A REGIOSELECTIVE SYNTHESIS OF 6-ARYLAZO-7-HYDROXYCOUMARINS AND 5'-ARYLAZOPSORALENS.

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Abstract: Azocoupling reactions of 7-hydroxycoumarins and psoralens with para-substituted aryldiazonium tetrafluoroborates have been studied in the presence of sodium hydroxide solution. The reaction is highly regioselective to yield only 6-arylazo-7-hydroxycoumarins and 5'-arylazopsoralens. The key step of the reaction is pyrone ring opening which activates positions 6 and 5' of the coumarins and psoralens respectively in electrophilic substitution. Reduction of 6-arylazo-7-hydroxy-4-methyl coumarin provides a convenient route to 6-amino-7-hydroxy-4-methylcoumarin with 70% overall yield.

Introduction

Many 7-hydroxycoumarin derivatives show anticancer [1,2], anticoagulant [3] and antibacterial [4] activities. Some furocoumarins such as 5-methoxypsoralen, 8-methoxypsoralen and 4,8,5'-trimethylpsoralen are currently used in PUVA therapy [5] to treat a variety of skin diseases, such as psoriasis, mycosis fungoides, etc. Therefore, chemical transformations of 7-hydroxycoumarins and furocoumarins are much of interest.

Many electrophilic substitution reactions of 7-hydroxycoumarins, halogenation, nitration, formylation, azocoupling in the presence of weak base as well as Claisen and Fries rearragements yield preferably 8-substituted 7-hydroxycoumarins [6-13]. 6-Substituted derivatives can be prepared by halogenation [14], Claisen rearrangement [15], Elb's oxidation [16] and base-catalysed cyclization of acylmethyl ethers of 7-hydroxycoumarins [17, 18] via the pyrone ring opening step.

Electrophilic substitution reactions of psoralens, e. g. Vilsmeier formylation and chloromethylation result in 4'-substitutied psoralens [19].

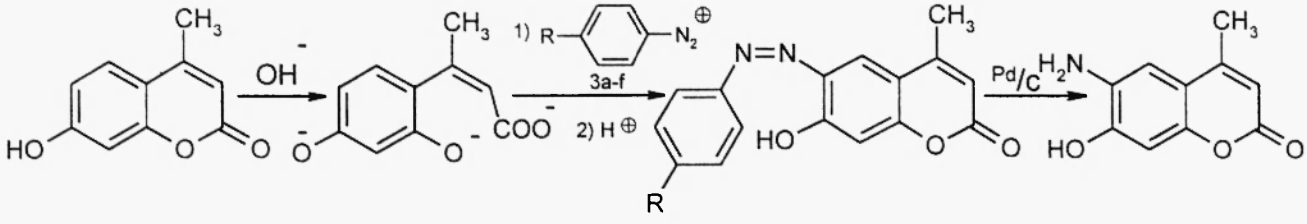
We have studied the azocoupling reaction of 7-hydroxycoumarins and psoralens based on the pyrone ring opening step. Psoralens have not been studied yet in this reaction. Azopsoralens seem to be a new series of biologically active photosensitive compounds.

Results and discussion

We carried out the azocoupling reaction of 7-hydroxy-4-methylcoumarin **1** with several para-substituted aryldiazonium fluoroborates in 5% aqueous sodium hydroxide solution (Scheme 1). The reaction

yields only 6-arylazo-7- hydroxy-4-methylcoumarins **4a-e**. Pyrone ring opening step generates phenoxide anion (Structure **2**) where position 6 is strongly activated. Yields of the reaction depend on substituent in the para-position of aryldiazonium tetrafluoroborate (Table 1).

Scheme 1



1 **2** **4a-f** **5**

Table 1. 6-Arylazocoumarins 4a-f

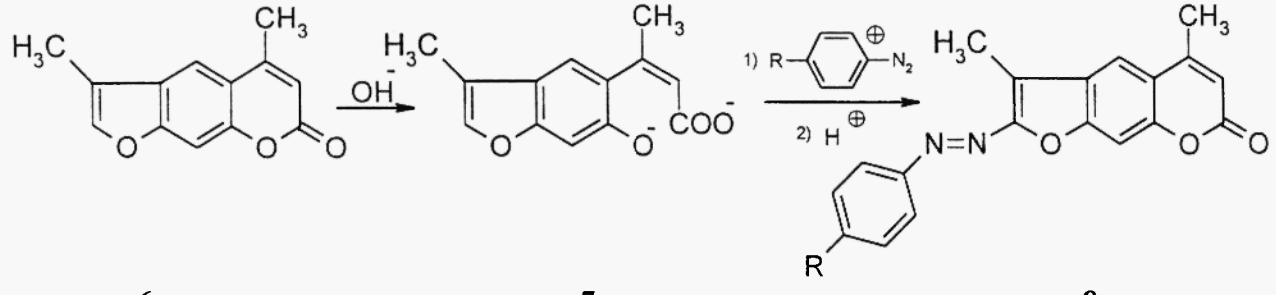
R	H	CH_3	OCH_3	Cl	Br	NO_2
compound	4a	4b	4c	4d	4e	4f
Yield, %	80	80	73	28	25	0

Single peaks at 13.1-13.5 ppm are seen in spectra ^1H NMR of phenylazocoumarins **4a-e** in accordance to their o-hydroxy-azo tautomeric forms.

We have studied effect of pyrone ring opening on azocoupling reaction of psoralens as well. Using psoralen **6** and standard azocoupling reaction procedure, we have synthesized series of 5'-arylazopsoralens **8a-e** with good yields (Table 2). Position 5' seems to be much stronger activated than position 8 under ring opening (Scheme 2).

In accordance to this conclusion, our attempts to carry out azocoupling of psoralens in slightly-acidic or neutral conditions failed and starting psoralen was only recovered.

Scheme 2



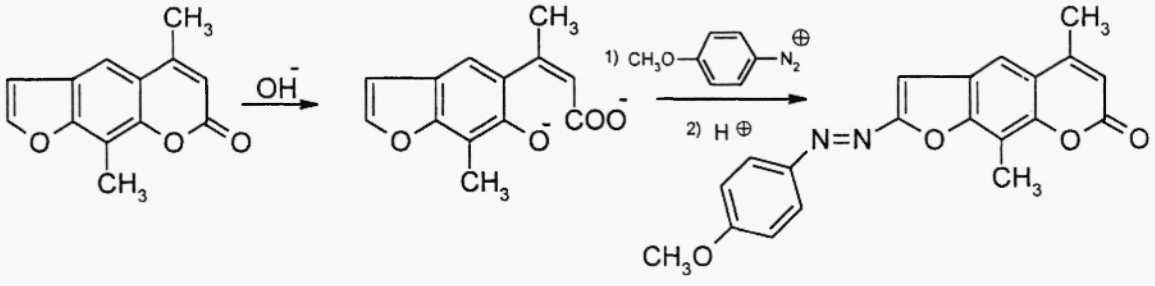
6 **7** **8**

Table 2. Arylazopsoralens 8 a-d

R	H	CH_3	OCH_3	Cl
Compound	8 a	8 b	8 c	8 d
Yield, %	85	82	70	50

We have also compared the effect of pyrone ring opening on reactivity of positions 4' and 5' of psoralen in the azocoupling reaction. Psoralen **9** has been prepared with 30% overall yield by [19]. The azocoupling reaction of psoralen **9** (Scheme 3) in basic conditions starts with pyrone ring opening to produce dianion **10** where position 5' seems to be stronger activated by the phenoxide oxygen group. Azocoupling and acidification steps lead to final product **11** with 75% yield.

Scheme 3



9 **10** **11**

We have used ^1H NMR spectral data to define location of arylazo group in the psoralen **11**. As one can see, introduction of arylazogroup to the position 6 of 4-methyl-7-hydroxycoumarin shifts peak H-5 for 0.7-0.8 ppm down field (Table 3). According to ^1H NMR spectra of compounds **8**, introduction of arylazogroup to the position 5' of 4, 4'-dimethylpsoralen shifts peak H-5 for 0.08-0.17 ppm down field (Table 4).

Table 3. Chemical shifts of proton H-5 in arylazocoumarins 1 and 4a-e

Coumarin	1	4a	4b	4c	4d	4e
R	H	H	CH_3	OCH_3	Cl	Br
H-5	7.38	8.18	8.14	8.10	8.17	8.17
δ**4a-e**-δ**1**	0	0.8	0.76	0.72	0.79	0.79

Table 4. Chemical shift of proton H-5 for set of psoralens 6 and 8a-d

Psoralen	6	8a	8b	8c	8d
R	H	H	CH3	OCH3	Cl
H-5	7.68	7.83	7.76	7.76	7.85
δ8a-d-δ6	-	0.15	0.08	0.08	0.17

Therefore, we can expect peak H-5 in the region 7.75-7.84 ppm both for 4`-arylazo and for 5`-arylazopsoralens. On other hand for 4`-arylazopsoralen, proton H-5' should appears at 8.42-8.50 ppm. In 5`-arylazopsoralen ^{1}H NMR spectrum we can expect peak H-4' at 6.98-7.06 ppm.

Initial psoralen **9** shows peaks of protons H-4', H-5 and H-5' at 6.26, 7.67 and 7.70 ppm respectively. In ^{1}H NMR spectrum of **11** we found two singlets at 7.33 and 7.77 ppm, which correspond to signals H-4` and H-5 peaks respectively. Peak at 7.33 ppm cannot correspond to proton H-5', because it appears in 4,8-dimethylpsoralen **9** at 7.67 ppm and introduction of electronowithdrawing arylazogroup would shift this signal much more down field.

To find synthetic advantages of azocoupling reactions of coumarin derivatives based on the ring opening we reduced azocoumarin **4a** for the amino derivative. Different reductive agents such as zinc powder with HCl, sodium hydrosulfite and hydrogen with 5% Pd on activated carbon catalyst have been used.

Reduction by Zn-HCl in ethanol takes 2-3 hours at 40-45 ^{0}C. Neutralization of the reaction mixture with aqueous ammonia solution gives aminocoumarin **5** with 45% yield.

Reduction of **4a** by sodium hydrosulfite in 20% aqueous ammonia turned to be unsuccessful: it goes slow and provides a poor yield of coumarin **5**.

In opposite, reduction by hydrogen on 5% palladium activated carbon in ethanol takes only 3 hours at 40-45^{0}C and provides aminocoumarin **5** with 85% yield. Earlier coumarin **5** has been prepared with 14% overall yield by nitration of coumarin **1** followed by separation of 6- nitro (28%) and 8-nitro (32%) coumarins and reduction of 6-nitro derivative [17].

Experimental

^{1}H NMR spectra were scanned with 200 MHz Varian Gemini-2000 instrument. Chemical shifts are given in ppm, splitting constants J are given in Hz. Mass spectra were scanned on a SSQ- 710 (Finnigan MAT) spectrometer at the energy of ionizing electrons equals to 70 eV. Thin layer chromatography was done on Silufol UV- 254 sheets with chloroform or chloroform- ethylacetate mixture as eluent. All melting points are uncorrected.

Azocoupling of hydroxycoumarins (general procedure).

A mixture of **1** (10 mmol) and aryldiazonium tetrafluoroborate (12 mmol) with 25 ml 5 % NaOH solution was stirred at 0-5 °C for 2- 4 hours. Then the reaction mixture was acidified with hydrochloric acid to pH=5. Formed precipitate was filtered off and purified by recrystallization from ethanol or by column chromatography (eluent-chloroform, silicagel 100-250 mesh). Yields, melting points and ^{1}H NMR data of prepared coumarins **4a-e** are listed below.

4a, 7-hydroxy-4-methyl-6-(phenylazo)coumarin, yield 80 %, mp 216- 218^{0}C;

^{1}H NMR: δ 2.49(d, 3H, $J_{CH3,\ H3}$=1.2, 4-CH_3); 6.20(q, 1H, $J_{H3,\ CH3}$=1.2 Hz, H-3); 6.91(s, 1H, H-8); 7.50-7.60(m, 3H, 2H-3'+H-4'); 7.90-8.00(m, 2H, H-2'); 8.18(s, 1H, H-5); 13.35(s, 1H, OH).

MS: m/z (%) 280(M^+, 100); 203(-C_6H_5, 35); 175(-$C_6H_5N_2$, 55); 147(-$C_6H_5N_2$, -CO, 20), 119(-$C_6H_5N_2$, -2CO, 45); 91(-$C_6H_5N_2$, -3CO, 20).

4b, 7-hydroxy-4-methyl-6-(p-methylphenylazo)coumarin, yield 80 %, mp 175-177^{0}C;

^{1}H NMR: δ 2.45(s, 3H, CH_3); 2.49(d, 3H, $J_{CH3,3}$=1.0 Hz, 4-CH_3); 6.18(q, 1H, $J_{3,CH3}$=1.0 Hz, H-3); 6.89(s, 1H, H-8); 7.35(d, 2H, $J_{3',2'}$=8.8 Hz, H-3'); 7.77(d, 2H, $J_{2',\ 3'}$=8.8 Hz, H-2'); 8.14(s, 1H, H-5); 13.42(s, 1H, OH).

MS: m/z (%) 294(M^+, 78); 203(-$CH_3C_6H_4$, 18); 175(-$CH_3C_6H_4N_2$, 33); 147(-$CH_3C_6H_4N_2$, -CO, 18), 119(-$C_6H_4N_2$, -2CO, 35); 91(-$C_6H_4N_2$, -3CO, 100).

4c, 7-hydroxy-6-(p-methoxyphenylazo)-4-methylcoumarin, yield 73 %, mp 223-225^{0}C;

^{1}H NMR: δ 2.49(d, 3H, $J_{CH3,\ 3}$=0.8 Hz, 4-CH_3); 3.91(s, 3H, OCH_3); 6.17(q, 1H, $J_{3,\ CH3}$=0.8 Hz, H-3); 6.88(s, 1H, H-8); 7.03(d, 2H, $J_{3',2'}$=8.8 Hz, H-3'); 7.85(d, 2H, $J_{2',3'}$=8.8 Hz, H-2'); 8.10(s, 1H, H-5); 13.39(s, 1H, OH).

MS: m/z (%) 310(M^+, 100); 203(-$CH_3OC_6H_4$, 7); 175(-$CH_3OC_6H_4N_2$, 20); 147(-$CH_3OC_6H_4N_2$, -CO, 7), 119(-$CH_3OC_6H_4N_2$, -2CO, 20); 91(-$CH_3OC_6H_4N_2$, -3CO, 15).

4d, 6-(p-chlorophenylazo)-7-hydroxy-4-methylcoumarin, yield 28 %, mp 240-242^{0}C;

^{1}H NMR: δ 2.50(d, 3H, $J_{CH3,\ 3}$=0.8 Hz, 4-CH_3); 6.21(q, 1H, $J_{3,\ CH3}$=0.8 Hz, H-3); 6.92(s, 1H, H-8); 7.52(d, 2H, $J_{3',2'}$=8.8 Hz, H-3'); 7.84(d, 2H, $J_{2',3'}$=8.8 Hz, H-2'); 8.17(s, 1H, H-5); 13.12(s, 1H, OH).

MS: m/z (%) 316(M^+ ^{37}Cl, 35); 314(M^+ ^{35}Cl,100); 203(-ClC_6H_4, 37); 175(-$ClC_6H_4N_2$, 60); 147(-$ClC_6H_4N_2$, -CO, 26), 119(-$ClC_6H_4N_2$, -2CO, 55); 91(-$ClC_6H_4N_2$, -3CO, 32).

4e, 6-(p-bromophenylazo)-7-hydroxy-4-methylcoumarin, yield 25 %, mp 222-224^{0}C;

^{1}H NMR: δ 2.49(d, 3H, $J_{CH3,\ 3}$=1.0 Hz, 4-CH_3); 6.21(q, 1H, $J_{3,\ CH3}$=0.8 Hz, H-3); 6.91(s, 1H, H-8); 7.64-7.80(m, 4H, H-Ar); 8.17(s, 1H, H-5)); 13.12(s, 1H, OH).

MS: m/z (%) 360(M^+ ^{81}Br, 100); 358(M^+ ^{79}Br,92); 203(-BrC_6H_4, 48); 175(-$BrC_6H_4N_2$, 91); 147 -$BrC_6H_4N_2$, -CO, 33), 119(-$BrC_6H_4N_2$, -2CO, 68); 91(-$BrC_6H_4N_2$, -3CO, 45).

Azocoupling of psoralens (general procedure).

10 mmol of psoralen **6** were dissolved in minimal amount of hot ethanol. The solution was mixed with 20 ml 5 % aqueous NaOH solution (avoid ppt formation), cooled to 0-5^{0}C. Then 15 mmol of aryldiazonium tetrafluoroborate was added to the prepared solution. Resulted reaction mixture was stirred at 0-5^{0}C for 2-4 hours with TLC test (eluent-chloroform) and was then acidified with diluted aqueous HCl solution. Formed precipitate was filtered and purified by recrystallization from ethanol or by column chromatography (eluent-chloroform, silicagel 100/250 mesh). Yields, melting points and ^{1}H NMR data of prepared psoralens **8a-d** and **11** are listed below.

8a, 4, 4'-dimethyl-5'-phenylazopsoralen, yield 85 %, mp 180-182 °C;
^{1}H NMR ($CDCl_3$, J/Hz): δ 2.53(s, 3H, 4-CH_3); 2.73(s, 3H, 4'-CH_3); 6.28(s, 1H, H-3); 7.47(s, 1H, H-8); 7.5(m, Hpara); 7.5(m, Hmeta); 7.83(s, 1H, 5-CH_3); 7.98(m, Hortho).
MS: m/z(%) 318(M^+ , 100).

8b, 4, 4'-dimethyl-5'-(p-methylphenylazo)psoralen, yield 82 %, mp 228-230 °C;
^{1}H NMR ($CDCl_3$, J/Hz): 2.42(s, 3H, 4'-CH_3); 2.49(d, 3H, $J_{CH3,3}$=1.0, 4-CH_3); 2.67(s, 3H, p-CH_3); 6.23(q, 1H, $J_{3,CH3}$=1.0, H-3); 7.28(d, 2H, $J_{m,o}$=8.8, Hortho); 7.45(s, 1H, H-8); 7.761(s, 1H, H-5); 7.85(d, 2H, $J_{o,m}$=8.8, Hmeta).
MS: m/z(%) 332(M^+ , 100).

8c, 4, 4'-dimethyl-5'-(p-methoxyphenylazo)psoralen, yield 70 %, mp 206-207 °C;
^{1}H NMR ($CDCl_3$, J/Hz): 2.50(d, 3H, $J_{CH3,3}$=1.0, 4-CH_3); 2.66(s, 3H, 4'-CH_3); 3.89(s, 3H, OCH_3); 6.24(q, 1H, $J_{3,CH3}$=1.0, H-3); 6.99(d, 2H, $J_{m,o}$=9.0, Hmeta); 7.46(s, 1H, H-8); 7.758(s, 1H, H-5); 7.95(d, 2H, $J_{o,m}$=9.0, Hortho).
MS: m/z(%) 348(M^+ ,100).

8d, 5'-(p-chlorophenylazo)-4,4'-dimethylpsoralen, yield 50 %, mp 167-168 °C;
^{1}H NMR ($CDCl_3$, J/Hz): 2.54(d, 3H, $J_{CH3,3}$=1.0, 4-CH_3); 2.73(s, 3H, 4'-CH_3); 6.30(q, 1H, $J_{3,CH3}$=1.0); 7.48(d, 2H, $J_{m,o}$=8.8, Hmeta); 7.50(s, 1H, H-8); 7.85(s, 1H, H-5); 7.93(d, 2H, $J_{o,m}$=8.8, Hortho).
MS: m/z(%) 352(M^+ , 100).

MS: m/z(%) 352(M^+ , 100).

11, 4, 8-dimethyl-5`-(p-methoxyphenylazo)psoralen, yield 75 %, mp 192-193 °C;

^{1}H NMR ($CDCl_3$, J/Hz): 2.52(d, 3H, $J_{CH3,3}$=1.0, 4-CH_3); 2.69(s, 3H, 8-CH_3); 3.92(s, 3H, OCH_3): 6.29(q, 1H, $J_{3,CH3}$=1.0, H-3); 7.03(d, 2H, $J_{m,o}$=8.0, Hmeta); 7.34(s, 1H, H-4`); 7.77(s, 1H, H-5); 7.98(d, 2H, $J_{o,m}$=8.0, Hortho);.

MS: m/z(%) 348(M^+ , 100).

Reduction of arylazocoumarins 4a.

A mixture of 400mg **4a** and 50 mg of 5% Pd/C in minimal amount of ethanol was heated to 45^{0}C. Hydrogen gas has been passed through the stirred reaction mixture for 3 hours until the solution becomes light green. Then the reaction mixture was filtered and ethanol was evaporated from filtrate. Remained solid mass was recrystallized from ethanol to produce light green crystals. 6-amino-7-hydroxy-4-methylcoumarin **5**, yield 85%, mp 251-253^{0}C;

^{1}H NMR: 2.26(s, 3H, CH_3); 5.95(s, 1H, H-3); 6.56(s, 1H, H-8); 5.90(s, 1H, H-5).

MS: m/z(%) 191(M^+ , 100).

Conclusion

The pyrone ring opening step has been used for regioselective synthesis of 6-arylazo-7-hydroxycoumarins **4** and 5'-arylazopsoralens **8** and **11**.

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