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PHOTOCHEMICAL SYNTHESIS OF DIINDOLYLMETHANES

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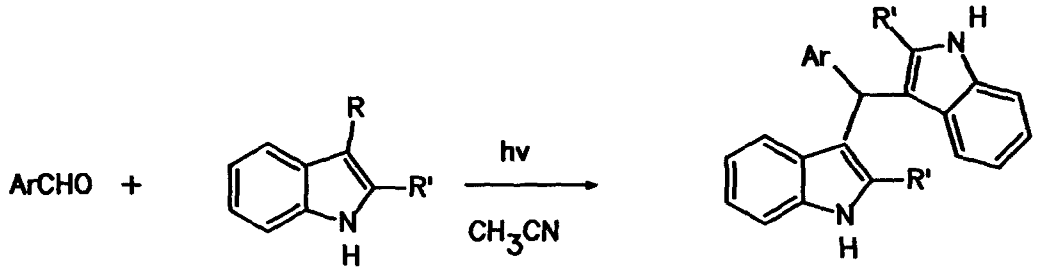
Summary - *The photochemical reaction of an aromatic aldehyde with indole or 2-methylindole gave 3,3'-diindolylmethanes in ca. 50% yield. A mechanism involving a single electron transfer process is proposed.*

Recently we have reported that irradiation of halofuran and halothienyl derivatives in the presence of arylalkenes gave the corresponding substitution products on the alkene [1] This type of reaction can be extended to cyclic vinyl compounds such as indene[2] or benzofuran[1]. In all the cases, we observed the formation of substitution products on the alkene moiety. In this communication we want to report the unusual reactivity observed when the same reaction was performed by using indole as "alkene".

Literature data on photochemical behaviour of indole are not clear While, with thermally generated benzyl radical, reaction in 2 and 3 positions of indole is described,[3] photoinduced Friedel-Crafts reaction with methyl chloroacetate gave a mixture of indoleacetic acid derivatives where 3- and 4-substituted compounds are the major components [4] This behaviour was confirmed by reaction of 2-methylindole with acrylonitrile that furnished comparable amounts of 3- and 4-substituted compounds [5] On the contrary, indole can react with 2-bromomaleic anhydride in 2-position.[6] Furthermore the only datum available on the photochemical interaction of indole with carbonyl compounds shows that no product was formed even though the molecule can quench triplet acetone through the formation of an adduct in its 2-position [7] Therefore, on the basis of previous works, we could not predict whether the reaction could occur on the C-halogen bond or on the carbonyl group; furthermore, we could not predict which position of indole could react with our substrate



1 2 3

5-Iodothiophene-2-carbaldehyde **1** was irradiated in the presence of indole **2** in acetonitrile for 6 h Column chromatography gave a single product that showed spectroscopic properties consistent with the formation of **3** (Table 1)

Considering that the C-I bond was not reactive in the described conversion, we have tested thereaction on thiophene-2-carbaldehyde (entry 2) and then on some other aromatic aldehydes, such as 5-methylthiophene-2- carbaldehyde (entry 5), furan-2-carbaldehyde (entries 6 and 7), and benzaldehyde (entries 8 and 9). in all the experiments we obtained the compound **3** in yields around 50% with the exception of 5-methylthiophene-2- carbaldehyde The exact position of indole substitution was determined using substituted indole derivatives: while 3-methylindole (entry 3) was completely unreactive under our photochemical conditions, 2-methylindole (entries 4, 7 and 8) gave the same type of products, showing that the reaction occurred in ß-position of indole

Up to date, we have found the carbonyl group did not participate in photochemical reactions between halothienyl derivatives and aromatic compounds, now we observe a new reaction where the carbonyl group attacks indole; furthermore, we observed the formation of products deriving from the attack in 3-position of the indole and we did not observe formation of both 2-substituted[7] and 4-substituted[4,5] products

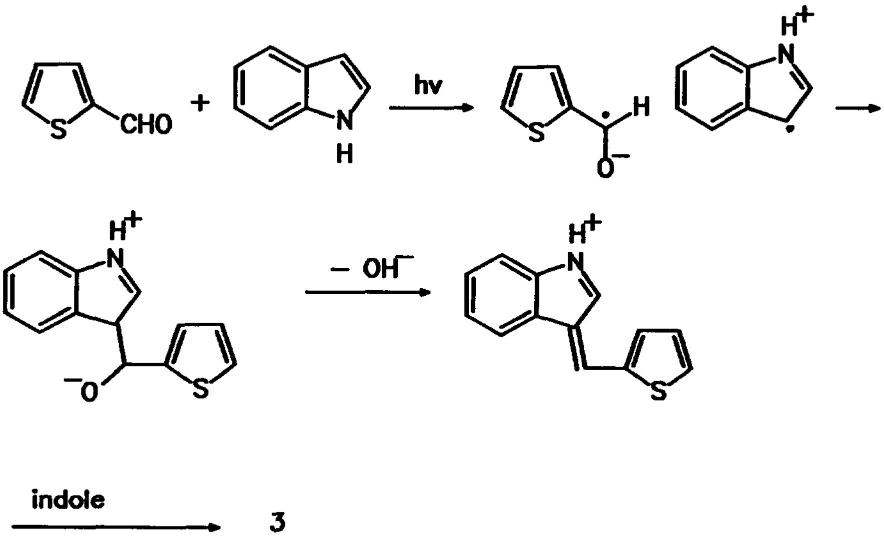
Compounds **3** can also be prepared by reaction of aldehydes with indole in acidic media [8,9] This is the first reported method to obtain **3** in neutral conditions The proposed mechanism for the reaction of aromatic aldehydes with indole in acid involves the formation of 3-indolylcarbinols that subsequently lose water to give an electrophilic alkylideneindolenine which acts as electrophile towards a second molecule of the indole The same situation can be obtained in our conditions through a monoelectron transfer process (Scheme 1)

Table 1 - Photochemical reaction of arylaldehydes with indole derivatives

Entry	Aldehyde Ar	Indole R	 R'	Product	Yield (%)[a]
1	5-Iodo-2-thienyl	H	H	**3a**	48
2	2-Thienyl	H	H	**3b**	50
3	2-Thienyl	CH_3	H	-	-
4	2-Thienyl	H	CH_3	**3c**	47
5	5-Methyl-2-thienyl	H	H	**3d**	30
6	2-Furyl	H	H	**3e**	52
7	2-Furyl	H	CH_3	**3f**	50
8	Phenyl	H	H	**3g**	48
9	Phenyl	H	CH_3	**3h**	47

a) All yields refer to isolated chromatographically pure compounds

SCHEME 1



ΔG value for electron transfer process can be evaluated using Weller equation.[10] 5-Iodothiophene-2-carbaldehyde shows E_T = 60 Kcal mol^{-1} and E^{red} = - 0 66 V.[1] E^{Ox} for indole can be estimated to be 0 94 V (vs. SCE) from the empirical relationship between ionization potential (IP) and E^{Ox}.[11] IP of indole is 7.76 eV [12] On the basis of these data a ΔG value of - 1.06 eV is then obtained in agreement with the proposed mechanism.

Experimental

^{1}H and ^{13}C-NMR were recorded with a Varian Gemini 200 instrument using $CDCl_3$ as solvent IR spectra were obtained on a Perkin-Elmer 457 spectrometer. Mass spectra were obtained with a Hewlett-Packard 5971A mass selective detector connected with a Hewlett-Packard 5890 gas chromatographic instrument and with a Hewlett-Packard 9000 central processor

Starting materials

All the compounds were commercialy available The only synthetized substrate was 5-iodothiophene-2-carbaldehyde. This compound was obtained from thiophene-2-carbaldehyde through reduction with $NaBH_4$, iodination of the corresponding alcohol with iodine and HgO, and subsequent oxidation of 5-iodothiophene-2-methanol with PCC (pyridinium chlorochromate)[13]

Synthesis of diindolylmethanes - General procedure

The aldehyde **1** (2 mmoles) was dissolved in acetonitrile (300 ml) in the presence of the indole **2** (25 mmoles) The solution was degassed with nitrogen for 1 h The mixture was then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket After 6 h, the solvent was evaporated and the crude product was chromatographed on SiO_2. Elution with *n*-hexane/ethyl acetate 4:1 gave pure **3**

Di-3-indolyl-2-(5-iodothienyl)methane 3a - ^{1}H-NMR ($CDCl_3$) δ· 7.97 (s, 1 H), 7.45 (d, 1 H, J = 8 Hz), 7.32 (d, 1 H, J = 8 Hz), 7 17 (dd, 1 H, J_1 = J_2 = 8 Hz), 7.02 (m, 0.5 H), 6.77 (m, 1 H), 6.56 (dd, 0 5 H, J_1 = 2 Hz, J_2 = 0.5 Hz), 6.10 (s, 0 5 H), ^{13}C-NMR ($CDCl_3$) δ : 155.52, 137.11, 136.96, 128.88, 127 37, 127.08, 123 80, 122.62, 120.13, 119 95, 119 38, 111 74, 71 42, MS (*m/z*)· 454 (M^+, 1.2), 339 (12), 212 (4), 135 (7), 117 (100%); IR ($CHCl_3$) ν_{max}: 3480, 1455, 1413, 1355, 1340, 1095, 1013, 945 cm^{-1}

Di-3-indolyl-2-thienylmethane 3b - ^{1}H-NMR ($CDCl_3$) δ: 7.79 (s, 1 H), 7.48 (d, 1 H, J = 8 Hz), 7.32 (d, 1 H, J = 8 Hz), 7 19 (dd, 1 H, J_1 = J_2 = 8 Hz), 7 15 (m, 0 5 H), 7.05 (dd, 1 H, J_1 = J_2 = 8 Hz), 6 91 (m, 1 H), 6.76 (d, 1 H, J = 2 Hz), 6 16 (s, 0 5 H), ^{13}C-NMR ($CDCl_3$) δ· 143.82, 131.72, 125 25, 121 87, 121.52, 120.24, 118.70, 118 27, 117 10, 114 85, 114.45, 106 17, 30 16, MS (*m/z*) 328 (M^+, 1), 117 (100%), IR ($CHCl_3$) ν_{max}: 3490, 1460, 1418, 1360, 1345, 1100, 1020 cm^{-1}

Di-(2-methyl-3-indolyl)-2-thienylmethane 3c - ^{1}H-NMR (acetone-d_6) δ: 9 88 (s, 1 H), 7 24 (d, 1 H, J = 9 Hz), 7.24 (m, 0 5 H), 7 05 (d, 1 H, J = 8 Hz), 6 92 (m, 1 5 H), 6 75 (m, 1.5 H), 6 22 (s, 0 5 H), 2 83 (s, 3 H), MS (*m/z*)· 356 (M^+, 1 2), 121 (100%).

Di-3-indolyl-(5-methyl-2-thienyl)methane 3d - ^{1}H-NMR ($CDCl_3$) δ. 7.90 (s, 1 H), 7 61 (d, 1 H, J = 8 Hz), 7 29 (m, 2 H), 7 16 (m, 1 H), 6.76 (m, 1.5 H), 6 66 (d, 0.5 H, J = 1 Hz), 6.17 (s, 0.5 H), 2.48 (s, 1.5 H); MS (*m/z*): 342 (M^+, 1 4), 117 (100%)

Di-3-indolyl-2-furylmethane 3e - ^{1}H-NMR ($CDCl_3$) δ: 7 74 (s, 1 H), 7 51 (d, 1 H, J = 8 Hz), 7.36 (d, 0 5 H, J = 2 Hz), 7.28 (d, 1 H, J = 8 Hz), 7 16 (dd, 1 H, J_1 = J_2 = 8 Hz), 7.10 (dd, 1 H, J_1 = J_2 = 8 Hz), 6.75 (s, 1 H), 6 31 (dd, 0.5 H, J_1 = 3 Hz, J_2 = 2 Hz), 6 07 (d, 0.5 H, J = 3 Hz), 5.95 (s, 0.5 H); MS (*m/z*) 312 (M^+, 1), 117 (100%), IR ($CHCl_3$) ν_{max} 3480, 1455, 1412, 1355, 1335, 1150, 1140, 1125, 1090, 1010, 910 cm^{-1}

Di-(2-methyl-3-indolyl)-2-furylmethane 3f - ^{1}H-NMR ($CDCl_3$) δ 7 78 (s, 1 H), 7.39 (d, 0 5 H, J = 2 Hz), 7 20 (d, 1 H, J = 8 Hz), 7 05 (d, 1 H, J = (Hz), 7.03 (dd, 1 H, J_1 = J_2 = 8 Hz), 6.89 (dd, 1 H, J_1 = J_2 = 8 Hz), 6 29 (dd, 0 5 H, J_1 = 3 Hz, J_2 = 2 Hz), 5.88 (m, 1 H), 2.15 (s, 3 H); MS (*m/z*) 340 (M^+, 2), 121 (100%); IR ($CHCl_3$) ν_{max}· 3480, 1615, 1460, 1300, 1110, 910 cm^{-1}

Di-3-indolyltoluene 3g - ^{1}H-NMR ($CDCl_3$) δ 7 67 (s, 1 H), 7.42 (d, 1 H, J = 8 Hz), 7.35 - 7.25 (m, 3 5 H), 7 19 (dd, 1 H, $J_1 = J_2 =$ 8 Hz), 7 03 (dd, 1 H, $J_1 = J_2 =$ 8 Hz), 6 54 (s, 1 H), 5.89 (s, 0.5 H); MS (*m/z*) 322 (M^+, 2), 117 (100%); IR ($CHCl_3$) ν_{max} 3480 cm^{-1}

Di-(2-methyl-3-indolyl)toluene 3h - ^{1}H-NMR ($CDCl_3$) δ: 8.22 (s, 1 H), 7.43 (d, 1 H, J = 8 Hz), 7.37 (d, 1 H, J = 8 Hz), 7.3 - 7 1 (m, 2 5 H), 7 05 (dd, 1 H, $J_1 = J_2 =$ 8 Hz), 6 95 (dd, 1 H, $J_1 = J_2 =$ 8 Hz), 6 13 (s, 0.5 H), 2 30 (s, 3 H); MS (*m/z*)· 350 (M^+, 2), 121 (100%), IR ($CHCl_3$) ν_{max}: 3480 cm^{-1}

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