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Photochemical Synthesis of Dipyrrylmethane Derivatives

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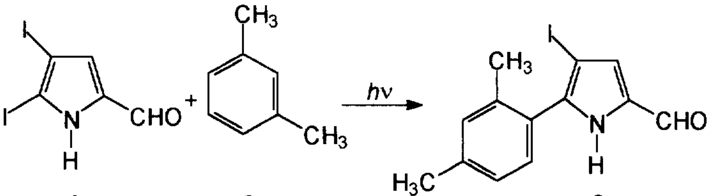
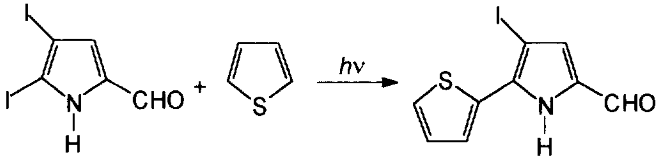
Abstract - The irradiation of aromatic and heteroaromatic aldehydes in the presence of pyrrole gave the corresponding dipyrryl derivatives in good yields. The reaction mechanism is discussed on the basis of the previous reported hypotheses on similar reactions by using indole. We showed that the most probably mechanism involves the presence of an electron transfer process between pyrrole, the donor, and the triplet of the aromatic aldehyde, the acceptor.

Recently we found that the previous reported reactivity of halofuran and halothiophene derivatives with aromatic and heteroaromatic compounds to give the corresponding arylation product can be extended to pyrrole derivatives.[1-3] This way, 4,5-diiodopyrrole-2-carbaldehyde (**1**) can be converted into the corresponding 5-aryl derivative by reaction with aromatic (such as **2**) or heteroaromatic compounds (such as **4**).

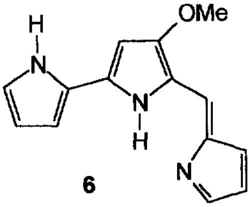


1 **2** **3**



1 **4** **5**

In this context, we attempted the photochemical coupling between 4,5-diiodopyrrole-2-carbaldehyde (**1**) and pyrrole in order to obtain an efficient synthetic method for the preparation of compounds strictly related to prodigiosin (**6**).[4,5]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Results and Discussion

The irradiation of **1** in the presence of pyrrole gave unexpectedly the tripyrrylmethane derivative **8** (Scheme 1, Table 1). The structure was assigned on the basis of its spectroscopic properties. ^{1}H NMR spectrum showed pyrrolic signals a 7.99, 6.63, 6.18 and 6.06 ppm while the peak related to CH is at 5.55 ppm. The ^{13}C NMR spectrum showed the pyrrolic signals at 131.2, 117.3, 108.5, and 106.7 ppm and the methine at 37.4 ppm. Finally, MS spectrum showed the molecular peak at 211 *m/z*, in agreement with the proposed structure. The obtained product did not show any iodine substitents. Probably, the product lost the iodine atoms through a homolytic fission after the disappearance of the carbonyl group. In fact, the presence of the carbonyl group at C-2 prevents the homolytic cleavage of the C-I bond at C-4 in similar compounds.[1,2]

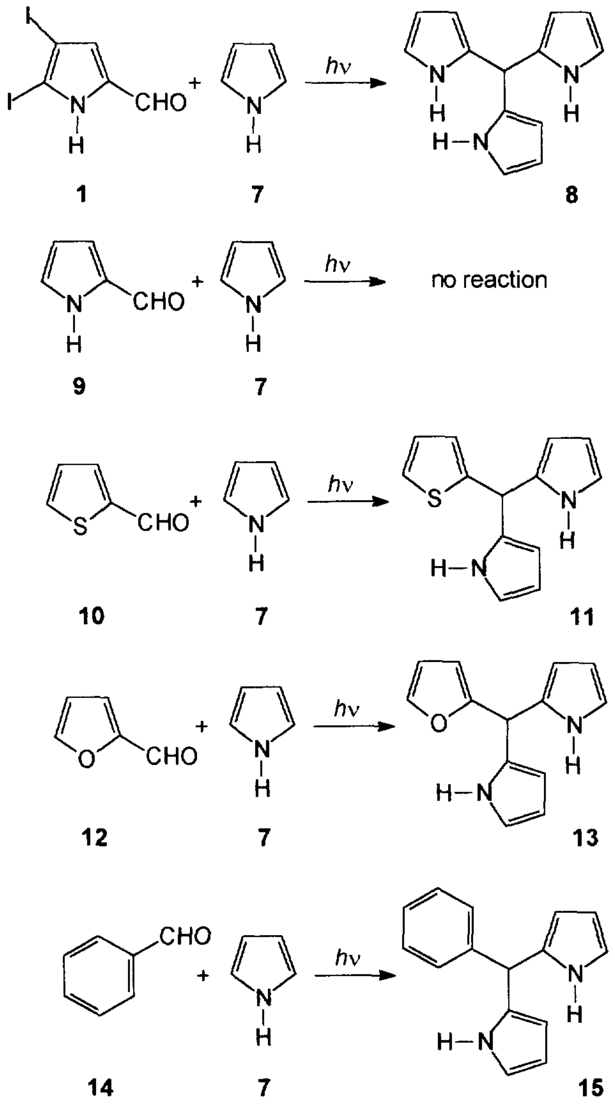
Table 1 - Photochemical reaction between aromatic aldehydes and pyrrole.

Entry	Aldehyde	Irradiation time (h)	Product	Yields (%)[a]
1	4,5-Diiodopyrrole-2-carbaldehyde	3	**8**	93
2	Pyrrole-2-carbaldehyde	9	-	-
3	Thiophene-2-carbaldehyde	9	**11**	59
4	Furan-2-carbaldehyde	8.5	**13**	63
5	Benzaldehyde	9	**15**	50

a) All the yields refer to isolated chromatographically pure compounds.

We attempted some other reactions in order to test the capability of pyrrole to react with other aromatic or heteroaromatic aldehydes. The results are reported in Scheme 1 and Table 1. When we used pyrrole-2-carbaldehyde (**9**) as starting material we did not observe any reaction at all. On the contrary, both thiophene-2-carbaldehyde (**10**) and furan-2-carbaldehyde (**12**) gave the corresponding dipyrrylmethane derivatives **11** and **13**, respectively. This type of reactivity was not restricted to heteroaromatic aldehydes. In fact, also benzaldehyde gave the corresponding dipyrrylmethane derivative **15**. This type of compounds can be obtained also by acid catalysed reaction of aromatic aldehydes with pyrrole.[6]

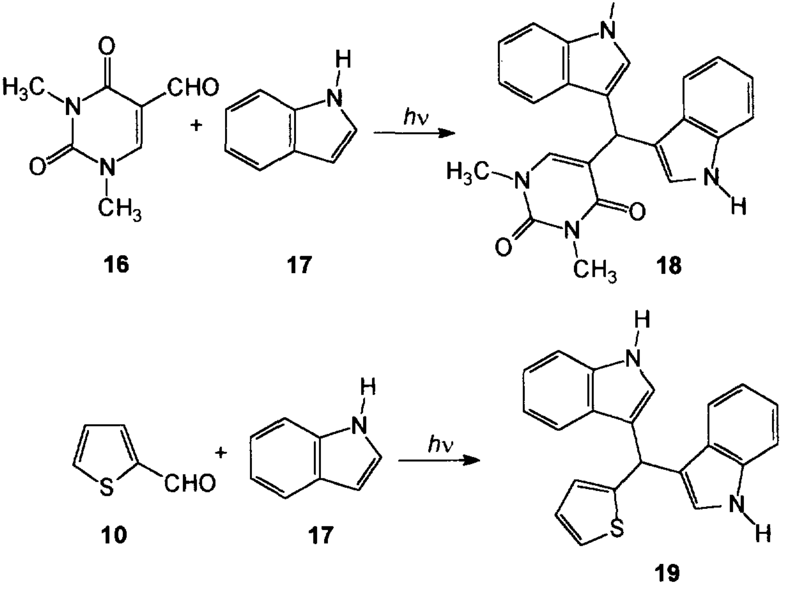
Scheme 1



The above described reactivity is very similar to that reported for indole. The photochemical reaction of indole with aromatic aldehydes has been described to give the corresponding diindolylmethane derivatives (Scheme 2).[7,8]

Two different mechanisms have been proposed. In the first (A) a 2+2 cycloaddition reaction beween the carbonyl group and the double bond C_2-C_3 of indole was the key step of the reaction followed by the cleavage of

Scheme 2



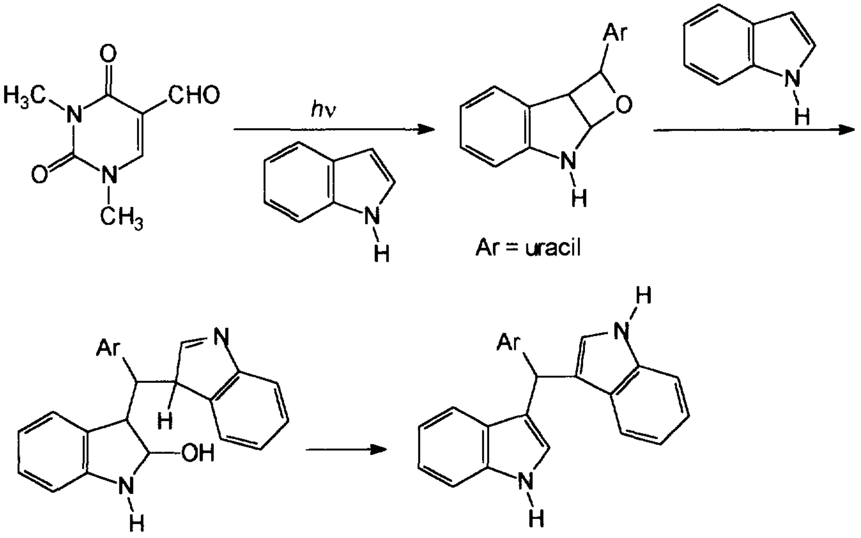
16 **17** **18**

10 **17** **19**

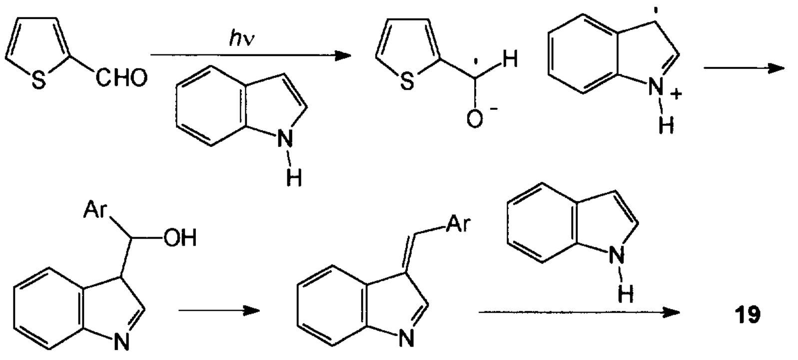
the resulting oxiethane through a nucleophilic attack of indole (Scheme 3). The second proposed mechanism (B) involves an electron transfer process followed by radical coupling. The resulting adduct lose water to give an electrophilic alkylideneindolenine which acts as electrophile towards a second molecule of the indole (Scheme 3).

Scheme 3

Hypothesis A



Hypothesis B

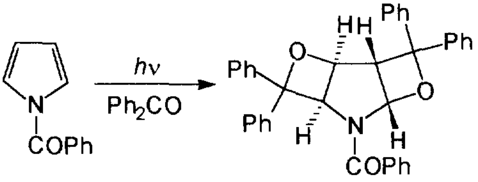


Ar = 2-thienyl

We decided to test these two mechanistic hypotheses on the basis of the above described results. In particular we wanted to verify whether one of the above described hypotheses was able to explain the reactivity of pyrrole and whether one of the mechanisms was able to explain the different behaviour showed by pyrrole and thiophene (the first gave a dipyrrylmethane derivative when it reacted with **1** while the second gave the arylation product).

The Paternò-Buchi reaction was the key step in the hypothesis A. This reaction has been described also for the reactions of carbonyl compounds with pyrrole derivatives. *N*-Benzoylpyrrole gave compound **20** when irradiated in benzene in the presence of benzophenone.[9] The authors reported that the benzoyl group was the only substituent able to give this reaction. Successively, they reported that also *N*-phenylpyrrole gave the reaction affording the carbinol **21**.[10] The authors reported that other substituents did not give interesting results. However, some years later, also pyrrole and *N*-methylpyrrole were described to give the corresponding alcohols if irradiated in the presence of carbonyl compounds.[11,12] It was interesting to note that a completely different regiochemical behaviour was observed. NMR evidences are in agreement with the previous formation of an oxiethane as intermediate in these reaction.

Here it is interesting to note that pyrrole can give the Paternò-Buchi reaction but this reaction does not give our observed products. In order to verify this statement, we carried out the photochemical reaction between thiophene-2-carbaldehyde and pyrrole in acetonitrile, using experimental conditions very similar to those reported in Ref. 11 and 12. We obtained compound **11** but only in 25% yield. Then, it seems very unusual that we was not able to have products similar to those described before, if the key step of the reaction was a Paternò-Buchi cycloaddition. Furthermore, the Paternò-Buchi reaction can occur from both the excited singlet (S_1) or triplet (T_1) state of the carbonyl compound.[13] In some cases, and in particular in the reaction of carbonyl compounds with pyrrole, the singlet excited state of the aliphatic carbonyl compound seems to be responsible for these reactions.[14] 4,5-Diodopyrrole-2-carbaldehyde did not show any fluorescence in agreement with a quantitative intersystem crossing to the lowest excited triplet state. In this case, then, the reaction has to occur from the T_1 state of the carbonyl compounds in contrast with previous reported data.



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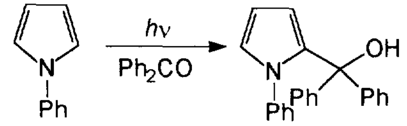

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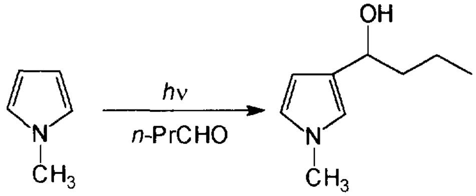
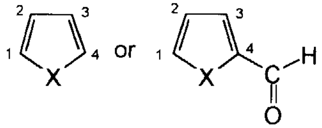


Assuming the reaction to occur from the T_1 state of the carbonyl compound, the reaction can be explained assuming an interaction between the lowest SOMO of the triplet carbonyl compound and the HOMO of the pyrrole.[15] We calculate these orbitals by using a semiempirical method (PM3) for 4,5-diiodopyrrole-2-carbaldehyde, thiophene-2-carbaldehyde, pyrrole, and thiophene. The results are reported in Table 2. Also in this case, the most important interaction between the frontier orbitals is between the LSOMO of the carbonyl compound and the HOMO of the heterocyclic compound (thiophene and pyrrole). However, while the LSOMO of thiophene-2-carbaldehyde is an *n* orbital mainly localized on the oxygen, the LSOMO of **1** is a π orbital mainly localized on the aromatic ring, and we can not wait for a similar reactivity. Furthermore, the Paternò-Buchi reaction occurs through the interaction between the oxygen of the carbonyl group with the carbon atom with the nearest value of the electronic coefficient. In this case, considering the reaction between thiophene-2-carbaldehyde and pyrrole, oxygen has to make a link with C-1 or C-4 of pyrrole in agreement with the regiochemistry observed by Jones for this type of reaction. In contrast, this behaviour is not in agreement with our observed reactivity.

Table 2 - Frontier orbitals for suitable compounds.



Compound	LSOMO (eV)	HSOMO (eV)	HOMO (eV)	Electronic Coefficients									
				C-1			C-2	C-3	C-4	C	O		
				Pz	Px	Py	Pz	Pz	Pz	Pz	Pz	Px	Py
Thiophene			- 9.53199	- 0.01	0	0	0.58	0.58	-0.01				
Pyrrole			- 8.99214	0.63	0	0	0.31	- 0.31	- 0.63				
Thiophene-2-carbaldehyde	- 7.58139			0	- 0.01	- 0.04	0	0	0	0	0	- 0.65	- 0.52
		- 3.79889		- 0.42	0	0	- 0.06	0.39	- 0.09	- 0.61	0.37	0	0
4,5-Diiodopyrrole-2-carbaldehyde	- 6.47864			0.35	0	0	0.34	- 0.02	- 0.39	- 0.06	0.19	0	0
		- 3.49773		0	0.23	- 0.39	0	0	0	0	0	- 0.01	- 0.03

In conclusion, there are some adverse considerations against a mechanism involving the presence of a 2+2 cycloadditon key step in the reaction between carbonyl compounds and pyrrole.

Considering the second mechanistic hypothesis, the capability of the reagents to give a monoelectron transfer process can be estimated by using the Weller equation (1).

$$\Delta G = F\left[E^{Ox}_{\frac{1}{2}}(D) - E^{Red}_{\frac{1}{2}}(A)\right] - \Delta E_{excit} + \frac{e^2 N}{4\pi\varepsilon_0 a}\left(\frac{1}{\varepsilon} - \frac{2}{37.5}\right) \qquad (1)$$

We decided to test two different processes: the photochemical reaction of benzaldehyde with pyrrole to give the corresponding dipyrrylmethane derivative and the reaction between benzaldehyde and thiophene that does not occur. Benzaldehyde shows a triplet energy (E_T) of 301 kJ mol^{-1}.[16] We obtained the oxidation potential of thiophene via cyclic voltammetry showing an oxidation potential of 1.890 V *vs* SCE in acetonitrile in the presence of $NaClO_4$, while for pyrrole a value of 0.46 V was reported in the literature.[17] The reduction potential of benzaldehyde was 1.85 V.[18] Finally, the dielectric constants for thiophene and pyrrole were 2.76 and 7.48, respectively.[19] This way, for the first process studied (the reaction between pyrrole and benzaldehyde) we obtained ΔG = - 0.46 eV in agreement with the presence of an electron trasfer process in the reaction, while for the reaction between thiophene and benzaldehyde we obtained ΔG = 1.26 eV in agreement with the experimental results (the reaction does not work). Finally, the electron transfer mechanism allows us to explain the total failure of the reaction between pyrrole-2-carbaldehyde and pyrrole. The reduction potential of pyrrole-2-carbaldehyde can be assumed to be - 1.96 V.[20] We calculate the triplet energy of this molecule using PM3 semi empirical method obtaining a value of 60 kcal mol^{-1}. Thus, we obtained ΔG = - 0.01 eV in agreement with the absence of an efficient electron transfer process.

In conclusion, we have shown that a previous described reaction for the indole can be extended to pyrrole. The discussion of the previous reported mechanisms shows that the electron transfer process is the most likely, being able to explain the different reactivity observed between different heterocycles.

Experimental

Mass spectra were obtained with a Hewlett-Packard 5971 mass selective detector on a Hewlett-Packard 5890 gaschromatograph. Gas-chromatographic analyses were obtained by using an OV-1 capillary column between 70 - 250 °C (20 °C/min). Alternatively mass spectra were obtained at 70 eV with a Kratos MS-80 instrument by direct insertion at a source temperature of 150 °C. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 AM instrument.

Voltammograms were obtained on an Amel Model 472 (Amel, Milano, Italy) polarograph equipped with a potentiostatic control, allowing potential scan rates up to 200 mV s^{-1}. As stationary working electrode the Metrohm 6.0302.000 platinum electrode was used, while a mercury pool was used as the counter electrode. Finally, potential values were referred to an Ag, AgCl/$LiCl_{sat}$ (in acetonitrile) reference electrode whose potential value *vs* the aqueous SCE is - 124 mV (at 27°C). The experiments were carried out in acetonitrile containing $NaClO_4$ (0.114 M) as supporting electrolyte. The experiments were performed at room temperature (from 25 to 28°C) on 25 ml of the solution. The solutions to be processed were first bubbled with nitrogen for a few seconds, and then a nitrogen atmosphere was maintained above the solution in order to prevent contact with air.

Photochemical reaction of aromatic aldehydes in the presence of pyrrole - General procedure.

4,5-Diiodopyrrole-2-carbaldehyde (72 mg) was dissolved in fresh distilled pyrrole (10 ml) and the solution was outgassed with nitrogen for 1 h. The mixture was then irradiated with a 125 W high pressure mercury arc (Helios Italquartz) sorrounded by a Pyrex water jacket. After 3 h, the mixture was diluted in diethyl ether, washed with 0.1 M $Na_2S_2O_3$, and dried (Na_2SO_4) (this work-up was not carried out with substrates which did not contain iodine). The removal of the solvent yielded a crude product that was chromatographed on silica gel. The elution with *n*-hexane - EtOAc 1:1 gave pure *tri-(2-pyrryl)methane* (**8**) (41 mg, 93%). ^{1}H NMR ($CDCl_3$) δ: 7.99 (s, 3 H), 6.63 (d, 3 H, J = 6 Hz), 6.18 (dd, 3 H, J_1 = 3 Hz, J_2 = 6 Hz), 6.06 (d, 3 H, J = 3 Hz), and 5.55 ppm (s, 1 H). ^{13}C NMR ($CDCl_3$) δ: 131.18, 117.31, 108.54, 106.74, and 37.36 ppm. MS, *m/z*: 212 (15%), 211 (100), 210 (50), 146 (37), 145 (34), 144 (30), and 117 (16).

Di-(2-pyrryl)-(2-thienyl)methane (**11**). ^{1}H NMR ($CDCl_3$) δ: 8.08 (s, 2 H), 7.22 (m, 1 H), 6.96 (m, 1 H), 6.90 (m, 1 H), 6.72 (m, 2 H), 6.18 (m, 2 H), 6.05 (m, 2 H), and 5.75 ppm (s, 1 H). MS, *m/z*: 230 (6%), 229 (17), 228 (100), 227 (42), 162 (48), 161 (35), 160 (32), 145 (29), 144 (16), 143 (12), 117 (17), 116 (8), 91 (14), and 89 (11).

Di-(2-pyrryl)-(2-furyl)methane (**13**). ^{1}H NMR ($CDCl_3$) δ: 8.10 (s, 2 H), 7.42 (m, 1 H), 6.70 (m, 2 H), 6.36 (m, 1 H), 6.18 (m, 3 H), 6.02 (m, 2 H), and 5.52 ppm (s, 1 H). MS, *m/z*: 213 (15%), 212 (100), 211 (28), 183 (27), 182 (11), 154 (10), 146 (39), 145 (18), 117 (44), 91 (20), 90 (10), and 89 (10).

Di-(2-pyrryl)-toluene (**15**). ^{1}H NMR ($CDCl_3$) δ: 7.95 (s, 1 H), 7.77 (s, 1 H), 7.4-7.2 (m, 5 H), 7.22 (m, 2 H), 6.70 (m, 1 H), 6.16 (m, 1 H), 5.88 (m, 1 H), 5.78 (m, 1 H), and 5.40 ppm (s, 1 H). MS, *m/z*: 223 (17%), 222 (100), 221 (37), 156 (37), 155 (14), 154 (29), 145 (79), 143 (11), 128 (11), 127 (10), and 117 (11).

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