Preparation of Polycyclic Azaarenes by an Extended Pomeranz–Fritsch Procedure

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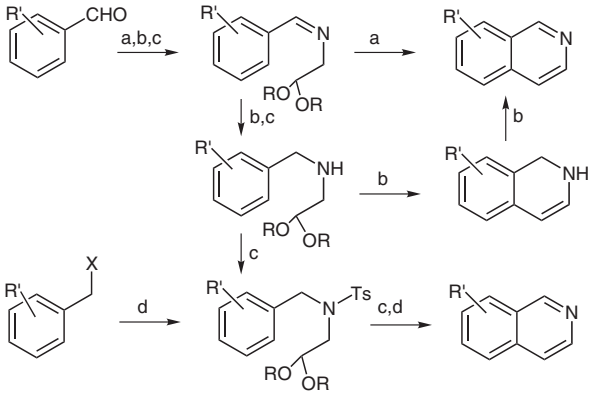
Received 12 April 2007

Abstract: An extension of the Pomeranz–Fritsch procedure has been evaluated as a route to some polycyclic azaarenes. Aromatic aldehydes were treated with the dimethyl and diethyl acetals of 2-aminoethanal, the resulting imines reduced to amines which were tosylated and the resulting sulfonamides treated under a range of acidic conditions. The two naphthaldehydes led to benzo[*f*]isoquinoline and benzo[*h*]isoquinoline in overall yields of 13% and 36%. Phenanthrene-9-carbaldehyde and phenanthrene-3-carbaldehyde gave dibenzo[*f,h*]isoquinoline and naphtho[2,1-*g*]isoquinoline, respectively, as the major tetracyclic products. No pentacyclic product was obtained from a similar sequence starting from pyrene-1-carbaldehyde.

Key words: heterocycles, polycycles, cyclizations, benzisoquinolines, naphthoisoquinolines

Studies over several decades have shown that azaarenes occur widely in environmental materials, usually in complex mixtures with other polycyclic aromatic compounds. There is continued interest in analytical methods for identification,[1] in studies of bio-availability[2] and biotransformations,[3] and in biological properties of metabolites.[4] Despite this importance, there remain gaps in information on preparations for some of the numerous possible polycyclic azaarenes. This paper describes our investigation of the preparation of some fused isoquinolines by a thermal cyclization, and the following paper describes a series of photochemical studies aimed at a further range of related azaarenes.

The most frequently used routes to isoquinolines have been based on the Pictet–Spengler reaction (which gives tetrahydroisoquinolines),[5] the Bischler–Napieralski reaction (which gives 3,4-dihydroisoquinolines) and its Pictet–Gams variation (which gives aromatic products directly),[6] and the Pomeranz–Fritsch reaction with several extensions.[7] The original Pomeranz–Fritsch reaction used strongly acidic conditions to cyclize a benzaliminoacetal (Scheme 1, path a) though usually with poor yield. Bobbit et al. showed that hydrogenation of the imine facilitated the cyclization step (Scheme 1, path b), but this required subsequent dehydrogenation to produce the aromatic product.[8] Later work by Birch et al. showed that N-tosylation of the benzylaminoacetals allows acid-catalyzed cyclization to aromatic products directly with elimination of *p*-toluenesulfinic acid (Scheme 1, path c).[9] Despite the additional steps in this approach, good yields are generally obtained provided that a strongly electron-donating group lies *ortho* or *para* to the cyclization site.[9,10] In a further modification, Boger et al. formed the *N*-tosylbenzylaminoacetal from a halo- or mesylmethylbenzene derivative (Scheme 1, path d).[11] Pomeranz–Fritsch procedures have been used for synthesis of a number of important isoquinolines, invariably with activating substituents in the original aromatic ring,[12] but rarely to polycyclic compounds.

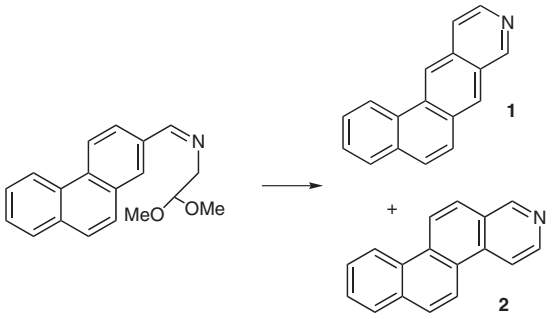


Scheme 1 Routes related to the Pomeranz–Fritsch reaction. Path a: original Pomeranz–Fritsch reaction; path b: Bobbit et al.;[8] path c: Birch et al.;[9] path d: Boger et al.[11]

A number of reduced polycycles have been produced by Pictet–Spengler[13] and Bischler–Napieralski[14] approaches, but these methods require dehydrogenation to obtain aromatic products. Direct formation of the aromatic polycyclic azaarenes has been rarely achieved. Tanga et al. converted the appropriate imine from phenanthrene-2-carbaldehyde into the naphthoisoquinoline isomers **1** and **2** in yields of 10% and 4% by the use of hot polyphosphoric acid (Scheme 2).[15]

Tanga et al. also reported the formation of phenanthro[9,10-*g*]isoquinoline from the appropriate imine after reduction, the cyclization apparently accompanied by dehydrogenation.[16] More recently, Caronna et al. used phosphorus pentoxide in sulfuric acid in cyclization of a bisimine from phenanthrene to obtain a diaza[5]helicene.[17] In 1960 Coppens reported failure of the Pomeranz–Fritsch method to yield benzisoquinolines from imines derived from naphthaldehyde, analogous to Scheme 1, path a.[18] We have now carried out a systematic study of the Birch–Jackson–Shannon variation[9] of the Pomeranz–Fritsch

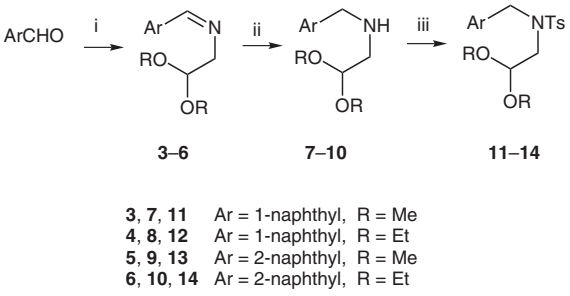
SYNTHESIS 2007, No. 14, pp 2157–2163
Advanced online publication: 10.07.2007
DOI: 10.1055/s-2007-983744; Art ID: P04407SS



Scheme 2 Work reported by Tanga et al.[15]

procedure to determine its suitability for preparation of polycyclic azaarenes.

Initial work was directed towards the tricyclic benzisoquinolines. The two isomeric naphthaldehydes were each condensed with the dimethyl acetal and the diethyl acetal of 2-aminoethanal (Dean–Stark procedure using refluxing toluene), in each case followed by hydrogenation of the imines **3**–**6** over PtO_2, to give amines **7**–**10** in essentially quantitative yield, followed by tosylation to give the four sulfonamides **11**–**14** (Scheme 3). Cyclization was studied for each of these four sulfonamides.

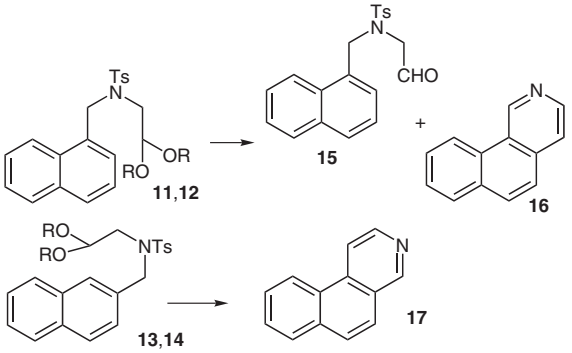


3, **7**, **11** Ar = 1-naphthyl, R = Me
4, **8**, **12** Ar = 1-naphthyl, R = Et
5, **9**, **13** Ar = 2-naphthyl, R = Me
6, **10**, **14** Ar = 2-naphthyl, R = Et

Scheme 3 Preparations of sulfonamides **11**–**14**. *Reagents*: i. $(RO)_2CHCH_2NH_2$; ii. H_2/PtO_2; iii. TsCl, Py.

The sulfonamide **12** was heated under reflux in dioxan (1,4-dioxane) with aqueous hydrochloric acid (6 M), affording only the aldehyde **15**. Under identical conditions the sulfonamide **11** gave predominantly the aldehyde **15**, but a small amount (1% yield) of the required benzo[*h*]isoquinoline **16** was also obtained. Consequently, non-aqueous conditions were selected, to remove the possibility of acetal hydrolysis. The sulfonamide **12** gave a 19% yield of benzo[*h*]isoquinoline on heating with boron trifluoride etherate in dioxan under reflux, and the sulfonamide **11** gave a 24% yield under these conditions (Scheme 4).

Similar results were obtained from the analogous sulfonamides **13** and **14** derived from 2-naphthaldehyde but with generally better yields of the required product, benzo[*f*]isoquinoline **17**. Even under the aqueous conditions, a yield of 18% was obtained, and significantly higher yields were obtained with boron trifluoride diethyl etherate in dioxan.



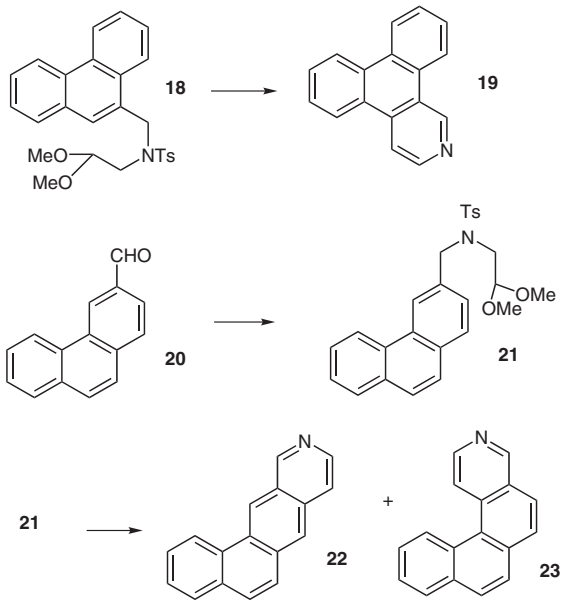
Scheme 4 Cyclizations of sulfonamides **11**–**14**. For conditions, see Table 1.

Table 1 shows the results for a series of experiments under a variety of conditions. The optimum yields of azaarene in both series were obtained from the dimethyl acetals using boron trifluoride etherate in dioxan as catalyst. The 1-naphthyl case gave a maximum yield of 24% by heating at 100 °C, and the 2-naphthyl case gave the best yield of 52% at 73 °C. These cyclization yields correspond to overall yields of benzisoquinoline from the naphthaldehyde of 13% and 36%, respectively.

Phenanthrene-9-carbaldehyde was converted analogously into the sulfonamide **18**. Heating with boron trifluoride etherate in dioxane under reflux gave dibenzo[*f*,*h*]isoquinoline **19**, isolated in 26% yield, comparable to that reported from a very different procedure[19] (Scheme 5).

Table 1 Cyclization of Sulfonamides **11**–**14**

Sulfonamide	R	Solvent	Temp (°C)	Catalyst	Yield of **16** (%)
12	Et	dioxan	100	HCl (6 M)	0
11	Me	dioxan	100	HCl (6 M)	1
12	Et	dioxan	100	$BF_3{\cdot}OEt_2$	19
11	Me	dioxan	100	$BF_3{\cdot}OEt_2$	24
11	Me	glycol	121	$BF_3{\cdot}OEt_2$	12
11	Me	dioxan	73	$BF_3{\cdot}OEt_2$	9
11	Me	dioxan	50	$BF_3{\cdot}OEt_2$	<1
Sulfonamide	R	Solvent	Temp (°C)	Catalyst	Yield of **17** (%)
14	Et	dioxan	100	HCl (6 M)	3
13	Me	dioxan	100	HCl (6 M)	18
14	Et	dioxan	100	$BF_3{\cdot}OEt_2$	42
13	Me	dioxan	100	$BF_3{\cdot}OEt_2$	47
13	Me	glycol	121	$BF_3{\cdot}OEt_2$	17
13	Me	dioxan	73	$BF_3{\cdot}OEt_2$	52
13	Me	dioxan	50	$BF_3{\cdot}OEt_2$	6

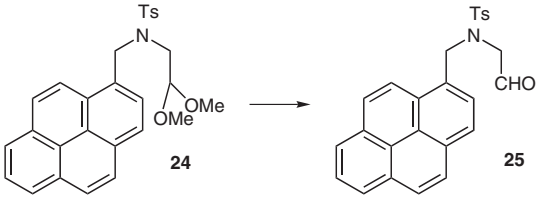


Scheme 5 Reactions in the phenanthrene series

As a starting material for other isomers, phenanthrene-3-carbaldehyde (**20**) was prepared from the commercially available 3-acetylphenanthrene using a route based on that described by Mosettig and van de Kamp.[20] The ketone was treated successively with alkaline sodium hypochlorite, thionyl chloride, and Rosenmund reduction of the acid chloride. As an alternative to the Rosenmund procedure we initially used bis(triphenylphosphine)copper(I) borohydride,[21] but the results were variable, yields of aldehyde between 0% and 71% being obtained over a number of attempts. The Rosenmund procedure in toluene as solvent gave the aldehyde in 66% yield. The aldehyde **20** was then converted into the corresponding sulfonamide **21** with some changes to the procedures used in the naphthalene series. Imine formation in toluene gave considerable decomposition, but was satisfactory at a lower temperature under reflux in benzene (requiring appropriate precautions with this generally avoided solvent). Hydrogenation over PtO_2 was also unsatisfactory, and the reduction was achieved with sodium borohydride in hot ethanol. The overall yield of sulfonamide **21** was 54% from the aldehyde.

Treatment of the sulfonamide **21** as for the 9-isomer **18**, but at a reduced temperature of 78 °C, gave napth[2,1-*g*]isoquinoline (**22**) in 9% yield after purification. ^{1}H NMR spectra showed evidence in the crude product of the isomer naphtho[1,2-*f*]isoquinoline **23**, identified by spectroscopic comparison with this compound prepared photochemically.[22] For comparison, the initial imine prepared from phenanthrene-3-carbaldehyde and 2,2-dimethoxyethanamine was heated with polyphosphoric acid and gave the same naphtho[1,2-*g*]isoquinoline (**22**), but impure and in only 1% yield. This result demonstrates the advantage of the reduction/tosylation procedure for polycyclic systems, though the greater success of Tanga et al. in preparing the isomeric products **1** and **2** from phenanthrene-2-carbaldehyde is recognized.[15]

Using the procedures applied in the naphthalene series, pyrene-1-carbaldehyde was converted into the sulfonamide **24**. Attempted cyclization failed under a variety of conditions: boron trifluoride etherate as described before, trifluoroacetic acid under reflux, polyphosphoric acid at 100 °C, and aluminum chloride. No product with the expected UV absorbance characteristic of a pentacyclic product was obtained. Treatment of **24** with hydrochloric acid (6 M) in dioxane under reflux gave the aldehyde **25**, a result of acetal hydrolysis.



Scheme 6 Reaction in the pyrene series

Naphtho[2,1-*g*]isoquinoline (**22**) has not been characterized previously to our knowledge. For this and the other azaarenes prepared, we have recorded ^{1}H and ^{13}C spectra under standard conditions as reference information, with assignments established by 2D methods and NOE where appropriate.

Previous work by Birch et al.[9] and others[12] showed that cyclization of the N-tosylated acetals occurs to give isoquinoline products, provided that there is sufficient electron density at the position of ring closure, as expected for an electrophilic attack. In the cyclization step, aromaticity is temporarily lost from the initial ring which has been most commonly a benzene ring. Generally, polycyclic aromatics undergo electrophilic substitution more readily than benzene.[23] In the naphthalene series, forming a benzisoquinoline, one benzene ring retains full aromaticity during the reaction. Cyclization to form benzo[*h*]isoquinoline was considerably easier than cyclization to benzo[*f*]isoquinoline, and this correlates with the generally greater ease of electrophilic reaction at the 1-position of naphthalene under conditions of kinetic control.[23] In the phenanthrene series, annulation was efficient at the '9,10-phenanthrene' position, and less efficient for cyclization from a 3-position. This accords with the generally found electrophilic reactivity of phenanthrene at the 9,10 bond. The ratio of isomeric products from the 3-phenanthryl case appears to be determined predominantly by a steric effect, the less hindered transition state leading to the 'linear' annulation product **22** rather than its isomer **23**. This procedure is in effect complementary to photocyclodehydrogenation which gives 'bent' annulation products such as **23**.[22] The failure of the pyrene case was disappointing, as pyrene is generally relatively reactive to electrophilic reagents. However, substitutions in pyrene itself are almost exclusively at the 1-position,[23] and failure to cyclize on to the 2-position may perhaps be understood.

Although we have obtained useful yields of polycyclic azaarenes in some cases, it is clear that the current procedure is limited in application. We have turned attention to other possible procedures for preparation of azaarenes, and the subsequent paper describes our investigations of photochemical cyclization.

Caution: Where information is available, azaarenes in general are less potent as mutagens and carcinogens than the isosteric parent carbocycles. Nevertheless, precautions should be taken with these compounds. The experiments described were carried out on small scales in a well-ventilated fume cupboard and all residues and waste were disposed of as potentially hazardous material. Benzene was used in some cases where toluene failed, requiring appropriate precautions for use and disposal.

Melting points were determined on a Reichert hot stage microscope. IR spectra were recorded in Nujol mulls on a PerkinElmer 1600 FTIR spectrometer. UV spectra were determined in Analar (AR) EtOH on a PerkinElmer Lambda 2 spectrophotometer. Microanalyses were performed on a PerkinElmer 240C Elemental Analyzer. Mass spectra at low resolution were measured with a Varian CH5-D double focusing spectrometer or a Fisons VG Platform II spectrometer using electron impact ionization. Accurate mass values were determined by the EPSRC Mass spectrometry service (Swansea) on a VG ZAB spectrometer. NMR spectra were recorded at 20 °C on Bruker WM360 and AMX360 instruments operating at 360 MHz for ^{1}H and 90 MHz for ^{13}C (with Waltz-16 ^{1}H decoupling or by DEPT-135), using sample concentrations of approximately 0.06 M. Chemical shifts are quoted relative to TMS (δ = 0). Correlations were determined from COSY-45, HETCOR and HMQC procedures using 256 sets of 1024 data points. Nuclear Overhauser enhancements (NOE) were determined by the difference method, using 12 repetitions of 8 'irradiated' and 8 'blank' pulses, the summed FIDs then subtracted and Fourier-transformed after line-broadening of 1 Hz. Standard Bruker software (DISNMR and UXNMR) was used throughout. TLC was carried out on Merck silica gel 60 F_{254}. Flash chromatography was carried out using Fisons matrix silica gel 60, 35–70 micron.

PE refers to petroleum ether fraction of boiling range 40–60 °C. Et_2O was dried over sodium wire. Dioxan (1,4-dioxane) was refluxed over KOH pellets and freshly distilled. Toluene was dried by azeotropic distillation. N_2 was passed through $CaCl_2$ and silica gel. Tosyl chloride was freshly recrystallized from PE. 1-Naphthaldehyde, 2-naphthaldehyde, phenanthrene-9-carbaldehyde, pyrene-1-carbaldehyde and 3-acetylphenanthrene were commercially available (Aldrich). Phenanthrene-3-carbaldehyde (**20**) was prepared by a modified literature[20] procedure.

Phenanthrene-3-carbaldehyde (20)[20]

A soln of 3-acetylphenanthrene (9 g, 0.041 mol) in dioxan (180 mL) was added to a soln of NaOCl (Fisons, 8% available chlorine at pH 12, 351 mL) and H_2O (1053 mL) containing NaOH (31 g). The mixture was stirred at 65 °C for 3 h and cooled to r.t. $NaHSO_3$ (ca. 80 g) was added until a sample of the soln no longer liberated I_2 from acidified KI soln. The stirred soln was cooled in ice and concd HCl (ca. 40 mL) added dropwise until pH 6. The white precipitate was collected by filtration, washed with ice-cold H_2O (2 × 80 mL), and dried to give phenanthrene-3-carboxylic acid as a white solid (9.10 g, ca. 100%). Phenanthrene-3-carboxylic acid (8 g, 0.036 mol) was stirred at reflux with $SOCl_2$ (16 mL, 0.216 mol) for 2 h. Excess $SOCl_2$ was distilled off at reduced pressure to give an oily solid. Anhyd benzene (HAZARD, 2 × 32 mL) was added and distilled off to leave pure phenanthrene-3-carboxylic acid chloride as a light beige solid (8.66 g, ca. 100%).

^{1}H NMR ($CDCl_3$): δ = 9.53 (br s, 1 H, H-4), 8.78 (d, *J* = 8 Hz, 1 H, H-5), 8.24 (dd, *J* = 8, 2 Hz, 1 H, H-2), 7.97 (d, *J* = 8 Hz, 1 H, H-1), 7.94 (d, *J* = 8 Hz, 1 H, H-8), 7.93 (d, *J* = 9 Hz, 1 H, H-9), 7.78 (d, *J* = 9 Hz, 1 H, H-10), 7.77 (td, *J* = 8, 1 Hz, 1 H, H-6), 7.69 (td, *J* = 8, 1 Hz, 1 H, H-7).

Reduction Using $(Ph_3P)_2CuBH_4$:[21] Phenanthrene-3-carboxylic acid chloride (7 g, 0.029 mol) in anhyd acetone (500 mL) was stirred for 1 h at r.t. with Ph_3P (15.52 g, 0.059 mol) and bis(triphenylphosphine)copper(I) borohydride (17.72 g, 0.029 mol). The white precipitate of tris(triphenylphosphine)copper (II) chloride was removed and the filtrate evaporated to dryness. The residue was shaken with Et_2O (500 mL) and the insoluble residue removed. Solvent was removed, the residue redissolved in $CHCl_3$ (300 mL) and the soln stirred over CuCl (6 g). After filtration, the $CHCl_3$ was evaporated and the residue extracted with MeOH. The extract was evaporated to dryness leaving a yellow oil which solidified. Purification by dry flash column chromatography (Et_2O–PE) gave phenanthrene-3-carbaldehyde (**20**); white solid; variable yield (4.26 g, 71% in the best result); mp 78–80 °C (Lit.[20]mp 79.5–80 °C).

^{1}H NMR ($CDCl_3$): δ = 10.27 (s, 1 H, CHO), 9.18 (s, 1 H, H-4), 8.78 (d, *J* = 8 Hz, 1 H, H-5), 8.08 (d, *J* = 8 Hz, 1 H, H-2), 8.00 (d, *J* = 8 Hz, 1 H, H-1), 7.94 (d, *J* = 8 Hz, 1 H, H-8), 7.90 (d, *J* = 9 Hz, 1 H, H-9), 7.79 (d, *J* = 9 Hz, 1 H, H-10), 7.75 (t, *J* = 8 Hz, 1 H, H-6), 7.67 (t, *J* = 8 Hz, 1 H, H-7).

MS (EI): *m*/*z* (%) = 207 (14, $[M + 1]^+$), 206 (100), 205, 177, 176, 88.

Anal. Calcd for $C_{15}H_{10}O$: C, 87.36; H, 4.89. Found: C, 87.55; H, 4.84.

Reduction by the Rosenmund Procedure:[20] A mixture of phenanthrene-3-carboxylic acid chloride (8 g, 0.333 mol), anhyd toluene (250 mL), and Pd/$BaSO_4$ (5%, 1 g) was stirred and heated for 3 h under reflux with drying tube and trap of aq $NaHCO_3$, while dry H_2 was gently bubbled through the mixture. The mixture was cooled, filtered (Celite) and the toluene evaporated. The residue was dissolved in Et_2O, and shaken with a sat. soln of $NaHSO_3$ for 12 h. The aldehyde–bisulfite complex was collected by filtration, washed with Et_2O (3 × 30 mL) and treated with a soln of NaOH (1.25 M, 250 mL). The basic soln was extracted into EtOAc (3 × 100 mL) and the combined extracts washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and evaporated to give phenanthrene-3-carbaldehyde (**20**) as a white solid (4.52 g, 66%). The mp, ^{1}H NMR, IR and mass spectra were identical to the product formed in the preceding method.

Formation of Sulfonamides; General Procedure

i) *Imine Formation*: A soln of the appropriate aldehyde (0.04 mol) in anhyd toluene (150 mL) containing 2,2-diethoxyethanamine or 2,2-dimethoxyethanamine (0.042 mol) was heated under reflux with a Dean–Stark apparatus for 4 h. Removal of the solvent afforded the imine as an oil, quantitatively and essentially pure.

ii) *Reduction of Imine*: Finely divided PtO_2 (100 mg) was added to a soln of this imine (0.02 mol) in AR EtOH (150 mL), and the stirred soln was shaken under H_2 at 1 atmosphere and 25 °C until the theoretical amount of H_2 was taken up. Filtration (Celite) and removal of solvent furnished the amine quantitatively and pure by NMR spectroscopy.

iii) *Tosylation*: A soln of tosyl chloride (0.011 mol) in anhyd pyridine (8 mL) was added to a soln of this amine (0.01 mol) in anhyd pyridine (8 mL) and the resulting dark colored soln was stirred at 20 °C for 72 h, during which time plates of pyridine hydrochloride separated. The mixture was poured into H_2O (50 mL) and extracted with Et_2O (3 × 25 mL). The combined extracts were washed with aq HCl (0.75 M, 2 × 25 mL), H_2O (2 × 25 mL), and dried ($MgSO_4$). Filtration and removal of solvent afforded the sulfonamide.

***N*-(2,2-Dimethoxyethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (11)**

Fine white crystals (PE–toluene, 19:1); yield from aldehyde: 56%; mp 85–86 °C.

^{1}H NMR ($CDCl_3$): δ = 8.21 (dd, *J* = 8, 0.5 Hz, 1 H, H-8), 7.85 (dd, *J* = 8, 0.5 Hz, 1 H, H-5), 7.79 (superimposed d, *J* = 8 Hz, 1 H and d, *J* = 8 Hz, 2 H, H-2 and tosyl H-2,6), 7.51 (m, 2 H, H-6 and H-7), 7.39–7.32 (m, 2 H, H-3 and H-4), 7.33 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.86 (s, 2 H, ArCH_2N), 4.12 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.18 (d, *J* = 5 Hz, 2 H, CHCH_2), 3.02 (s, 6 H, 2 OCH_3), 2.45 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 399 (1, $[M]^+$), 336, 244, 141, 115, 76, 75 (100).

Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.41; H, 6.48; N, 3.79.

***N*-(2,2-Diethoxyethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (12)**

Colorless crystals (PE–toluene, 19:1); yield from aldehyde: 60%; mp 87.5–88.5 °C.

^{1}H NMR ($CDCl_3$): δ = 8.17 (d, *J* = 8 Hz, 1 H, H-8), 7.84 (d, *J* = 8 Hz, 1 H, H-5), 7.78 (superimposed d, *J* = 8 Hz, 1 H, and d, *J* = 8 Hz, 2 H, H-2 and tosyl H-2,6), 7.49 (m, 2 H, H-6 and H-7), 7.36–7.33 (m, 2 H, H-3 and H-4), 7.32 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.91 (s, 2 H, ArCH_2N), 4.36 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.43 and 3.17 (each dq, *J* = 9, 7 Hz, each 2 H, 2 OC$H_aH_b$$CH_3$), 3.20 (d, *J* = 5 Hz, 2 H, CHCH_2), 2.44 (s, 3 H, tosyl CH_3), 0.96 (t, *J* = 7 Hz, 6 H, 2 OCH_2CH_3).

MS (EI): *m*/*z* (%) = 336 (3, $[M - 2\ OCH_2CH_3 - H]^+$), 272, 141, 104, 103 (100), 75.

Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.27. Found: C, 67.43; H, 7.03; N, 3.46.

***N*-(2,2-Dimethoxyethyl)-*N*-(2-naphthylmethyl)toluenesulfonamide (13)**

Fine white needles (EtOAc–Et_2O, 1:1); yield from aldehyde: 71%; mp 80–81 °C.

^{1}H NMR ($CDCl_3$): δ = 7.80 (dd, *J* = 6, 3 Hz, 1 H, H-8), 7.76 (superimposed d, *J* = 8 Hz, 1 H and d, *J* = 8 Hz, 2 H, H-4 and tosyl H-2,6), 7.71 (dd, *J* = 6, 3 Hz, 1 H, H-5), 7.57 (br s, 1 H, H-1), 7.45 (m, 2 H, H-6 and H-7), 7.34 (dd, *J* = 8, 0.7 Hz, 1 H, H-3), 7.30 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.64 (s, 2 H, ArCH_2N), 4.38 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.26 (d, *J* = 5 Hz, 2 H, CHCH_2), 3.22 (s, 6 H, 2 OCH_3), 2.44 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 336 (2, $[M - 2\ OCH_3 - H]^+$), 244, 141, 115, 76, 75 (100).

Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.36; H, 6.53; N, 3.48.

***N*-(2,2-Diethoxyethyl)-*N*-(2-naphthylmethyl)toluenesulfonamide (14)**

White crystals (PE–toluene, 17:3); yield from aldehyde: 39%; mp 58.5–59.5 °C.

^{1}H NMR ($CDCl_3$): δ = 7.79 (dd, *J* = 6, 3 Hz, 1 H, H-8), 7.75 (d, *J* = 8 Hz, 2 H, tosyl H-2,6), 7.73 (d, *J* = 7.5 Hz, 1 H, H-4), 7.69 (dd, *J* = 6, 3 Hz, 1 H, H-5), 7.54 (br s, 1 H, H-1), 7.45 (m, 2 H, H-6 and H-7), 7.31 (br d, *J* = ca. 8 Hz, 1 H, H-3), 7.28 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.70 (s, 2 H, ArCH_2N), 4.56 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.59 and 3.36 (each dq, *J* = 9, 7 Hz, each 2 H, 2 OC$H_aH_b$$CH_3$), 3.27 (d, *J* = 5 Hz, 2 H, CHCH_2), 2.44 (s, 3 H, tosyl CH_3), 1.12 (t, *J* = 7 Hz, 6 H, 2 OCH_2CH_3).

MS (EI): *m*/*z* (%) = 336 (2, $[M - 2\ OCH_2CH_3 - H]^+$), 272, 141, 104, 103 (100), 75.

Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.27. Found: C, 67.56; H, 7.07; N, 3.10.

***N*-(2,2-Dimethoxyethyl)-*N*-(9-phenanthrylmethyl)toluenesulfonamide (18)**

White crystals (PE–EtOAc, 1:1); yield from aldehyde: 75%; mp 117–118 °C.

^{1}H NMR ($CDCl_3$): δ = 8.70 (dd, *J* = 8, 2 Hz, 1 H, H-4 or H-5), 8.64 (dd, *J* = 8, 1 Hz, 1 H, H-5 or H-4), 8.23 (dd, *J* = 8, 2 Hz, 1 H, H-8), 7.79 (d, *J* = 8 Hz, 2 H, tosyl H-2,6), 7.71–7.53 (m, 5 H, H-1,2,3,6,7), 7.47 (s, 1 H, H-10), 7.31 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.93 (s, 2 H, ArCH_2N), 4.27 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.27 (d, *J* = 5 Hz, 2 H, CHCH_2), 3.05 (s, 6 H, 2 OCH_3), 2.44 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 449 (2, $[M]^+$), 294, 192, 189, 75 (100).

Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.51; H, 6.22; N, 3.15.

***N*-(2,2-Dimethoxyethyl)-*N*-(1-pyrenylmethyl)toluenesulfonamide (24)**

Off-white crystals (toluene–Et_2O, 1:1); yield from aldehyde: 97%; mp 133–137 °C.

^{1}H NMR ($CDCl_3$): δ = 8.44 (d, *J* = 9 Hz, 1 H, H-10), 8.21 and 8.19 (2 d, each *J* = 8 Hz, each 1 H, H-6 and H-8), 8.13 (d, *J* = 9 Hz, 1 H, H-9), 8.09 (d, *J* = 8 Hz, 1 H, H-3), 8.07 (d, *J* = 9 Hz, 1 H, H-4), 8.04 (d, *J* = 9 Hz, 1 H, H-5), 8.02 (t, *J* = 8 Hz, 1 H, H-7), 7.92 (d, *J* = 8 Hz, 1 H, H-2), 7.78 (d, *J* = 8 Hz, 2 H, tosyl H-2,6), 7.28 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 5.16 (s, 2 H, ArCH_2N), 4.19 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.25 (d, *J* = 5 Hz, 2 H, CHCH_2), 3.00 (s, 6 H, 2 OCH_3), 2.40 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 473 (5, $[M]^+$), 318, 216, 215, 76, 75 (100).

Anal. Calcd for $C_{28}H_{27}NO_4S$: C, 71.01; H, 5.75; N, 2.96. Found: C, 71.07; H, 5.91; N, 3.19.

***N*-(2,2-Dimethoxyethyl)-*N*-(3-phenanthrylmethyl)toluenesulfonamide (21)**

Phenanthrene-3-carbaldehyde reacted with 2,2-dimethoxyethanal as in the general procedure above, but using benzene (HAZARD) instead of toluene as the azeotropic solvent. The resulting imine (5 g, 0.017 mol) was reduced by stirring gently for 2 h in AR EtOH (100 mL) under reflux with $NaBH_4$ (0.97 g, 0.026 mol). Removal of the solvent produced an oily solid which was extracted with Et_2O (100 mL) and the residue (3.21 g) was filtered off. The extract was washed with NaOH soln (0.5 M, 150 mL), H_2O (100 mL), and dried (Na_2SO_4). The Et_2O was evaporated to leave 2,2-dimethoxy-*N*-(3-phenanthrylmethyl)ethanamine; pale yellow oil; yield: 4.13 g (82%).

^{1}H NMR ($CDCl_3$): δ = 8.71 (d, *J* = 8 Hz, 1 H, H-5), 8.62 (s, 1 H, H-4), 7.88 and 7.85 (2 d, each *J* = 8 Hz, each 1 H, H-1 and H-8), 7.72 (app s, 2 H, H-9 and H-10), 7.68–7.56 (m, 3 H, H-2,6,7), 4.55 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 4.08 (s, 2 H, ArCH_2N), 3.38 (s, 6 H, 2 OCH_3), 2.84 (d, *J* = 5 Hz, 2 H, CHCH_2).

MS (EI): *m*/*z* (%) = 295 (4, $[M]^+$), 222, 191, 95, 88, 75 (100).

This amine reacted with tosyl chloride according to the general procedure to give **21**.

White crystals (EtOAc–PE, 1:1); yield: 66%; mp 130–131 °C.

^{1}H NMR ($CDCl_3$): δ = 8.42 (dd, *J* = 7, 2 Hz, 1 H, H-5), 8.36 (br s, 1 H, H-4), 7.87 (dd, *J* = 7, 2 Hz, 1 H, H-8), 7.81 (d, *J* = 8 Hz, 1 H, H-1), 7.79 (d, *J* = 8 Hz, 2 H, tosyl H-2,6), 7.68 and 7.72 (AB system, *J* = 9 Hz, 2 H, H-9 and H-10), 7.60 (m, 2 H, H-6 and H-7), 7.46 (dd, *J* = 8, 2 Hz, 1 H, H-2), 7.30 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 4.77 (s, 2 H, ArCH_2N), 4.45 (t, *J* = 5 Hz, 1 H, C*H*CH_2), 3.32 (d, *J* = 5 Hz, 2 H, CHCH_2), 3.25 (s, 6 H, 2 OCH_3), 2.40 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 449 (2, $[M]^+$), 234, 191, 189, 76, 75 (100).

Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.68; H, 6.29; N, 3.01.

Cyclization of Sulfonamides; General Procedures

(*i*) *Under Aqueous Conditions:* The appropriate sulfonamide (1.17 mmol) was dissolved in anhyd dioxan (10 mL) under dry N_2 in the dark. HCl (6 M, 0.9 mL) was added under dry N_2 and the soln heated under reflux for 24 h, poured into HCl (2 M, 30 mL) and extracted with Et_2O (3 × 15 mL). The aqueous layer was made alkaline with NH_4Cl (2 M, 20 mL) and re-extracted with Et_2O (3 × 15 mL). The combined second extracts were washed with NaOH soln (2.5 M, 2 × 15 mL) followed by H_2O (2 × 15 mL), and dried ($MgSO_4$). Solvent was removed to leave the product.

(*ii*) *Under Anhydrous Conditions.* The procedure was as described in (*i*) but with the HCl replaced by freshly distilled $BF_3{\cdot}OEt_2$ (0.72 mL), and heating at various temperatures as given in Table 1.

Attempted Cyclization of *N*-(2,2-Diethoxyethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (12) under Aqueous Conditions; *N*-(Formylmethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (15)

General procedure (i) gave only *N*-(formylmethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (**15**); white crystals (PE); yield: 190 mg (46%); mp 106–111 °C.

^{1}H NMR ($CDCl_3$): δ = 8.90 (br s, 1 H, CHO), 8.41 (d, *J* = 8 Hz, 1 H, H-8), 7.86 (d, *J* = 8 Hz, 1 H, H-5), 7.84 (d, *J* = 8 Hz, 1 H, H-2), 7.80 (d, *J* = 8 Hz, 2 H, tosyl H-2,6), 7.62 (t, *J* = 8 Hz, 1 H, H-7), 7.54 (t, *J* = 8 Hz, 1 H, H-6), 7.42 (d, *J* = 8 Hz, 2 H, tosyl H-3,5), 7.34 (dd, *J* = 8, 7 Hz, 1 H, H-3), 7.21 (d, *J* = 7 Hz, 1 H, H-4), 4.75 (s, 2 H, ArCH_2N), 3.60 (d, *J* = 1 Hz, 2 H, CH_2CHO), 2.50 (s, 3 H, tosyl CH_3).

MS (EI): *m*/*z* (%) = 353 (4, $[M]^+$), 324, 142, 141 (100), 115, 83.

Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96. Found C, 68.11; H, 5.62; N, 3.90.

Cyclization of *N*-(2,2-Dimethoxyethyl)-*N*-(2-naphthylmethyl)toluenesulfonamide (13) under Aqueous Conditions; Benzo[*f*]isoquinoline (17)

General procedure (*i*) gave benzo[*f*]isoquinoline (**17**); pale yellow needles (PE); yield: 38 mg (18%); mp 97–99 °C (Lit.[18] mp 98–99.5 °C).

^{1}H NMR ($CDCl_3$): δ = 9.25 (s, 1 H, H-4), 8.76 (d, *J* = 6 Hz, 1 H, H-2), 8.68 (dd, *J* = 6, 3 Hz, 1 H, H-10), 8.42 (d, *J* = 6 Hz, 1 H, H-1), 7.95 (dd, *J* = 6, 3 Hz, 1 H, H-7), 7.86 (d, *J* = 9 Hz, 1 H, H-6), 7.82 (d, *J* = 9 Hz, 1 H, H-5), 7.74–7.72 (m, 2 H, H-8 and H-9).

^{13}C NMR ($CDCl_3$): δ = 151.5 (C-4), 144.9 (C-2), 134.6 (C-10b), 133.3 (C-6a), 128.6 and 127.0 (C-8 and C-9), 128.5 (C-7), 128.3 (C-10a), 128.2 (C-6), 126.8 (C-4a), 124.4 (C-5), 123.0 (C-10), 115.85 (C-1).

MS (EI): *m*/*z* (%) = 179 (80, $[M]^+$), 107, 91 (100), 76, 65, 63.

Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.81. Found: C, 86.89; H, 5.05; N, 7.57.

Cyclization of *N*-(2,2-Dimethoxyethyl)-*N*-(1-naphthylmethyl)toluenesulfonamide (11) under Anhydrous Conditions; Benzo[*h*]isoquinoline (16)

General procedure (*ii*) in dioxan at 100 °C gave benzo[*h*]isoquinoline (**16**); yellow solid crude (50 mg, 24%), recrystallized (PE) as off-white crystals; mp 52–54 °C (Lit.[18] mp 53–54 °C).

^{1}H NMR ($CDCl_3$): δ = 10.05 (s, 1 H, H-1), 8.79 (d, *J* = 8 Hz, 1 H, H-10), 8.71 (d, *J* = 5 Hz, 1 H, H-3), 7.93 and 7.68 (2 d, each *J* = 9 Hz, each 1 H, H-5 and H-6), 7.92 (dd, *J* = 8, 1 Hz, 1 H, H-7), 7.74 (td, *J* = 8, 1 Hz, 1 H, H-9), 7.71 (d, *J* = 5 Hz, 1 H, H-4), 7.67 (td, *J* = 8, 1 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$): δ = 146.7 (C-1), 145.0 (C-3), 135.9 (C-4a), 132.2 (C-6a), 131.7 and 124.8 (C-5 and C-6), 129.3 (C10a), 128.9 (C-7), 127.9 (C-9), 127.4 (C-8), 125.1 (C-10b), 121.95 (C-10), 121.2 (C-4).

MS (EI): *m*/*z* (%) = 180 (14, $[M + 1]^+$), 179 (100), 178, 151, 150, 76.

Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.81. Found: C, 86.96; H, 5.11; N, 7.77.

Other Cyclizations of Sulfonamides 11–14

Table 1 lists details of other experiments using **11**–**14**, carried out under comparable conditions.

Cyclization of *N*-(2,2-Dimethoxyethyl)-*N*-(9-phenanthrylmethyl)toluenesulfonamide (18); Dibenzo[*f*,*h*]isoquinoline (19)

General procedure (*ii*) in dioxan at 100 °C followed by column chromatography gave dibenzo[*f*,*h*]isoquinoline (**19**); white crystals; yield: 26%; mp 167–169 °C (Lit.[19] mp 169–171 °C); one spot R_f = 0.37 (EtOAc–PE, 1:1).

^{1}H NMR ($CDCl_3$): δ = 9.94 (br s, 1 H, H-1), 8.77 (br d, *J* = 5.6 Hz, 1 H, H-3), 8.71 (m, 1 H, H-12), 8.65-8.62 (m, 2 H, H-8 and H-9), 8.60 (dd, *J* = 8.4, 1.2 Hz, 1 H, H-5), 8.34 (d, *J* = 5.6 Hz, 1 H, H-4), 7.76 and 7.70 (2 td, each *J* = 7.1, 1.4 Hz, each 1 H, H-6 and H-7), 7.72-7.67 (m, 2 H, H-10 and H-11); NOE 9.94 → 8.71 (14%); 8.34 → 8.60 (10%) and 8.77 (4%).

^{13}C NMR ($CDCl_3$): δ = 146.7 (C-1), 146.2 (C-3), 135.2, 131.3, 129.9, 129.4 and 127.5 (C-6 and C-7), 128.05 and 127.8 (C-10 and C-11), 127.45, 123.8 (C-5), 123.4 (C-8 and C-9), 122.6 (C-12), 116.3 (C-4), 2 obscured.

MS (EI): *m*/*z* (%) = 230 (20, $[M + 1]^+$), 229 (100), 228, 201, 101, 100.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{17}H_{11}N$: 229.0891; found: 229.0891.

Cyclization of *N*-(2,2-Dimethoxyethyl)-*N*-(3-phenanthrylmethyl)toluenesulfonamide (21); Naphtho[2,1-*g*]isoquinoline (22)

General procedure (*ii*) in dioxan at 100 °C followed by column chromatography gave naphtho[2,1-*g*]isoquinoline (**22**); off-white solid; yield: 9%; mp 135–138 °C; one spot R_f = 0.42 (EtOAc–PE, 1:1).

^{1}H NMR ($CDCl_3$): δ = 9.58 (br s, 1 H, H-11), 9.28 (s, 1 H, H-12), 8.84 (br d, *J* = ca. 8.5 Hz, 1 H, H-1), 8.56 (br d, *J* = 5.9 Hz, 1 H, H-9), 8.31 (s, 1 H, H-7), 7.88 (dd, *J* = 7.6, 1.4 Hz, 1 H, H-4), 7.81 (d, *J* = 5.9 Hz, 1 H, H-8), 7.80 (d, *J* = 8.7 Hz, 1 H, H-6), 7.74 (d, *J* = 8.7 Hz, 1 H, H-5), 7.74 (td, *J* = 7.6, 1.4 Hz, 1 H, H-2), 7.67 (td, *J* = 7.6, 1.4 Hz, 1 H, H-3); NOE 9.58 → 9.28 (8%); 8.31 → 7.81 and 7.80 (14%).

^{13}C NMR ($CDCl_3$): δ = 153.95 (C-11), 141.8 (C-9), 133.8, 133.0, 131.8, 130.35, 129.9, 129.3 (C-5), 128.8 (C-4), 127.7 (C-3), 127.4 (C-2), 127.0, 126.8 (C-6), 125.2 (C-7), 123.0 (C-1), 122.1 (C-12), 119.7 (C-8).

UV (EtOH): λ_{max} (ε) = 383 (1440), 372 (2970), 353 (4790), 338 (4310), 323 (3260), 290 (58590), 279 (51500), 270 (34480), 231 (32210), 224 nm (28730).

MS (EI): *m*/*z* (%) = 230 (25, $[M + 1]^+$), 229 (100), 228, 200, 115, 100.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{17}H_{11}N$: 229.0891; found: 229.0891.

When this reaction was repeated on a larger scale, the ^{1}H NMR spectrum of the crude mixture showed a trace (<1%) of the isomeric naphtho[1,2-*f*]isoquinoline (**23**), identified by comparison with spectra from an authentic sample prepared photochemically as reported elsewhere.[22]

Cyclization of 2,2-Dimethoxy-*N*-(3-phenanthrylmethylene)ethanamine

The imine (2.13 g, 7.3 mmol) was added to PPA (20 mL) under N_2 in the dark and the mixture heated at 100 °C for 2 h. The red syrup was poured into ice-water (60 mL) and stirred until all the gummy material had dissolved. The soln was washed with Et_2O (2 × 100 mL) and basified using NH_4OH soln. The precipitate was extracted with Et_2O (3 × 100 mL) and the combined extracts washed with NaOH soln (2.5 M, 2 × 50 mL), then H_2O (2 × 50 mL), and dried ($MgSO_4$). Removal of the solvent afforded a brown oily solid (ca. 2 mg) consisting of ca. 1:1 mixture of naphtho[2,1-*g*]isoquinoline (**22**) and an unidentified byproduct.

Attempted Cyclizations of *N*-(2,2-Dimethoxyethyl)-*N*-(1-pyrenylmethyl)toluenesulfonamide (24)

1. *Under Aqueous Conditions*: General procedure (*i*) gave *N*-(formylmethyl)-*N*-(1-pyrenylmethyl)toluenesulfonamide (**25**).

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White crystals; mp 167–169 °C.

^{1}H NMR ($CDCl_3$): δ = 8.88 (br s, 1 H, CHO), 8.60 (d, *J* = 9 Hz, 1 H, H-10), 8.25 (d, *J* = 8 Hz, 1 H, H-8 or H-6), 8.22 (2 d superimposed, *J* = ca. 8 Hz, 2 H, H-6 or H-8, and H-9), 8.10 (d, *J* = 9 Hz, 1 H, H-4 or H-5), 8.07 (d, *J* = 8 Hz, 1 H, H-3), 8.05 (t, *J* = 7.7 Hz, 1, H-7), 8.02 (d, *J* = 9 Hz, 1 H, H-5 or H-4), 7.85 (d, *J* = 8.2 Hz, 2 H, tosyl H-2,6), 7.73 (d, *J* = 8 Hz, 1 H, H-2), 7.43 (d, *J* = 8.2 Hz, 2 H, tosyl H-3,3′), 5.02 (s, 2 H, ArCH_2), 3.63 (br s, 2 H, CH_2CHO), 2.50 (s, 3 H, tosyl CH_3); NOE 5.02 → 8.60 (20%), 7.85 (6%) and 7.73 (13%).

^{13}C NMR ($CDCl_3$, DEPT): δ = 197.5 (CHO), 130.1, 128.8, 128.5, 128.2, 127.7, 127.2, 126.3, 125.8, 125.7, 124.6, 123.0 (all CH), 56.0 and 51.9 (CH_2), 21.6 (CH_3).

MS (EI): *m*/*z* (%) = 427 (3, $[M]^+$), 271, 242, 216, 215 (100), 94.

Anal. Calcd for $C_{26}H_{21}NO_3S$: C, 73.04; H, 4.95; N, 3.27. Found: C, 73.33; H, 5.11; N, 3.22.

2. *Under Anhydrous Conditions*: In each of the following attempts based on General Procedure (*ii*), a standard work-up afforded material which did not show the UV spectrum expected for a pentacyclic product:

- **24** was heated with $BF_3{\cdot}OEt_2$ in dioxan at 100 °C;

- **24** (500 mg, 1.1 mmol) was heated at reflux in trifluoroacetic acid (10 mL) for 12 h;

- **24** (500 mg, 1.1 mmol) was heated at 80 °C in PPA (27 g) for 6 h;

- **24** (473 mg, 1.0 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise to a stirred mixture of $AlCl_3$ (1.33 g) in CH_2Cl_2 (5 mL) under dry N_2. The purple-red mixture was stirred for 24 h at r.t., then quenched slowly with H_2O (15 mL).

Acknowledgment

We thank the EPSRC for a studentship to R.S. and for support towards the NMR and MS instruments, and the Mass Spectrometry Service (Swansea) for accurate mass measurements.

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