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The synthesis and electronic absorption spectra of 3-phenyl-3(4-pyrrolidino-2-substituted phenyl)-3*H*-naphtho[2,1-*b*]pyrans: further exploration of the *ortho* substituent effect

Christopher D. Gabbutt, B. Mark Heron* and Alicia C. Instone

Department of Colour and Polymer Chemistry, The University of Leeds, Leeds LS2 9JT, UK

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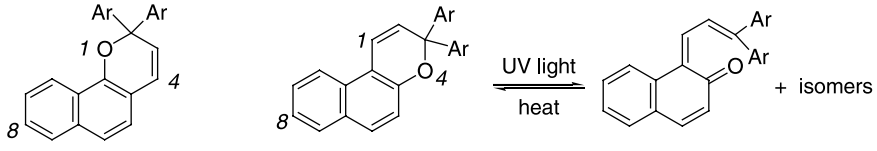
Abstract—Introduction of a substituent into a sterically demanding 2-position of a 3-(4-pyrrolidinophenyl) ring of a 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran results in the generation of an additional short wavelength absorption band leading to organic photochromes that appear as dull shades of orange and red.

1. Introduction

The electrocyclic ring-opening–ring-closing sequence of the isomeric diaryl substituted naphthopyrans **1** and **2** (Scheme 1) with the accompanying colour change has rendered these compounds invaluable to the ophthalmic photochromic sun and contact lens industries.[1] Other applications of photochromic naphthopyrans, for example, in fuel[2] and security markers,[3] as UV light intensity indicators[4] and as hair dyes[5] have been documented.

Optimising the photochromic response of these T-type[6] naphthopyrans has attracted significant academic[7] and industrial attention.[1] Perhaps the simplest and most significant means to achieve control of the hue and persistence of the ring-opened isomer of the naphthopyran system is through the manipulation of substituents located on the geminal diaryl unit.[8] The intensification of the photo-generated colour of **2** has been accomplished through the introduction of a group into at least one of the *ortho* positions of one of the aryl groups attached to 3-C, for example, **3**.[9] This phenomenon has been attributed to a steric effect in which the *ortho* substituent hinders the thermal ring closure of the photo-generated coloured species to the colourless pyran form; a feature that has recently been correlated to the size of the introduced group in **4**.[10] The net result of this steric effect is a photostationary state in which there is an appreciable concentration of the ring-opened form, which is manifest in an intensification of the developed colour. Further manipulation of the photochromism of naphthopyrans has been accomplished through steric interactions between a terminal pyrrolidine donor function and neighbouring substituents, for example, **5**. In this instance, as the magnitude of these steric interactions increase λ_{max} is shifted hypsochromically until a maximum interaction is observed with **5**, X=Br.[11]



1
2*H*-naphtho[1,2-*b*]pyran

2
3*H*-naphtho[2,1-*b*]pyran

Scheme 1.

Keywords: Naphthopyrans; Photochromism; Steric effects; Dual absorption bands; Synthesis.
* Corresponding author. Tel.: +44 113 3432925; fax: +44 113 3432947; e-mail: b.m.heron@leeds.ac.uk

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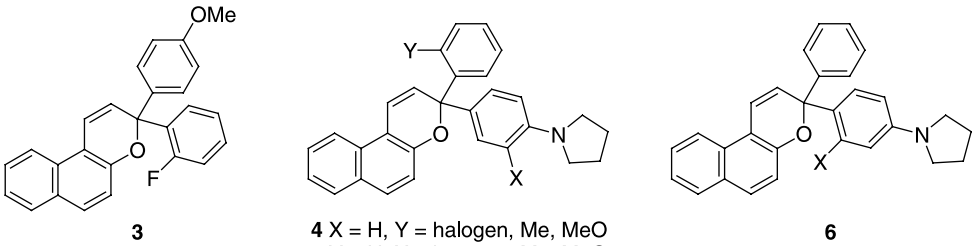


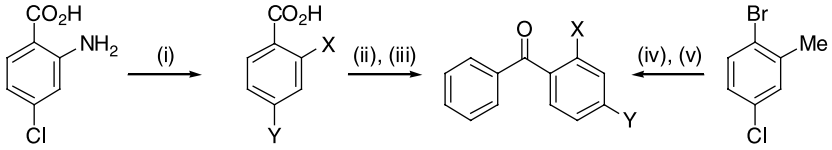
3 **4** X = H, Y = halogen, Me, MeO; **5** Y = H, X = halogen, Me, MeO **6**

We were interested in exploring novel naphthopyrans of type **6** in which the influence of alternating the nature of X, located in a sterically demanding position in the main electron donating aryl moiety, upon the photochromic response could be investigated.[12]

2. Results and discussion

In order to synthesise **6** we required access to a range of 2-substituted 4-pyrrolidinobenzophenones. Thus, the dihalogenobenzoic acids **7a**,**b** were accessed by diazonium salt chemistry from 4-chloroanthranilic acid.[13] Conversion to the acid chlorides and a subsequent Friedel-Crafts reaction with benzene afforded the benzophenones **8a**,**b** (Scheme 2). 2-Chloro-4-fluorobenzophenone **8c** was obtained in a similar manner from 2-chloro-4-fluorobenzoic acid. Using this Friedel-Crafts protocol with 4-chloro-2-methoxybenzoic acid resulted in concomitant demethylation and benzoylation[14] to give 4-chloro-2-hydroxybenzophenone **8e**. *O*-Methylation of **8e** was only accomplished in low yield using excess MeI and powdered KOH in DMSO to afford the 2-methoxybenzophenone **8f**. 4-Chloro-2-methybenzophenone was accessed in 76% yield by the action of the Grignard reagent derived from 2-bromo-5-chlorotoluene on the Weinreb amide,[11,15] *N*-methoxy-*N*-methylbenzamide.

We have previously employed the nucleophilic substitution of an activated halogen atom from benzophenones to afford aminosubstituted benzophenones.[11,16] However, the present benzophenones, **8a–d**, contain two halogen atoms that are activated towards nucleophilic displacement. Heating **8d** in an excess of pyrrolidine resulted in the formation of 2,4-dipyrrolidinobenzophenone **9** (72%) and 4-fluoro-2-pyrrolidinobenzophenone **10a** (17%) which were separated by column chromatography. None of the desired benzophenone **11d** was isolated from the crude product. It is likely that the initial reaction involves preferential displacement of the 4-fluorine atom of **8d** to afford 2-fluoro-4-pyrrolidinobenzophenone **11d** together with a smaller amount of **10a** as a consequence of the simultaneous but less favoured displacement of the 2-fluorine atom. However, under prolonged heating, the 2-fluorine atom of **11d**, although electronically deactivated towards displacement due to the 4-pyrrolidine substituent diminishing the electron withdrawing influence of the C=O group, is still sufficiently activated towards displacement leading to **9**. Displacement of the 4-fluorine atom from **10a** is less likely since the steric interaction between the 2-pyrrolidine unit and the C=O group result in rotation of the C=O unit out of conjugation with the fluorophenyl ring, which renders the F atom inactive towards displacement. A modified version of this protocol was next investigated in which 1 equiv of pyrrolidine was employed with added K_2CO_3 base (Method 1). Termination of the reaction after ~1 h gave a product from which **10a** (28%) and the desired **11d** (37%) were isolated by column chromatography. Repeating this protocol with benzophenones **8a–c** provided access to the desired 2-substituted 4-pyrrolidinobenzophenones though in each case their formation was accompanied by varying amounts of the 2-pyrrolidino substituted benzophenone **10a** or **10b** and **9** (Scheme 3). The conversion of benzophenones **8f**,**g** to **11f**,**g**, respectively, was particularly sluggish requiring 4 days heating in the presence of DMSO to effect even a mediocre yield of the products (Method 2). Interestingly the formation of **11f** was accompanied by some of the demethylated compound **11e** (19%).



7a X = I, Y = Cl (60%)
7b X = Br, Y = Cl (61%)
7c X = Cl, Y = F
7d X = MeO, Y = Cl

8a X = I, Y = Cl (66%)
8b X = Br, Y = Cl (70%)
8c X = Cl, Y = F (99%)
8d X = Y = F
8e X = OH, Y = Cl (81%)
8f X = MeO, Y = Cl (25%)
8g X = Me, Y = Cl (76%)

(vi)

Reagents: (i) c.HCl, $NaNO_2$, H_2O, 0 °C then either CuBr or KI and heat; (ii) $SOCl_2$, heat; (iii) $AlCl_3$, PhH, heat; (iv) Mg, anhyd. Et_2O, heat; (v) *N*-methoxy-*N*-methylbenzamide, anhyd. Et_2O, heat then aq. HCl; (vi) excess MeI, KOH, DMSO, 40 °C

Scheme 2.