PHOTOCHEMICAL REACTIVITY OF HALOFURAN AND HALOTHIOPHENE DERIVATIVES WITH BENZIMIDAZOLE

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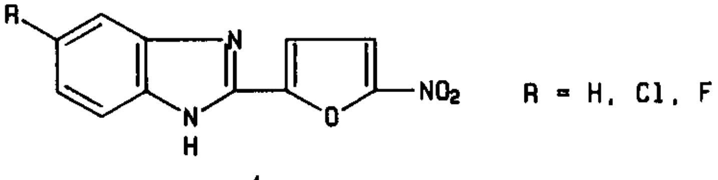
Abstract - A photochemical approach to the synthesis of 5-(4-benzimidazolyl)-2-thiophene and 2-furan derivatives is described.

Recently antileukemic activity against Murine P_{388} of 2-furylbenzimidazoles (**1**) was described:[1] these compounds showed to inhibit the DNA synthesis of P_{388} cells at dose almost coinciding with its DL_{50}.



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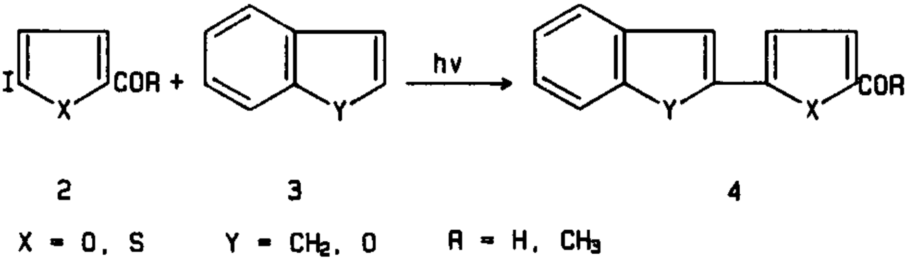
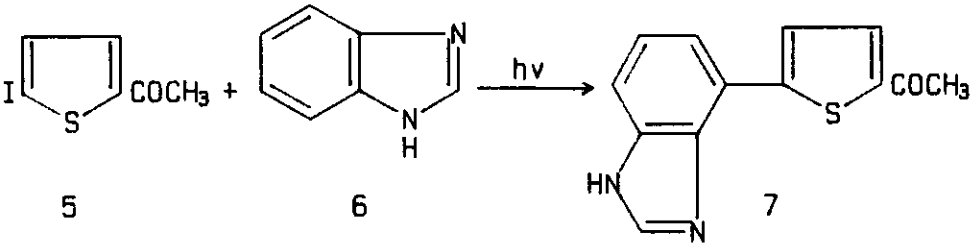
In previous papers we described the photochemical coupling of halofuran and halothiophene derivatives (**2**) with indene and benzofuran (**3**) to give **4**.[2,3]



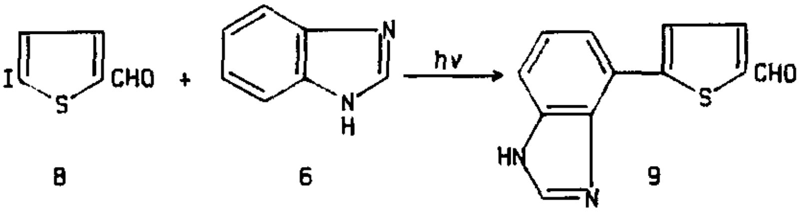
In order to test the capability of the above described photochemical procedure with other benzo-compounds, we carried out the irradiation of halothiophene derivatives with benzimidazole: this reaction could be a new way to synthesize analogues of **1**.

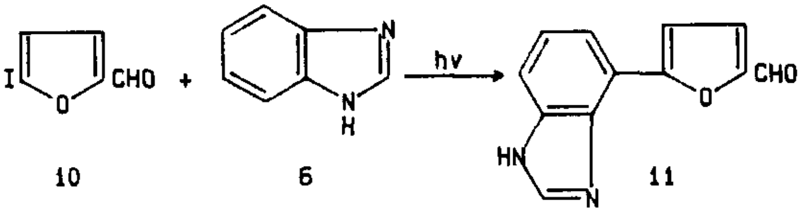
The irradiation of 2-acetyl-5-iodothiophene (**5**) (0.5 g, 2.1 mmol) in the presence of benzimidazole (**6**) (3 g, 25 mmol) in acetonitrile (300 ml) in an immersion apparatus with a 500 W high pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket for 6 h gave the product (**7**) (52%).

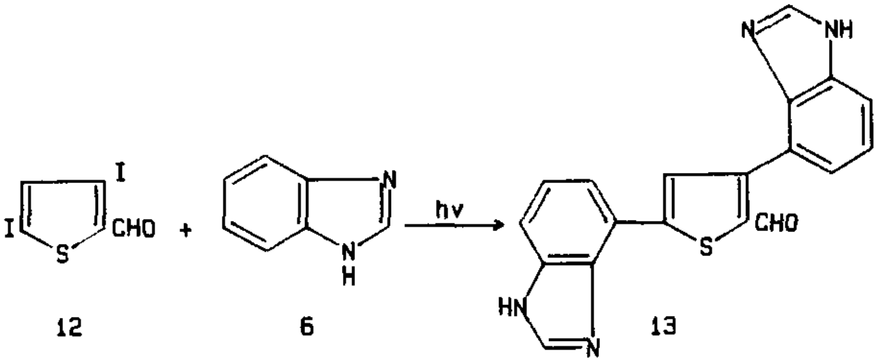


^{1}H-Nmr spectrum (CD_3OD) of **7** showed a singlet at δ 8.11 (1 H, N-C$\underline{H}$=N), a singlet at δ 7.70 (2 H, thienyl protons), a multiplet at δ 7.51 (2 H, aromatic protons), a doublet of doublet at δ 7.26 (1 H, $J_1 = J_2 = 8$ Hz) and a singlet at δ 2.54 (3 H, $COCH_3$). These data are in a full agreement with the proposed structure.

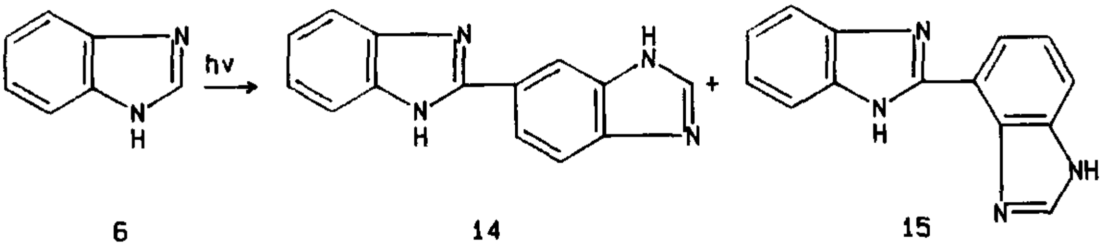
This behaviour was confirmed by the reaction of benzimidazole with 5-iodothiophene-2-carbaldehyde (**8**) to give **9** (48%), 5-iodofuran-2-carbaldehyde (**10**) to give **11** (40%), and by the reaction of **6** with 3,5-diiodothiophene-2-carbaldehyde (**12**) to give **13** (30%).







It is noteworthy that the only photochemical reaction on benzimidazole is the photodehydrodimerization to give **14** and **15**.[4,5]



Our results represents the first report on the photochemical behaviour of benzimidazole in the presence of other molecules. Furthermore, we observed an enhanced regioselectivity: while **6** attacks benzimidazole both in α and β position, we observed only the formation of the product deriving from α-attack on the benzenic ring of benzimidazole. It is noteworthy that the presence of an aza-group on the pentatomic aromatic ring inhibits the reactivity observed by using indene or benzofuran as substrate. This behaviour can be explained considering that imidazole ring is worse electrondonor molecule than, i.e., furan (see below). On the contrary, we can not explain why α position of benzimidazole is more reactive than β position in these reactions.

The conversion **8** + **6** $\longrightarrow$ **9** *can be explained in term of monoelectron* transfer process. ΔG Value for this type of photochemical events can be evaluated using the Weller equation.[6] 5-Iodothiophene-2-carbaldehyde shows E_T = 60 Kcal mol^{-1} and $E_{1/2}^{Red}$ = - 0.66 V.[3] $E_{1/2}^{Ox}$ for benzimidazole can be estimated to be 1.45 V (vs. SCE) from the empirical relationship between ionization potential (IP) and $E_{1/2}^{Ox}$.[7] IP for benzimidazole is 8.31 eV.[8] On the basis of these data, a ΔG value of - 0.55 eV is then obtained in agreement with the proposed mechanism.

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