone (entries e and f) or ketoester (entry b). In the case of the addition of a tertiary radical, a quaternary centre is generated and this is worth underlining. Replacing the methyl group on the nitrogen with hydrogen or with an acetyl group caused a lowering in the yield (entries g and h). In one example, a 2-aminopyridine derivative could be used instead of an aniline (entry k).

Heating the cyclised derivatives in refluxing *o*-dichlorobenzene caused a retro-cheletropic loss of sulfur dioxide to give a highly reactive intermediate diene **6** followed by a 1,5-sigmatropic shift of a hydrogen to give the 2-substituted aniline **7**,[6] as outlined in Scheme 2. This transformation is illustrated by the conversion of **5a**, **5c** and **5d** into anilines **7a**, **7c** and **7d** in 68%, 60% and 77% yields, respectively[7] (Scheme 3). Although such extrusions of sulfur dioxide have been previously described,[6] they have seldom found use in synthesis because of a lack of convenient routes to the cyclic precursors **5**.

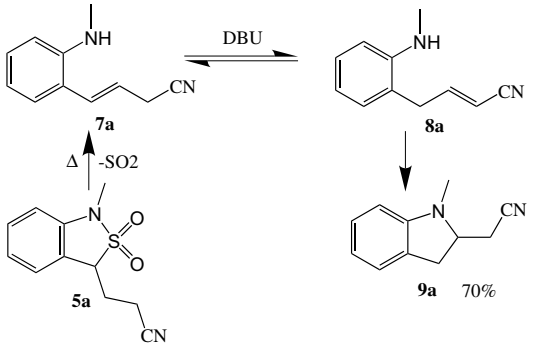
In the case of **5a**, heating in the presence of DBU caused a further transformation of the initial product **7a** into indoline **9a** through base induced migration of the olefinic bond followed by intramolecular Michael addition (Scheme 4). The yield of this sequence was 70%, a quite good yield given the nature of the intermediates.[8] This modification could be applied to the adducts possessing an electron withdrawing group, which facilitates the migration of the olefin and subsequent conjugate addition of the aniline nitrogen. In this way, indolines **9e**,**f** and **9i**–**k** were prepared from compounds **5e**,**f** and **5i**–**k** in 65%, 66%, 59%, 50% and 45% yields, respectively



Scheme 2.



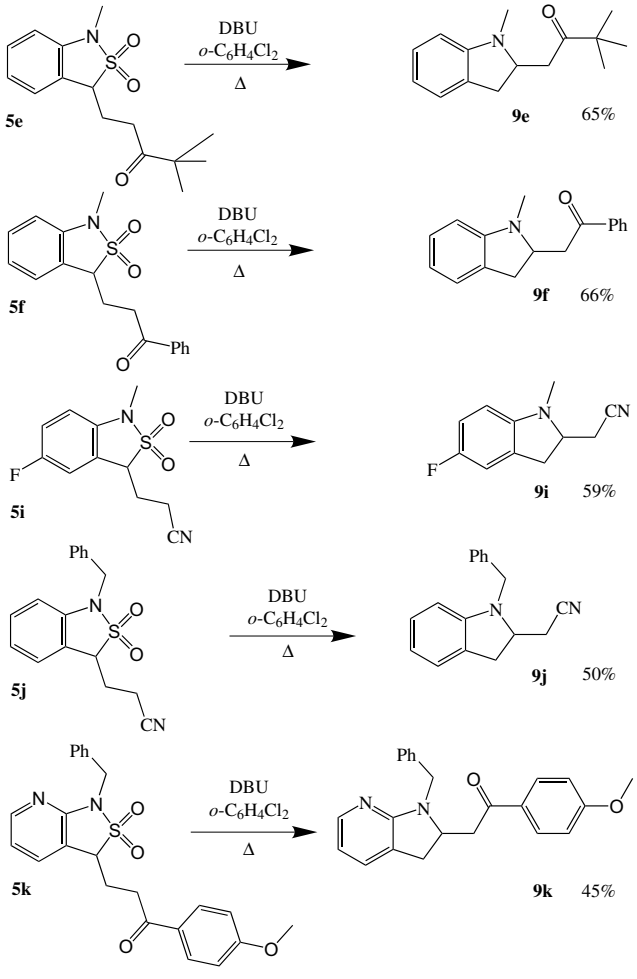
Scheme 3.



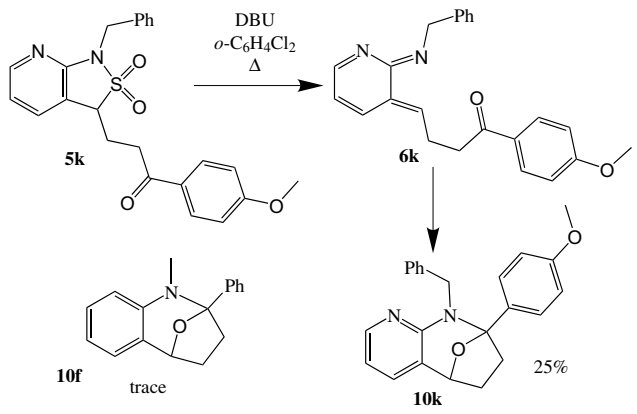
Scheme 4.

(Scheme 5). Under the same conditions, for compounds **5g** and **5h**, with no substituent on the nitrogen or with an *N*-acetyl group, only a complex mixture was obtained. The reason for this behaviour is still not clear.

One final twist observed with compound **5k** is the concomitant formation of tricyclic derivative **10k** in 25% yield, in addition to the 'normal' product **9k** (45%). This substance arises by capture of the especially reactive intermediate diene **6k** by the carbonyl group through an intramolecular Diels–Alder reaction (Scheme 6). With this knowledge in hand, a more careful re-examination of the crude reaction mixture in the case of the aniline analogue **5f** indicated the presence of trace amounts of the corresponding tricyclic derivative **10f**.



Scheme 5.



Scheme 6.

In summary, we have established a flexible, versatile route to anilines functionalised in the *ortho* position. The starting materials and reagents are cheap and readily available. The approach can further be modified to access indolines and in principle the corresponding indoles through dehydrogenation. These compounds are of special interest in medicinal chemistry and many of those described in the present study would be difficult to obtain by more classical approaches. Further studies aimed at exploring the scope and improving the yield of the addition–cyclisation sequence are under way.

Acknowledgements

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5. Typical procedure is as follows: to a boiling solution of **2a** (200 mg, 1.0 mmol) and **3a** (330 mg, 2.0 mmol) in 1,2-dichloroethane (2 mL), 10% of lauroyl peroxide was added every hour until disappearance of starting materials (usually 120% was necessary). The reaction mixture was purified by flash chromatography on silica gel to give an orange oil (165 mg, 0.7 mmol, 70% yield). δ_H ($CDCl_3$, 400 MHz): 2.33–2.48 (m, 2H, CH_2–CH_2–CN), 2.62 (ddd, 1H, $J = 5.9$, 8.2, 17.3 Hz, CH_2–CH_2–CN), 2.75 (ddd, 1H, $J = 7.9$, 7.9, 17.3 Hz, CH_2–CH_2–CN), 3.13 (s, 3H, N–CH_3), 4.34 (dd, 1H, $J = 5.3$, 8.2 Hz, CH–SO_2), 6.76 (d, 1H, $J = 8.2$ Hz, CH_{Ar}), 7.07 (dt, 1H, $J = 0.9$, 7.6 Hz, CH_{Ar}), 7.25 (d, 1H, $J = 7.6$ Hz, CH_{Ar}), 7.38 (t, 1H, $J = 7.9$ Hz, CH_{Ar}); δ_C ($CDCl_3$, 100 MHz): 14.3 (N–CH_3), 26.2 (CH_2), 26.5 (CH_2), 58.6 (CH–SO_2), 109.5 (CH_{Ar}), 118.2 (C_q), 120.9 (C_q), 122.4 (CH_{Ar}), 124.9 (CH_{Ar}), 130.2 (CH_{Ar}), 140.9 (C_{qAr}). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12. Found: C, 55.71; H, 5.18.
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7. Typical procedure is as follows: a solution of **5a** was heated to reflux in *o*-dichlorobenzene for 30 min. The reaction mixture was purified by flash chromatography on silica gel to give an orange oil. δ_H ($CDCl_3$, 400 MHz): 2.89 (s, 3H, CH_3–N), 3.32 (dd, 2H, $J = 1.8$, 5.3 Hz, CH_2–CN), 4.05 (br s, 1H, NH), 5.93 (dt, 1H, $J = 5.3$, 15.6 Hz, CH=CH–CH_2–CN), 6.69 (d, 1H, $J = 8.2$ Hz, CH_{Ar}), 6.73–6.77 (m, 1H, CH_{Ar}), 6.80 (dt, 1H, $J = 1.8$, 15.6 Hz, CH=CH–CH_2–CN), 7.20–7.28 (m, 2H, CH_{Ar}); δ_C ($CDCl_3$, 100 MHz): 21.1 (CH_2), 30.9 (CH_3), 110.5 (CH), 111.5 (C_q), 117.5 (CH), 118.9 (CH), 122.3 (C_q), 127.5 (CH), 129.6 (CH), 130.4 (CH), 146.1 (C_q). ν (cm^{-1}) 3449, 3046, 2985, 2918, 2873, 2816, 2253 (w), 1604 (s), 1579, 1511 (s), 1463, 1418, 1340, 1310, 1266, 1166, 1067, 970. Mass (ICP NH_3) m/z 173 = MH^+.
8. Typical procedure is as follows: a solution of **5a** and DBU was heated to reflux in *o*-dichlorobenzene for 30 min. The reaction mixture was purified by flash chromatography on silica gel to give an orange oil. δ_H ($CDCl_3$, 400 MHz): 2.67 (dd, 1H, $J = 6.8$, 16.7 Hz, Ph–CH_2–CH), 2.76 (dd, 1H, $J = 4.4$, 16.7 Hz, Ph–CH_2–CH), 2.81 (s, 3H, CH_3–N), 2.92 (dd, 1H, $J = 9.1$, 15.6 Hz, CN–CH_2–CH), 3.30 (dd, 1H, $J = 8.8$, 15.6 Hz, CN–CH_2–CH), 3.69 (m, 1H, CH_2–CH–CH_2), 6.52 (d, 1H, $J = 7.9$ Hz, CH_{Ar}), 6.76 (dt, 1H, $J = 0.9$, 7.6 Hz, CH_{Ar}), 7.11–7.17 (m, 2H, CH_{Ar}); δ_C ($CDCl_3$, 100 MHz): 21.9 (CH_2), 34.4 (CH_3), 35.1 (CH_2), 62.9 (CH), 107.7 (CH), 117.5 (C_q), 118.8 (CH), 124.3 (CH), 127.3 (C_q), 127.9 (CH), 152.3 (C_q). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 76.53; H, 7.03.