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$S_{RN}1$ C–ARYLATION OF PHENOLS BY AZOSULFIDES: A NOVEL SYNTHESIS OF DIBENZO[*b,d*]PYRAN–6–ONES

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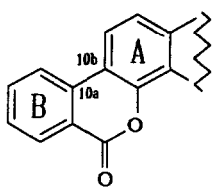
Abstract: The *ortho*-arylation of phenols by (2-cyanoaryl)azo *t*-butyl (or phenyl) sulfides in $S_{RN}1$ conditions, followed by a silica-gel-catalysed lactonisation of the resulting 2-cyano-2'-hydroxybiphenyls, leads to dibenzo[*b,d*]pyran-6-ones.

The most common synthetic strategy to the biologically and pharmacologically interesting dibenzo[*b,d*]pyran-6-one skeleton **1** of benzocoumarins[1,2] and related



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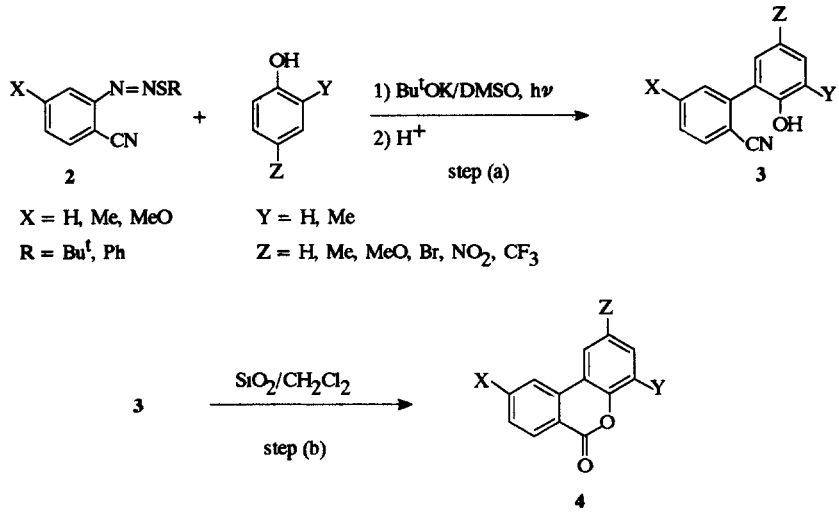
compounds[3] involves the assembly of ring systems A and B *via* sequential C(10a)-C(10b) bond formation and cyclisation In particular, the former step is realised by means of well established procedures such as (i) the coupling between highly activated phenols and o-bromobenzoic acids (Hurtley reaction),[2,4] (ii) the employment of aryl Grignards in nucleophilic substitutions[3a,b] or of aryllithiums in addition reactions,[3d] (iii) the Meerwein arylation of halobenzoquinones,[3e,f] or (iv) a Suzuki-type coupling of arylboronic acids with haloarenes [3g,5,6]

Our interest in the exploitation of azosulfides (ArN=NSR; R = Ph, Bu^t) as arylating agents[7,8] in $S_{RN}1$ processes[9] has now provided us with a rather straightforward two-step route to **1** (Scheme I) where the photostimulated 2-cyanoarylation of a phenol is followed by a lactonisation in very mild conditions, with no need for the isolation of the intermediate hydroxybiaryl **3**: representative results are reported in the Table.

Scheme I



The key step (a) most likely represents a particular case of a more general process we have recently described for the synthesis of hydroxybiaryls [8] It hinges on the tenet that, while oxygen nucleophiles repeatedly proved to be unreactive in $S_{RN}1$ substitutions,[9] in these reactions aryloxide ions behave as carbon nucleophiles, arylation by a suitable substrate (*e g.* haloarenes[10-12] or azosulfides[8]) occurring at nuclear positions which are conjugated with the ionised hydroxy group. In particular, the employment of azosulfides (Scheme II, path b) allows to avoid the classical azo-coupling[13] of diazonium salts (Scheme II, path a) through the generation of aryl radicals which participate in an efficient $S_{RN}1$ propagation cycle [eqns (i)-(iii)] The

Scheme II

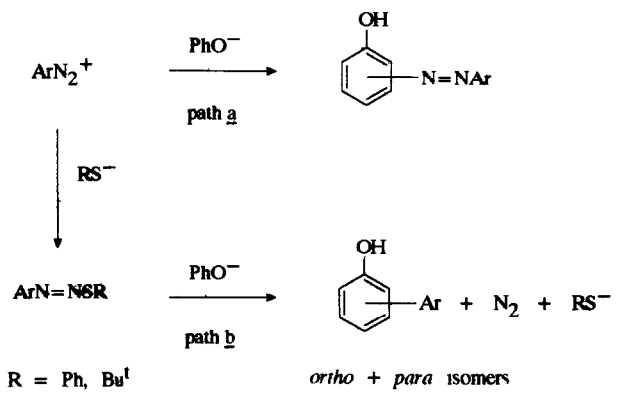
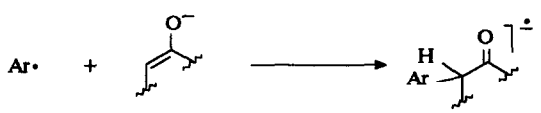


Table. Reaction between azosulfides **2**[a] and aryloxides according to Scheme I.[b]

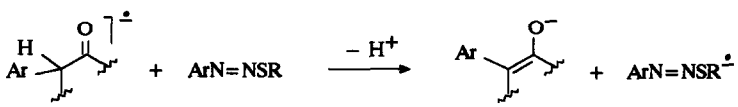
				Yield[c]	
Expt	X	Y	Z	Me–**3**[d]	**4**
1	H	H	H		**4a**: 31%
2	H	H	Me	50%	**4b**: 48%
3	H	Me	Me	21%	**4c**: 20%
4	H	H	MeO	62%	**4d**: 56%
5	H	H	Br		**4e**: 57%
6[e]	H	H	NO_2		**4f**: 59%
7	H	H	CF_3		**4g**: 55%
8	Me	H	Me		**4h**: 40%
9	MeO	H	Me		**4i** 38%

[a] *tert*-Butyl sulfides (**2**: R = Bu^t), unless otherwise stated [b] [**2**] = 0.07 M; 10 mol equiv of aryloxide always employed [c] Yields of isolated products calculated on azosulfide **2** [d] Methyl ethers of hydroxybiphenyls **3** (see text). [e] The phenyl sulfide (**2**: R = Ph) was employed

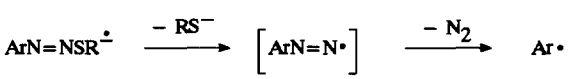
reaction was found to be favoured by electron-withdrawing groups on the Ar moiety[8b] and the results herein clearly indicate that the *ortho*-cyano group makes no exception.



(i)



(ii)



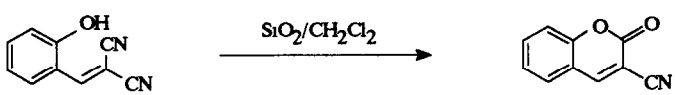
(iii)

R = Ph, Bu^t

As far as yields of benzocoumarins **4** are concerned, it should be stressed that step (a) undoubtedly represents the critical one, as control experiments have evidenced an almost quantitative yield for the cyclisation to **4b–d**: thus, the relevant biaryl precursors **3** have been isolated as methyl ethers (**Me–3**, see Experimental) in yields which closely match those reported for **4** (see Table). An obvious limit to the final target herein is represented by the arylation of the *para*-ring-carbon of the aryloxide, which effectively competes with *ortho*-arylation when such position is unsubstituted,[8] this surely contributes to explain the lower benzocoumarin yield of expt 1 in the Table and justifies the employment of a *para*-substituted phenoxide in the remaining experiments. Furthermore, although not isolated herein, by-products of like arylation processes[7c,e,8] are typically represented by ArH (generated by termination steps on the aryl radical) or ArSR [stemming from a concurrent $S_{RN}1$ cycle which involves the highly competitive "internal" nucleophile RS^- originating from the fragmentation step (iii)], the low yield reported for expt 3 possibly finds a rationalisation in an enhanced competitivity of side-reactions with respect to an *ortho*-arylation for which only one *ortho*-position is available.

If step (a) sets evident limitations as to the attainment of satisfactory final yields, step (b) proves to be extremely effective notwithstanding the very mild conditions employed. Actually, while attempts to isolate the intermediate hydroxybiaryls **3** by chromatography on silica-gel resulted in an extensive transformation into **4** during elution, the cyclisation generally goes to completion within a few hours if a CH_2Cl_2 solution of the product mixture from step (a) is kept under stirring over silica-gel at room temperature (see Experimental); from a practical point of view, the procedure very simply consists in the replacement of solvent (CH_2Cl_2 for DMSO) after acidic quenching.

It should be pointed out that the reaction between a cyano and a hydroxy group in aqueous medium to eventually furnish an ester function[14] has also been applied to the synthesis of lactones,[15] but the rather strongly acidic conditions employed would presumably not be tolerated by a number of functionalities. On the other hand O-acylations[16] and, more specifically, lactonisation processes[17] on silica-gel have been reported, but, to our knowledge, the application of such mild conditions to the "condensation" between a nitrile and a phenol is unprecedented In our opinion, the practical advantages offered by the procedure of step (b) herein justify a more detailed investigation in order to better define its synthetic potentialities: as a further example, we have applied the method to the lactonisation of **5** and the yield (85%) of the



5 **6**

3-cyanocoumarin (**6**) isolated after 1 day at room temperature very well compares with that (92%) reported[15a] for the acid-catalysed (4N HCl) process on the same precursor.

Thus we believe that the results presented herein not only open a new viable and appealing route (although with no pretence at generality, as discussed above) to the condensed nucleus **1** from readily available precursors, but also significantly expand the applicability range of such a mild and convenient catalyst as silica-gel[18] to lactonisation, mainly in the perspective of its exploitation along more complex and demanding synthetic sequences.

Experimental

Melting points were taken on a Buchi 535 apparatus and are uncorrected. ^1H NMR spectra were taken in $CDCl_3$ (TMS as internal standard) on a Varian Gemini 200 spectrometer IR spectra (neat or nujol mull) were recorded on a Perkin-Elmer 881 Infrared Spectrophotometer

New compounds (italicised) gave satisfactory elemental analyses, spectral data being in full agreement with the proposed structure

Materials - Petroleum ether and light petroleum refer to the fractions with bp 30-50 °C and 80-100 °C respectively Dimethyl sulfoxide (Fluka AG) was used as received after storage over molecular sieves (4 Å), CH_2Cl_2 was used after distillation Potassium *tert*-butoxide (Aldrich, 97%) was used without further purification. Silica-gel (60-200 μ) was purchased from Merck Phenols were all commercial samples used as received with the exception of *p*-chresol, which was distilled before use

Substrates - Azosulfides were prepared from the corresponding anilines (which were commercial samples, with the exception of the 2-cyano-5-methylaniline[19] and the 2-cyano-5-methoxyaniline,[20] synthesized according to literature) and purified as reported elsewhere;[8b] (*Z*)-**2**(R = Bu^t, X = H) and (*E*)-**2**(R = Ph, X = H) have been already described.[7e]

(Z)-tert-Butyl (2-cyano-5-methylphenyl)azo sulfide [(*Z*)-**2**(R = Bu^t, X = Me)] mp 56.0-56.7 °C, ^1H NMR: δ 1 64 (9 H, s), 2.47 (3 H, s), 6 87 (1 H, m), 7.21 (1 H, dm, *J* = 7 9 Hz), 7.64 (1 H, d, *J* = 7 9 Hz), IR 2228 cm^{-1} (CN) (Found C, 61 51, H, 6 31, N, 17 74%. $C_{12}H_{15}N_3S$ requires C, 61 77, H, 6 48, N, 18 01%)

(Z)-tert-Butyl (2-cyano-5-methoxyphenyl)azo sulfide [(*Z*)-**2**(R = Bu^t, X = MeO)] mp 63 0-64 4 °C, ^1H NMR· δ 1 64 (9 H, s), 3 89 (3 H, s), 6.55 (1 H, d, *J* = 2 5 Hz), 6.90 (1 H, dd, *J* = 2 5 and 8 7 Hz), 7 67 (1 H, d, *J* = 8 7 Hz), IR 2224 cm^{-1} (CN) (Found: C, 57 70, H, 5.91, N, 16 80% $C_{12}H_{15}N_3OS$ requires C, 57 81; H, 6.06, N, 16 85%).

General procedure - Arylations were carried out under argon, the apparatus being deaerated using three freeze-pump-thaw cycles Reactions were started by dropping a DMSO solution of substrate (2.3 mmol) into a double volume of a magnetically stirred solution of the nucleophile (23 mmol) prepared *in situ* from equimolar amounts of the appropriate phenol and potassium *tert*-butoxide The initial substrate concentration was 0.07 M. Irradiation was performed with a 300 W Osram sunlamp placed *ca.* 15 cm from the reaction vessel (Pyrex flask) and an appropriately positioned fan served to maintain the reaction temperature around 25 °C. The end of reaction (which was generally complete within 1 5-2 h) was judged by ceasing of gas evolution and/or TLC analysis Usual workup involved pouring of the reaction mixture into ice/5% HCl (5-6 vol) and a 4-fold extraction with Et_2O, followed by washing of the combined extracts with brine The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure at room temperature. The residue was dissolved in CH_2Cl_2 (50 ml) and kept for 1 day at room temperature under magnetic stirring over silica-gel (12 g), filtration, washing of the organic solution with 5% NaOH (to remove the excess phenol), and rotoevaporation yielded a crude material from which **4** was isolated by column chromatography (petroleum ether/CH_2Cl_2 mixtures as eluant)

In a few cases the intermediate hydroxybiaryls **3** were characterised as methyl ethers (**Me–3**) by overnight treatment of the final arylation mixture with MeI (46 mmol) at room temperature After dilution with brine and extraction with Et_2O separation of **Me–3** was performed by column chromatography.

Methoxybiaryls (**Me–3**)

2-Cyano-2′-methoxy-5′-methylbiphenyl oil, ^{1}H NMR δ 2 34 (3 H, s), 3.81 (3 H, s), 7 00 (2 H, m), 7 21 (1 H, m), 7 41 (2 H, m), 7 65 (2 H, m), IR 2226 cm^{-1} (CN) (Found C, 80 61, H, 5 68, N, 6 15% $C_{15}H_{13}NO$ requires C, 80.69, H, 5 87, N, 6 27%)

2-Cyano-2′-methoxy-3′,5′-dimethylbiphenyl mp 107 6-108 8 °C (light petroleum), ^{1}H NMR. δ 2.32 (6 H, br s), 3 34 (3 H, s), 7 02 (2 H, m), 7 53 (3 H, m), 7 75 (1 H, m), IR 2223 cm^{-1} (CN) (Found C, 80 87, H, 6 27, N, 6 02% $C_{16}H_{15}NO$ requires C, 80 98, H, 6 37, N, 5 90%)

2-Cyano-2′,5′-dimethoxybiphenyl mp 83-84 °C (petroleum ether), ^{1}H NMR δ 3 79 (3 H, s), 3 81 (3 H, s), 6 83 (1 H, m), 6 95 (2 H, m), 7.43 (2 H, m), 7 66 (2 H, m), IR 2225 cm^{-1} (CN) (Found C, 75.26, H, 5 49, N, 5 81% $C_{15}H_{13}NO_2$ requires C, 75 29, H, 5 48, N, 5 85%)

Dibenzo[b,d]pyran-6-ones (**4**)

Dibenzo[*b,d*]pyran-6-one (**4a**) mp 90 6-91 6 °C (lit [21] 91 5-92 5°C)

2-Methyldibenzo[*b,d*]pyran-6-one (**4b**) mp 130.5-131 5 °C (lit [22] 133 °C)

2,4-Dimethyldibenzo[b,d]pyran-6-one (**4c**) mp 181 6-182 4 °C (toluene/petroleum ether), ^{1}H NMR δ 2 42 (3 H, s), 2 46 (3 H, s), 7 15 (1 H, br s), 7 56 (1 H, m), 7 69 (1 H, br

s), 7.80 (1 H, m), 8.11 (1 H, m), 8 40 (1 H, m); IR 1714 cm^{-1} (CO) (Found C, 80.53, H, 5 58%. $C_{15}H_{12}O_2$ requires C, 80.34, H, 5 39%).

2-Methoxydibenzo[*b,d*]pyran-6-one (**4d**) mp 118.7-119 6 °C (light petroleum) (lit [23] 121-123 °C).

2-Bromodibenzo[b,d]pyran-6-one (**4e**) mp 197 2-198 6 °C (EtOH/dioxane), ^1H NMR δ 7 27 (1 H, d, J = 8.8 Hz), 7 58 and 7.64 [2 H, dd (J = 2 2 and 8 8 Hz) and m partly overlapped], 7.87 (1 H, m), 8 08 (1 H, m), 8 19 (1 H, d, J = 2 2 Hz), 8 42 (1 H, m), IR 1739 cm^{-1} (CO) (Found C, 56 50, H, 2.51% $C_{13}H_7BrO_2$ requires C, 56 76, H, 2 56%).

2-Nitrodibenzo[*b,d*]pyran-6-one (**4f**) mp 261 0-262 1 °C (dioxane) (lit :[21] 261 5-262 5 °C)

2-(Trifluoromethyl)dibenzo[b,d]pyran-6-one (**4g**): mp 178 8-179 8 °C (light petroleum), ^1H NMR δ 7 49 (1 H, d, J = 8 8 Hz), 7.70 (2 H, m), 7 91 (1 H, m), 8 19 (1 H, m), 8.35 (1 H, br s), 8 45 (1 H, m) (Found C, 64 01, H, 2 67% $C_{14}H_7F_3O_2$ requires C, 63 65, H, 2.67%).

2,9-Dimethyldibenzo[b,d]pyran-6-one (**4h**) mp 174 3-175.0 °C (light petroleum), ^1H NMR δ 2.47 (3 H, s), 2 56 (3 H, s), 7 26 (2 H, AB system), 7.38 (1 H, d, J = 8 0 Hz), 7.84 (1 H, br s), 7 90 (1 H, br s), 8 28 (1 H, d, J = 8 0 Hz), IR 1723 cm^{-1} (CO) (Found C, 80.33; H, 5.42%. $C_{15}H_{12}O_2$ requires C, 80 34; H, 5.39%)

9-Methoxy-2-methyldibenzo[b,d]pyran-6-one (**4i**) mp 211 6-212 3 °C (toluene), ^1H NMR: δ 2 47 (3 H, s), 4 01 (3 H, s), 7 11 (1 H, dd, J = 2.4 and 8 8 Hz), 7 27 (2 H, AB system), 7 48 (1 H, d, J = 2.4 Hz), 7 78 (1 H, br s), 8 34 (1 H, d, J = 8 8 Hz); IR· 1711 cm^{-1} (CO) (Found C, 75 20, H, 5 06% $C_{15}H_{12}O_3$ requires C, 74 99, H, 5 03%)

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