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A SHORT SYNTHESIS OF A THIENYL ANALOGUE OF UNDECYLPRODIGIOSIN

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ABSTRACT- The photochemical coupling between 4,5-diiodopyrrole-2-carbaldehyde and thiophene gave 4-iodo-5-(2-thienyl)pyrrole-2-carbaldehyde. Dehalogenation reaction and the coupling of the product with undecylpyrrole gave an analogue of undecylprodigiosin, an immunosuppressive drug.

The discovery of the immunosuppresant cyclosporyn A has revolutionised the field of organ transplant.[1] However, cyclosporin A is not very potent in reducing chronic rejections and shows several important undesirable side effects, in particular renal toxicity and frequent association with B cell lymphomas.[2] The study on new immunosuppressive agents involves the search of new compounds showing a different mechanism of action and cellular target than cyclosporin A. Undecylprodigiosin (**1**) is a red pigment produced by *Streptomyces*[3,4] and has been shown to have immunosupressive activity through inhibition of the proliferation of T lymphocytes.[5-8]

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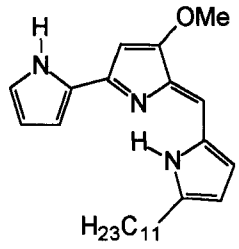
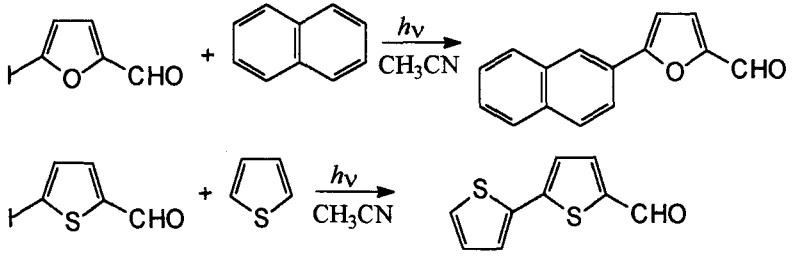


1

In this paper we want to report a simple approach to the synthesis of a thienyl analogue of undecylprodigosin. This work represents an application of the previous reported photochemical arylation of furan and thiophene derivatives (Scheme 1).[9,10]

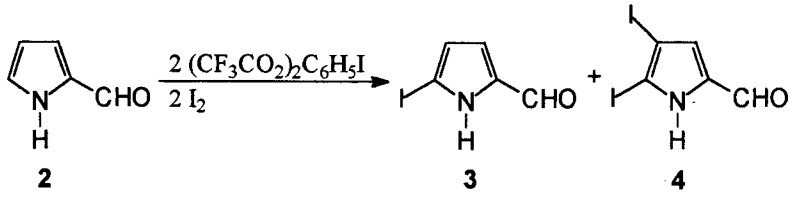
Scheme 1



Recently we showed that bis(trifluoroacetoxy)iodobenzene in the presence of iodine[11] conveniently iodinates thiophene derivatives.[12] This reagent, used with pyrrole-2-carbaldehyde (**2**), gave 5-iodopyrrole-2-carbaldehyde (**3**), while, by using an excess of the reagent, the major product was 4,5-diiodopyrrole-2-carbaldehyde (**4**) (Scheme 2).

The compound **4** showed absorptions in the UV spectrum at 211 nm (log ε 3.54), 255 nm (log ε 3.68), and 299 nm (log ε 3.71). While 5-iodopyrrole-2-carbaldehyde showed no photochemical reaction when irradiated in the presence

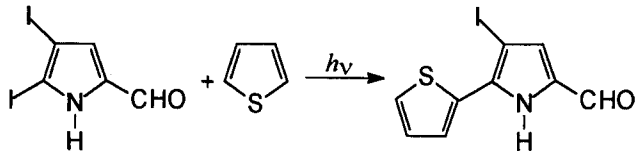
Scheme 2



2 3 4

of an aromatic compound, the irradiation of 4,5-diiodopyrrole-2-carbaldehyde (**4**) in thiophene gave the corresponding arylation product (**5**) in 78% yield (Scheme 3).

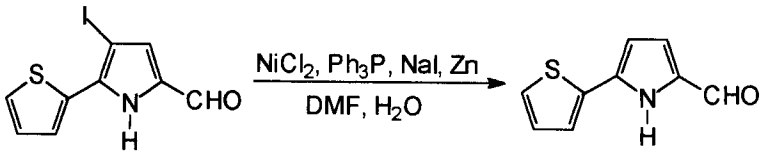
Scheme 3



4 5

Compound **5** can be transformed into the corresponding deiodination product **6** through a reaction with a reagent prepared starting from $NiCl_2$, Ph_3P, NaI, and zinc (Scheme 4).[13] In our knowledge, this is the first synthetic application of this method, and it seems to work well in deiodination of heterocyclic derivatives.

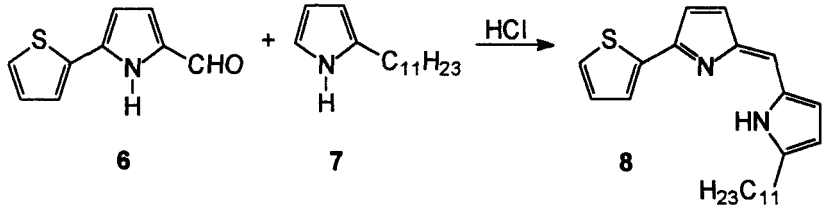
Scheme 4



5 6

The coupling of compound **6** with undecylpyrrole (**7**)[14] under acidic condition gave in good yields a thienyl analogue of undecylprodigiosin (**8**) (Scheme 5).

Scheme 5



6 **7** **8**

This is the first synthesis of heterocyclic analogues of the biological active undecylprodigiosin. The evaluation of the biological properties of this compound will be the object of our work in the near future.

Experimental

4,5-Diiodopyrrole-2-carbaldehyde (4) – A solution of pyrrole-2-carbaldehyde (176 mg) in CCl_4 (3 ml) was treated with iodine (495 mg) and bis(trifluoroacetoxy)iodobenzene (843 mg). The mixture was stirred for 24r h after which it was extracted with ether. The extract was washed with 0.1 M aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and evaporated to yield a crude product that was chromatographed on silica gel. Elution with hexane-EtOAc (8:2) gave 5-iodopyrrole-2-carbaldehyde (**3**) (43 mg, 10%) and 4,5-diiodopyrrole-2-carbaldehyde (**4**) (200 mg, 31%). Compound **3**: mp 93-94 °C (lit.[13] 94 °C); ^{1}H-NMR ($CDCl_3$) δ: 9.47 (s, 1 H), 7.19 (d, 1 H, J = 3 Hz), and 7.08 ppm (d, 1 H, J = 3 Hz); MS, *m/z*: 221 (100%), 220 (28), 192 (24), 127 (27), 65 (18), 39 (15), and

38 (18). Compound **4**: mp 175-176 °C (lit.,[15] 176 °C); ^{1}H-NMR ($CDCl_3$) δ: 9.26 (s, 1 H) and 6.97 ppm (s, 1 H); MS, *m/z*: 347 (100%), 346 (27), 254 (10), 191 (16), 165 (28), 164 (23), 127 (45), 65 (18), 64 (14), 38 (15), and 37 (13).

4-Iodo-5-(2-thienyl)pyrrole-2-carbaldehyde (5) – A solution of 4,5-diiodopyrrole-2-carbaldehyde (54 mg) in thiophene (10 ml) was flushed with nitrogen for 1 h. The mixture was then irradiated with a 125-W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket. After 6 h, the mixture was diluted with ether, washed with 0.1 M aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and evaporated to yield a crude product which was chromatographed on silica gel. Elution with hexane-Et_2O (1:1) gave pure 4-iodo-5-(2-thienyl)pyrrole-2-carbaldehyde (37 mg, 78%) as a very dense oil. Anal: Found: C, 35.5; H, 2.2; N, 4.5. Calc. For C_9H_6IONS: C, 35.65; H, 2.00; N, 4.62%; ^{1}H-NMR ($CDCl_3$) δ: 9.45 (s, 1 H), 7.61 (dd, 1 H, J_1 = 4 Hz, J_2 = 1 Hz), 7.44 (dd, 1 H, J_1 = 5 Hz, J_2 = 1 Hz), 7.16 (m, 1 H), and 7.07 ppm (m, 1 H); MS, *m/z*: 304 (12%), 303 (100), 302 (20), 148 (11), 147 (11), 121 (19), and 120 (19).

5-(2-thienyl)pyrrole-2-carbaldehyde (6) – A two-necked flask equipped with a magnetic stirring bar was charged with $NiCl_2$ (2.1 mg, 0.089 mmol), Ph_3P (13 mg, 0.051 mmol), NaI (9.0 mg, 0.060 mmol), and zinc powder (18 mg, 0.27 mmol). The flask was flushed with nitrogen. Nitrogen-purged DMF – H_2O 25:1 (0.3 ml) was then introduced. The mixture was stirred for 40 min at 50-60 °C to form a green-brown catalyst. A solution of 4-iodo-5-(2-thienyl)pyrrole-2-carbaldehyde

(54 mg, 0.178 mmol) in DMF – H_2O (25:1) (0.5 ml) was then added and reacted for about 20 h. The mixture was diluted with ether, washed with 0.1 M aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated to yield a crude product which was chromatographed on silica gel. Elution with *n*-hexane – Et_2O (1:1) gave pure 5-(2-thienyl)pyrrole-2-carbaldehyde (20 mg, 63%). Anal: Found: C, 61.2; H, 4.0; N, 7.8. Calc. For C_9H_7ONS: C, 61.00; H, 3.98; N, 7.90%; ^1H NMR ($CDCl_3$) δ: 9.48 (s, 1 H), 7.42 (d, 1 H, J = 4.8 Hz), 7.34 (d, 1 H, J = 7.6 Hz), 7.10 (d, 1 H, J = 7.6 Hz), 7.00 (dd, 1 H, J_1 = 4.8 Hz, J_2 = 2 Hz), and 6.50 ppm (d, 1 H, J = 2 Hz); MS, *m/z*: 178 (14%), 177 (100), 176 (56), 148 (16), 121 (48).

5-[5-(2-thienyl)-2-(2H-pyrrolyl)methylene]-2-*n*-undecylpyrrole (8) – A solution of 2-*n*-undecylpyrrole (38 mg, 0.17 mmol) in ethanol (3.5 ml) was added to 5-(2-thienyl)pyrrole-2-carbaldehyde (15 mg, 0.085 mmol) dissolved in warm ethanol (5 ml). Upon dropwise addition of 6 drops of conc. hydrochloric acid the solution turned deep red. The stirred solution was allowed to stand at room temperature for 28 h. The reaction mixture was diluted with 50 ml of water and extracted with CH_2Cl_2. The organic extract was washed with 1 N NaOH and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was taken up in petroleum ether and applied to a column of basic alumina (Brockman activity 1). Elution with petroleum ether – chloroform gave 16 mg of pure compound **8** (49%). Anal: Found: C, 75.6; H, 8.6; N, 7.5. Calcd for $C_{24}H_{32}N_2S$: C, 75.74; H, 8.47; N, 7.36%. ^1H NMR ($CDCl_3$) δ: 7.93 (s, 1 H), 7.54 (dd, 1 H, J_1 = 5 Hz, J_2 = 3 Hz), 7.27 (s, 1 H), 7.16 (dd, 1 H, J_1 = 5 Hz, J_2 = 2 Hz), 7.04 (m, 1 H), 6.82 (m, 1

H), 6.68 (dd, 1 H, J_1 = 5 Hz, J_2 = 2 Hz), 6.15 (dd, 1 H, J_1 = 5 Hz, J_2 = 3 Hz), 5.95 (m, 1 H), 2.60 (t, 2 H, J = 7 Hz), 1.30 (s, 18 H), 0.87 (t, 3 H).

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