Tetrahedron Letters,Vol.23,No.8,pp 821-824,1982 0040-4039/82/080824-04$03.00/0
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ARYLSULFENYLATION OF 2,3-DIALKYLINDOLES; PREPARATION OF 3-ARYLTHIOINDOLENINES AND THERMAL CONVERSION TO AN N-SULFENYLINDOLE

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Reaction of 2,3-dialkylindoles with o-nitrophenylsulfenyl chloride in the presence of triethylamine gives good yields of previously unknown 3-o-nitrophenylsulfenyl-2,3-dialkylindolenines which decompose thermally to give the corresponding 2,3-dialkylindole and N_1-o-nitrophenylsulfenyl indoles.

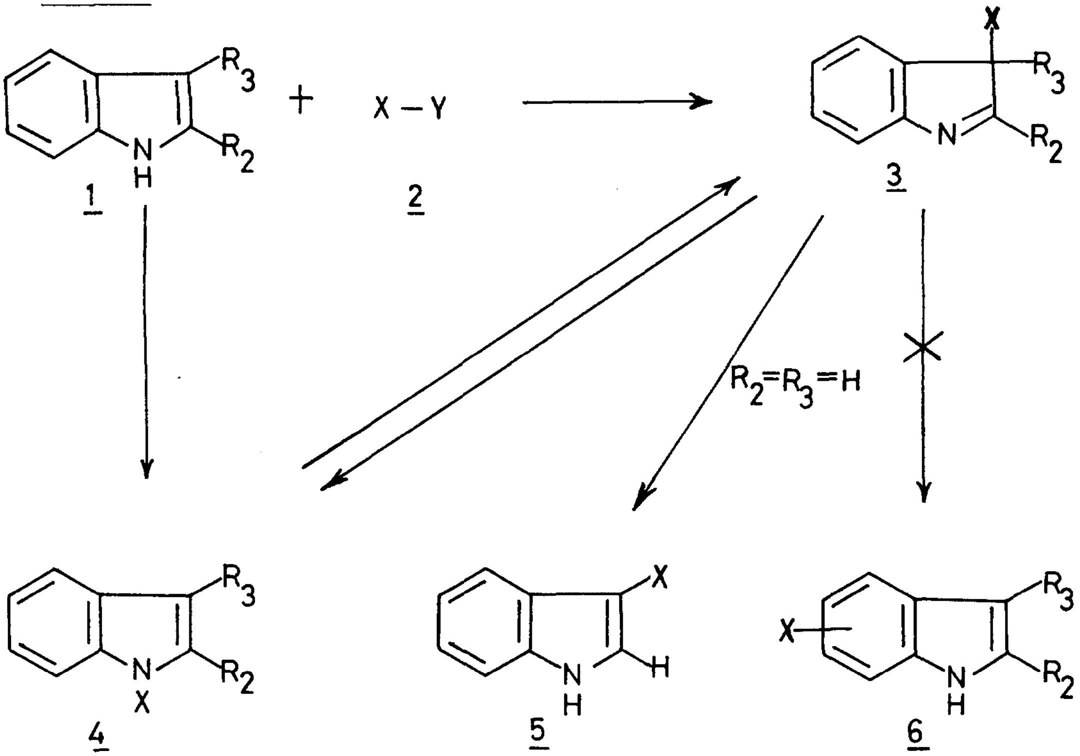
The fact that indoles are ambident nucleophiles has been well established through numerous reactions with carbon electrophiles.[1] Reaction conditions have been developed which favour electrophilic attack at N_1 or C_3. Studies of the mechanism of reaction of indoles with heteroatom electrophiles are complicated by the possibility, first suggested by Gassman and co-workers[2], of facile $N_1 \rightarrow C_3$ heteroatom rearrangements.

Thus although chlorination of 2,3-dimethylindole 1b yields the corresponding indolenine 3bh, arising by apparent electrophilic attack at C_3, the possibility exists that the N-chloroindole 4bh is formed initially but undergoes a sufficiently facile rearrangement to 3bh that it escapes detection. In the case of chlorination of indole, 1a, N-chloroindole 4ah, is a spectroscopically detectable intermediate which upon heating gives 3-chloroindole, 5h, presumably via the indolenine 3ah.[3] The failure to detect 3bh suggested that the N-chloroindole → 3-chloroindolenine rearrangement was facilitated by the presence of alkyl substituents at C_2 and C_3.

More recently Raban and Chern[4] have reported that reaction of indole, 1a, with arylsulfenyl chlorides (eg. 2ik) yields the corresponding 3-arylthioindoles, 5i, correcting earlier reports[5] claiming the formation of sulfenamides such as 4ai in these reactions. Although it was clear that 3-arylthioindoles and not sulfenamides were the isolated products in these reactions, it was pointed out that the sulfenamide 4ai might be formed as a kinetic product but might be converted very rapidly to the indole 5i via the indolenine 3ai.

In connection with our continuing interest in the preparation of 3-heteroatom substituted indolenines and their use in the synthetic elaboration of 2,3-dialkylindoles[6], we have now examined the reaction of 2,3-dialkylindoles with o-nitrophenylsulfenyl chloride, 2ik. In

Scheme 1:



	R_2	R_3		X		Y
(a)	H	H	(h)	Cl	(j)	ONa
(b)	CH_3	CH_3	(i)	-S (o-NO$_2$Ph)	(k)	Cl
(c)	CH_2CH_3	CH_3				
(d)	CH_3	CH_2CH_3				
(e)	- $(CH_2)_3$-					
(f)	- $(CH_2)_5$-					
(g)	- $(CH_2)_6$-					

light of the conclusions of the previous studies outlined above, it was not surprising that treatment of several 2,3-dialkylindoles 1b-1g with o-nitrophenylsulfenyl chloride in the presence of triethylamine yielded the corresponding 3-arylthioindolenines 3i and not the isomeric sulfenamides 4i. In each case the indolenines were obtained in good yield as crystalline yellow products (see Table 1 below). Although 3-methylthioindolenines are known[7], to our knowledge these compounds represent the first reported 3-arylthioindolenines. The presence of an indolenine C=N bond in each of these compounds was revealed by a band of medium intensity at ∿1570 cm^{-1} in their infra red spectra. An intense base peak at (M-154)$^+$ corresponding to loss of (o-NO$_2$-ArS•) was observed in the mass spectrum of each of the indolenines **3i**. The nmr spectra are compatible with the assigned structures and are in good agreement with those reported earlier for the corresponding 3-methoxy and 3-bromoindolenines[6].

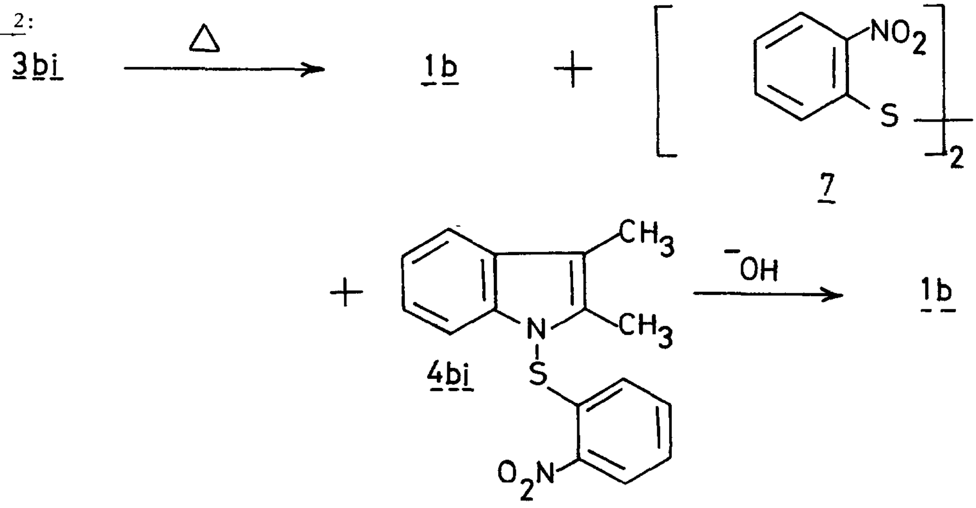
TABLE: Reactions of Indoles with o-nitrophenylsulfenylchloride

Indole	Product	Yield† (%)
1b	**3bi**	90
1c	**3ci**	85
1d	**3di**	75
1e	**3ei**	92
1f	**3fi**	92
1g	**3gi**	98

† Yields of homogeneous crystalline products after chromatography on silica gel.

It was soon discovered that these materials were relatively unstable undergoing decomposition upon heating or simply upon standing at room temperature. Closer inspection of this thermal behaviour in the case of **3bi** has revealed that heating the indolenine at 95° for 15 minutes leads to complete decomposition and yields a complex mixture of products. Careful chromatography of this material on silica gel has given a 23% isolated yield of 2,3-dimethylindole and traces of the known disulfide **7**. More interesting, however, was the isolation in 14% yield of a new orange crystalline compound isomeric with the indolenine **3bi**. The infra red spectrum of this material clearly demonstrated the absence of an indole N-H bond thus eliminating the possibility of $C_{4,5,6}$ or 7- arylthioindole structures **6bi**. In addition, the presence of eight tertiary aromatic carbon atoms was clearly indicated by the ^{13}C nmr spectrum. The presence of eight aromatic protons was confirmed by the proton nmr spectrum. At 80 MHz the only other signal in the proton nmr spectrum was a six proton singlet at $\delta = 2.32$ ppm. At 400 MHz two 3 proton singlets are observed; one at $\delta = 2.31$ and the other at 2.33 ppm. The only reasonable structure compatible with all of the spectroscopic data was clearly the sulfenamide **4bi**.

Scheme 2:



In agreement with the presence of a weak N-S bond in **4ai** is the observation of a facile loss of (o-NO_2-Ph-S·) from the parent ion in the mass spectrum. In addition the sulfenamide **4bi** was smoothly hydrolyzed 2,3-dimethylindole in refluxing aqueous-methanolic sodium hydroxide. Although examples of analagous hydrolysis of simple aryl sulfenamide are rare they are not unknown[8].

To our knowledge, this is the first report of the preparation of an N-sulfenylindole. In addition, it is the first observation of what is, formally at least, a $C_3 \rightarrow N_1$ heteroatom migration in a C_3-heteroatom substituted indolenine. It is clear now that the indolenine **3bi** and not the sulfenamide **4bi** is the kinetic product of sulfenylation of **1b** and that the sulfenamide is thermodynamically more stable than the indolenine. It is tempting to extrapolate these mechanistic conclusions to the sulfenylation of the unsubstituted indole system and to suggest that **4ai** is not an intermediate in the formation of **5i**. However, although it is not clear why N_1 reactivity should be more favourable for **1a** than for **1b** or why $N_1 \rightarrow C_3$ migration should be so facile for **4ai** as to preclude detection of **4ai** if formed, the available evidence does not eliminate the possibility of such mechanistic differences in the reactions of **1a** and **1b**.

Further experiments aimed at exploring the synthetic utility of 3-arylthioindolenines and at elucidating the mechanism of the 3-arylthioindolenine → N-arylsulfenyl indole conversion are in progress.

ACKNOWLEDGEMENTS:

Operating grants from the Natural Sciences and Engineering Research Council Canada and the University of Waterloo and a NSERC scholarship to one of us (S.F.V.) are gratefully acknowledged. 400 MHz nmr spectra were recorded at the South Western Ontario NMR Centre.

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(Received in USA 4 September 1981)