Unexpected Acid-catalysed Rearrangement of Certain 3-(Arylthio)indoles to 2-(2-Aminophenyl)benzothiophenes

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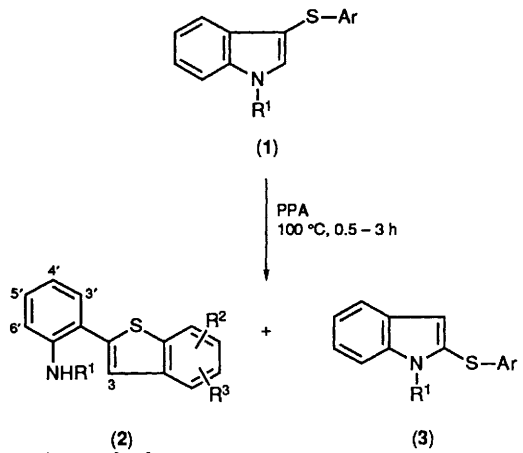
3-(Arylthio)indoles (**1**), in which the aryl group is an electron-rich ring system, undergo a novel structural rearrangement to 2-(2-aminophenyl)benzothiophenes (**2**) upon heating in polyphosphoric acid.

We have previously reported the unusual two-step intermolecular mechanism of the acid-catalysed isomerization of indol-3-yl sulphides to the corresponding indol-2-yl sulphides.[1] We report herein on an unexpected and completely different type of structural rearrangement of a series of 3-(arylthio)indoles (**1**). They have been found to undergo indole ring cleavage and benzothiophene formation, upon heating in polyphosphoric acid (PPA). The resulting isomeric compounds have been identified as 2-(2-aminophenyl)benzothiophenes (**2**) (Scheme 1).

Variable amounts of the corresponding 2-(arylthio)indoles (**3**) are also obtained under these conditions (Table 1). In contrast, compounds (**3**) are the sole products of the trifluoroacetic acid (TFA)-promoted rearrangement[1,2] of these substrates (see footnote b to Table 1). The formation of the benzothiophenes (**2**) is a function of the capability of the aryl group to stabilize a positively charged intermediate [*e.g.*, (**4d**$_2$)], as only activated, electron-rich aryls suffer this type of rearrangement. Thus, not even the relatively neutral 3-(phenylthio)indole (**1f**) gives any detectable amount of the corresponding benzothiophene (**2f**), but yields only 2-(phenylthio)indole (**3f**).

As a general procedure, the substrate (**1**)[3] is heated in 50—60 parts of commercial PPA, at 100—120 °C for 0.5—2 h. The cooled mixture is diluted and triturated with water, then extracted with ether or ethyl acetate, affording a mixture of (**2**) and (**3**) from which the components are separated by chromatography.



a; R^1 = H, R^2, R^3 = 4, 5-CH=CH–CH=CH–
d$_1$; R^1 = R^2 = H, R^3 = 4-OMe
d$_2$; R^1 = R^2 = H, R^3 = 6-OMe

Scheme 1. Rearrangement of 3-(arylthio)indoles in hot PPA.

Table 1.[a] Isomerization of 3-(arylthio)indoles to 2-(2-aminophenyl)benzothiophenes and 2-(arylthio)indoles in PPA at 100 °C: (**1**) → (**2**) + (**3**).

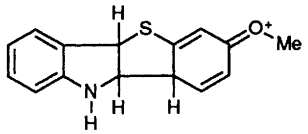
Cpd.	R^1	Ar	R^2, R^3 in (**2**)	% yield (**2**) (m.p./°C)	% yield (**3**)[b] (m.p./°C)
a	H	2-Naphthyl	4,5-CH=CH–CH=CH–	64 (144—146)	0 (117—119)
b	Me	2-Naphthyl	4,5-CH=CH–CH=CH–	10 (92—94)	44 (85—87)
c	H	1-Naphthyl	6,7-CH=CH–CH=CH–	36 (86—88)	17 (96—98)
d	H	3-$MeOC_6H_4$	4-MeO (**d_1**)	9 (111—113)	8 (71—73)
			6-MeO (**d_2**)	22 (123—125)	
e	H	2,5-$Me_2C_6H_3$	4,7-Me_2	14 (oil)	31 (126—128)
f	H	Ph	H	0	35 (72—74)

[a] All new compounds have been fully characterized by IR, ^{1}H NMR, and mass spectra and elemental analysis, and the data were in accord with the proposed structures. [b] % yields of (**3**) in TFA, room temp., 1—3 h: **a**, 67; **b**, 87.5; **c**, 60; **d**, 53; **e**, 64; **f**, 56.

Table 2. ^{1}H NMR spectral parameters for (**2a**) ($CDCl_3$ solution), (**2d$_1$**) ($CDCl_3$ solution), and (**2d$_2$**) ([$^2H_6$]acetone solution). 300 MHz spectra were recorded at 300 K and referenced to internal Me_4Si.

	Ring position												
Compound	3	4	5	6	7	8	9	3′	4′	5′	6′	NH_2	OMe
(**2a**)	8.08 ^5J 0.7[c]	8.31 ^3J 8.3 ^4J 1.4	7.60 ^3J 7.0 ^4J 1.5	7.52 ^3J 8.1	7.94 ^4J 1.4	7.73 ^3J 8.8	7.86	6.82 ^3J 7.4 ^4J 1.2	7.21 ^3J 7.4 ^4J 1.6	6.87 ^3J 7.4	7.41	—[b]	—
(**2d$_1$**)	7.58 ^5J 0.7[d]	—	6.75 ^3J 8.0 ^4J 0.7	7.27 ^3J 8.0	7.43	—	—	6.8[a]	7.16 ^4J 1.6	6.8[a] ^3J 6.9	7.34	4.13	3.96
(**2d$_2$**)	7.40 ^5J 0.5[d]	7.70 ^3J 8.7	7.00 ^4J 2.4	—	7.47	—	—	6.86 ^3J 8.1 ^4J 1.0	7.10 ^3J 7.6 ^4J 1.5	6.70 ^3J 7.7	7.27	4.88	3.90

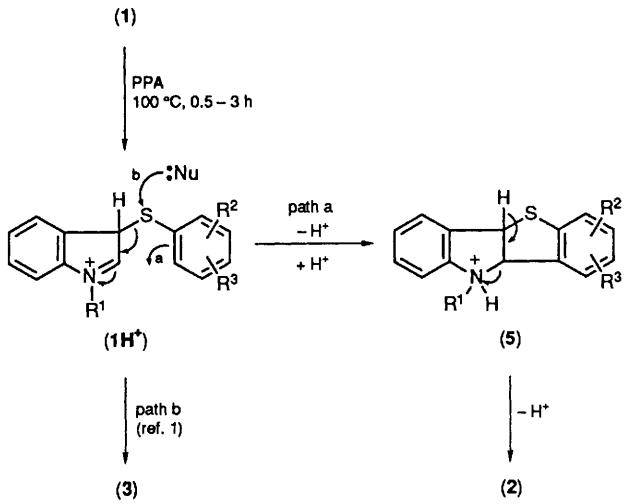
[a] Spectra complicated by second order effects. [b] Not observed because of D_2O wash. [c] J (3,9). [d] J (3,7).



(**4d$_2$**)

Thus, 3-(2-naphthylthio)indole (**1a**) afforded, as the sole rearrangement product, isolated in 64% yield, 2-(2-aminophenyl)naphtho[2,1-*b*]thiophene (**2a**). Its structure was proven by detailed high field ^{1}H NMR analysis as described below. In this experiment, no trace (<1% by TLC) of 2-(2-naphthylthio)indole (**3a**) was observed, whereas this compound was obtained in 67% yield on stirring (**1a**) in twelve parts of TFA at room temperature for 1.5 h, with no detectable amount of (**2a**) being formed. In the case of 3-(3-methoxyphenylthio)indole (**1d**), a 1 : 2.5 mixture of the isomeric 4- and 6-methoxy-2-(2-aminophenyl) benzothiophenes, (**2d$_1$**) and (**2d$_2$**), is obtained in 31% yield by ring closure *ortho* and *para* to the methoxy group.

A full structural proof by ^{1}H NMR analysis was conducted on (**2a**) and the regioisomeric (**2d$_1$**) and (**2d$_2$**), and the data are compiled in Table 2. In the case of the benzothiophenes, the position of the OMe was established by NOE experiments.[4] Homonuclear decoupling and 2D-COSY experiments were performed where appropriate. The key NOE observations affording structural information were as follows. For (**2d$_1$**), irradiation of the OMe signal resulted in a 9.8% enhancement in the signal of a proton having the expected coupling pattern for H-5, and a 1.0% enhancement in a signal attributable to H-3. Thus, the OMe was concluded to be on C-4. For (**2d$_2$**), irradiation of the OMe signal resulted in a 12.2% enhancement in a resonance attributable to H-7, and a 3.0% NOE to H-5; thus the OMe substituent was deduced to occupy the C-6 position. With (**2a**), the question of whether the tricyclic portion is linear or angular was at issue. The angular product was proven correct on the basis of the deshielded bay-region protons, and close proximity between H-3 and H-4 was indicated by a 2D-NOESY experiment. Finally, the linear structure would be expected to display three aromatic singlet proton resonances, while only one such resonance was observed. This is consistent with the angular product, (**2a**).



Scheme 2. Mechanism of formation of 2-(2-aminophenyl)benzothiophene, (**2**), from 3-(arylthio)indoles, (**1**).

Scheme 2 presents a rationale for the formation of the benzothiophenes (**2**). When the aryl ring of the sulphide is sufficiently electron-rich, intramolecular nucleophilic attack can occur on the 2-position (path a) of the protonated indole moiety (**1H**$^+$) giving rise to transient species such as (**4**) and (**5**); the latter then aromatizes through loss of a proton and rupture of the C–N bond, leading to benzothiophene (**2**). Competitive initial desulphenylation of (**1H**$^+$) leads, through a complex series of steps (path b), to 2-(arylthio)indoles (**3**), as we have described previously.[1] The contrast in the results between PPA and TFA may be attributable to several factors. The more viscous PPA may permit the intramolecular rearrangement leading to the benzothiophenes (**2**), and the greater nucleophilicity of the trifluoroacetate anion would favour the process leading to formation of 2-(arylthio)indoles (**3**) by path b.

The work described herein represents a novel molecular rearrangement in which an indole ring is cleaved, concomitant with the formation of a benzothiophene nucleus. It also provides a synthesis of 2-(2-aminophenyl)benzothiophenes which is fundamentally different from those previously described,[5] and thus broadens the availability of this class of compounds.

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