

Photocoupling between Haloheterocyclic Derivatives and Arylalkenes and Arylalkynes: Instruments to Predict Reactivity

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Parameters useful to predict reactivity and regiochemical control of photocoupling reactions between haloheterocyclic derivatives and arylalkenes or arylalkynes have been studied. Electrochemical properties of arylalkenes and arylalkynes are shown to be useful to predict the reactivity of the substrates. However, oxidation potentials fail as reactivity indices if very fast photochemical processes are in competition with the observed complex formation between substrates and halogen atoms. The regiochemical behavior of the reaction can be estimated on the basis of dipoles of the reagents. In this case the assumptions that a reagent approaches the other on parallel planes and that the prevalent interaction is between the SOMO of the radical and the LUMO of the other reagent have been accepted.

In previous papers we reported that both 5-iodofuran-2-carbaldehyde (**1a**) and 5-iodothiophene-2-carbaldehyde (**1b**) reacted with arylalkenes **2** to give the corresponding coupling products (Scheme 1).¹ In this case we observed the formation of the product deriving from the attack of the haloheterocyclic derivatives on the alkene to give a *cis-trans* mixture of **3**. While the reaction did not show the same selectivity when a methyl group is present on the molecule in α position on the alkene,² this type of reaction worked very well when the substrate had an alkyl group in the β position on the alkene to give **5** (Scheme 1).³ It is noteworthy that this type of compound showed interesting photochemical and photobiological properties.^{4,5} However, if an electron-withdrawing group was present on the molecule, such as in **6**, the expected photocoupling reaction did not occur and dimerization of the starting material was detected (Scheme 1).^{6,7} On the contrary, if a weak electron-withdrawing group was present on the substrate, the photocoupling reaction did occur. However, while using 2-ethynylthiophene as substrate, a photocoupling reaction occurred on the alkene; in this case only coupling on the thiophene ring was observed (Scheme 1).⁸

The same reactions were observed when alkynes were used as substrates. In this case 2-ethynylthiophene (**10b**) gave a mixture of regioisomeric products **11** and **12** deriving from the attack of the haloheterocyclic derivatives on the alkyne and on the thienyl ring, respectively (Scheme 1).¹ The formation of this mixture can be avoided by using a protected compound, such as **13** (Scheme 1).⁹ However, the use of [5-(trimethylsilyl)-2-

thienyl]acetylene as substrate in order to obtain selective photoarylation product failed because the trimethylsilyl group was removed under photochemical conditions. Selective photoarylation could be obtained using ethynyl derivatives substituted with a weak electron-withdrawing group, such as in **15** (Scheme 1).⁸

In this paper we report our efforts devoted to explain this complex scheme of reactivity. In particular we explain the reasons governing the regiochemical behavior of the above described reactions.

Results and Discussion

Recently we obtained interesting results on the mechanism of a photoarylation reaction (Scheme 2).¹⁰ Excitation of the substrate gave a n,π^* triplet state, but this excited state is unable to give dissociation of the carbon-iodine bond. This assumption was demonstrated considering that, if this n,π^* triplet state was sensitized by chrysene, it did not produce coupling products. Then, probably the reaction occurred in an excited σ,σ^* triplet state mainly localized on the carbon-iodine bond.

Furthermore, the interaction between this triplet state of the substrate and aromatic compounds led to the homolytic cleavage of C-I bond with the formation of both radical **17** and a complex between the aromatic compound and halogen atom. The formation of this complex was demonstrated by the presence of a short-lived transient with $\lambda_{\max} = 510$ nm, showing a second-order decay kinetics and a half-life of ca. 0.4 μ s in laser flash photolysis. The thienyl radical thus formed reacted rapidly with the aromatic compound to form the corresponding arylation product.

The capability of the aromatic compounds used to give the observed complex can be estimated on the basis of their $E_{1/2}^{ox}$. For example, we were not able to isolate any coupling product using nitrobenzene, benzonitrile, and methyl benzoate as a partner of **1**. This behavior can be understood by considering the electrochemical properties of nitrobenzene,¹¹ benzonitrile,¹² and methyl benzoate.¹³

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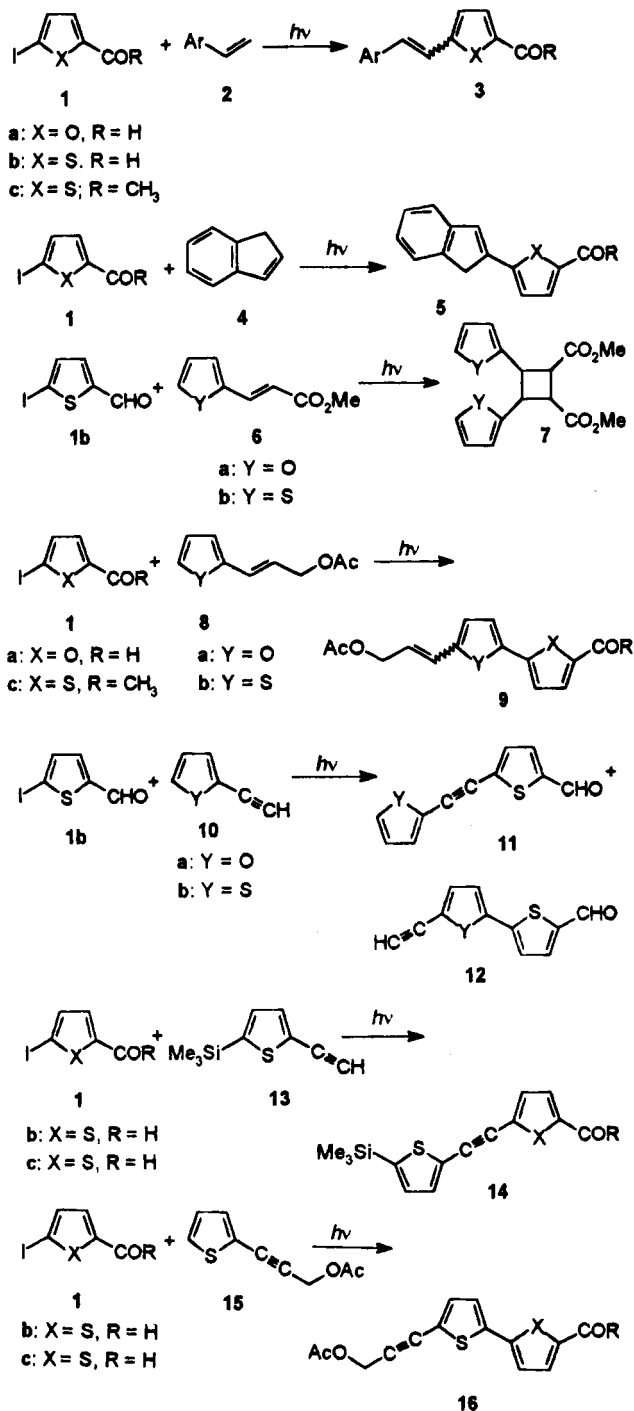
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Scheme 1



These data showed that they could not be donors in an electron transfer process. This behavior clearly was due to the presence of a strong electron-withdrawing group on the aromatic ring. We determined oxidation potentials of some arylalkenes and arylalkynes in order to obtain useful information about the reactivity of these molecules. Oxidation potentials were determined in acetonitrile with sodium perchlorate as supporting electrolyte. In this medium, selected compounds showed an anodic signal whose peak potentials versus the adopted

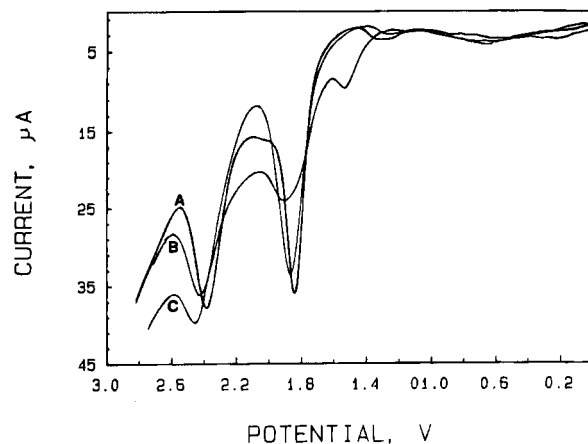
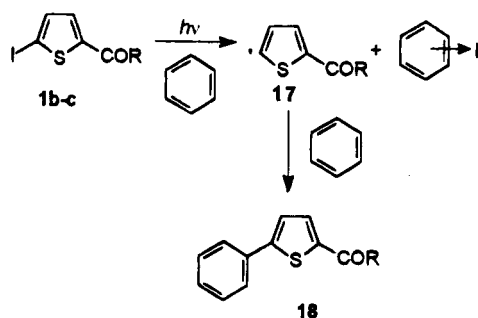


Figure 1. Voltammograms of 3-(2-thienyl)allylic alcohol (B), 2-(3-acetoxy-1-propenyl)thiophene (A), and 2-(3-acetoxy-1-propynyl)thiophene (C).

Table 1. Oxidation Potentials of Thienyl Derivatives

entry	substrate	E_1 (mV)
1	2-ethynylthiophene	1890
2	methyl 3-(2-furyl)acrylate	1710
3	3-(2-thienyl)allylic alcohol	1905
4	2-(3-acetoxy-1-propenyl)thiophene	1845
5	2-(3-acetoxy-1-propynyl)thiophene	1870

Scheme 2



reference electrode are collected in Table 1. The voltammograms of 3-(2-thienyl)allylic alcohol (B), 2-(3-acetoxy-1-propenyl)thiophene (A), and 2-(3-acetoxy-1-propynyl)thiophene (C) are reported in Figure 1.

The results reported in Table 1 clearly show that all of the compounds tested are very similar for their electrochemical properties. These data can be considered to be in agreement with the experimental results. In particular, entries 1, 4, and 5 clearly show that 2-ethynylthiophene, 2-(3-acetoxy-1-propenyl)thiophene, and the corresponding alkyne should have the same reactivity, and this expectation is in good agreement with experimental results.^{1,8} On the contrary, entries 2 and 3 relate to compounds that did not give any photocoupling reaction. In fact, as reported before, methyl 3-(2-furyl)acrylate gave a dimerization reaction,⁶ while 3-(2-thienyl)allylic alcohol gave photoreduction of the carbonyl compounds.⁸ Nevertheless, the different reactivity is probably due to kinetic factors: two competitive processes inhibit electron transfer process. In the case of methyl 3-(2-furyl)acrylate a very fast energy transfer occurs between **1** and **6** followed by the subsequent dimerization of the triplet state of **6**,⁷ while, in the case of 3-(2-thienyl)allylic alcohol, hydrogen abstraction from the alcohol quenches transient radical species.⁸

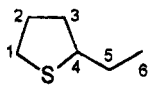
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Table 2. HOMO and LUMO of Selected Compounds

compound	HOMO (eV)	LUMO (eV)
2-ethenylthiophene	-8.89	-0.24
2-ethynylthiophene	-9.16	-0.27
2-(3-acetoxy-1-propenyl)thiophene	-8.85	-0.38

Table 3. HOMO and LUMO Coefficients for Selected Molecules


compound	orbital	S	C-1	C-2	C-3	C-4	C-5	C-6
2-ethenylthiophene	HOMO	0.18	-0.47	-0.31	0.28	0.49	-0.31	-0.47
	LUMO	-0.39	0.47	-0.20	-0.38	0.46	0.26	-0.40
2-ethynylthiophene	HOMO	0.23	-0.50	-0.38	0.23	0.53	-0.23	-0.41
	LUMO	-0.41	0.50	-0.22	-0.39	0.49	0.18	-0.33
2-(3-acetoxy-1-propenyl)thiophene	HOMO	-0.17	0.45	0.28	-0.29	-0.46	0.30	0.48
	LUMO	-0.38	0.03	-0.18	-0.39	0.44	0.28	-0.43

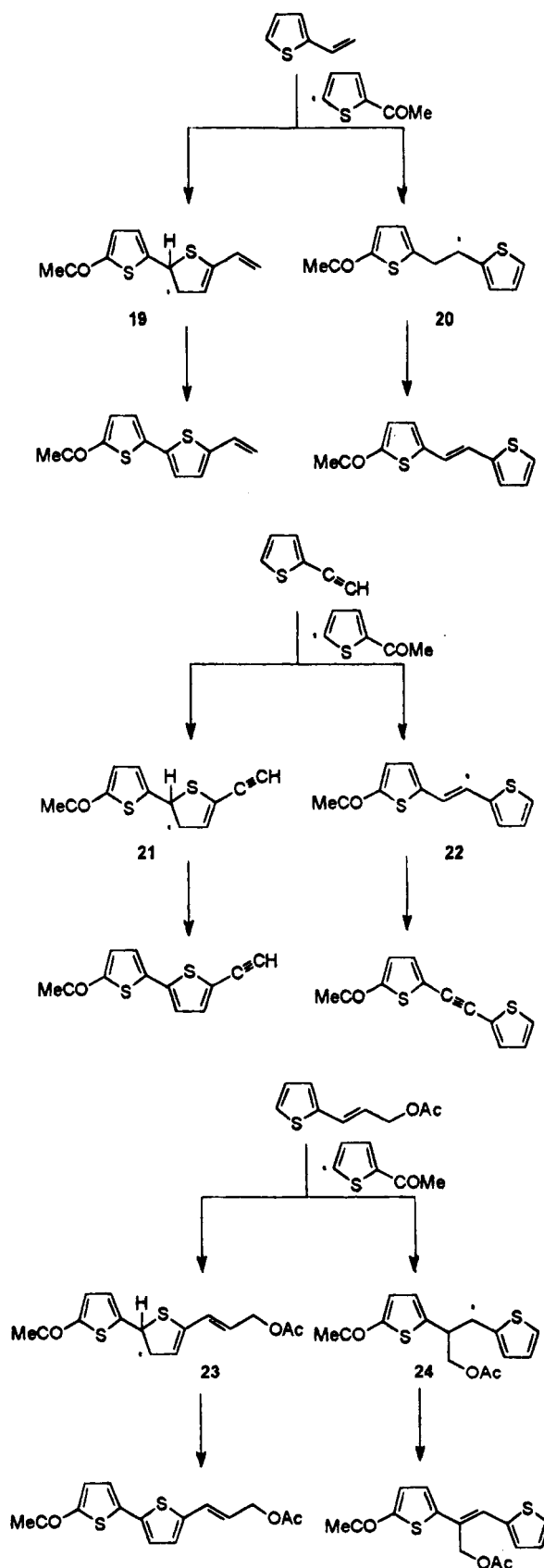
Thus, the observed trend in the oxidation potentials of arylalkenes and arylalkynes used in the coupling reactions can account for the observed reactivity. Nevertheless, they do not account for the reactivity of the substrates where competitive processes are possible. Furthermore, no information about the regiochemical behavior of these reactions (i.e. the different regiochemical behavior observed in the products deriving from **10b** and **8b**) was obtained by using this method.

Because the homolytic cleavage of the carbon-iodine bond is the key step of the reaction, the interaction between the SOMO of the electrophilic radical thus formed and the HOMO of arylalkenes and arylalkynes can be studied. We have estimated the HOMO and LUMO energies for some compounds by using the AM1 semiempirical method, and the results are collected in Table 2.^{14,15} We used for the calculations compounds showing a very different regiochemical behavior, as described before. The energy of the HOMO for selected molecules allows us to explain the observed reactivity. The HOMO energies are quite similar for all the compounds that can give the coupling reaction. Nevertheless, the HOMO coefficients do not allow us to explain the observed regiochemical behavior of the reaction (Table 3).

All the HOMOs showed the same trend. In particular, there is not any real difference between the C-1 and C-6 coefficients. The electron density on these carbons in the HOMO is quite similar, and we cannot explain the experimental regiochemical results on the basis of these data.

In order to solve this problem we studied the stability of all the possible radical intermediates of the reaction. Regiochemical results could be explained on the basis of the different stability of the radical intermediates deriving from the attack of the thienyl radical **17** on arylalkenes or arylalkynes as described in Scheme 3. This hypothesis could be acceptable if the radical intermediates **19**–**24** have an energy higher than the energy of **17**.

We estimated the total electronic energy of the radicals **19**–**24** using the AM1 semiempirical method, and the results are collected in Table 4.

Scheme 3

On the basis of these data the radical intermediates deriving from the attack of **17** on thiophene are more stable than the ones deriving from the attack of **17** on the alkene or alkyne moiety. These results are not in agreement with experimental results. Furthermore, we

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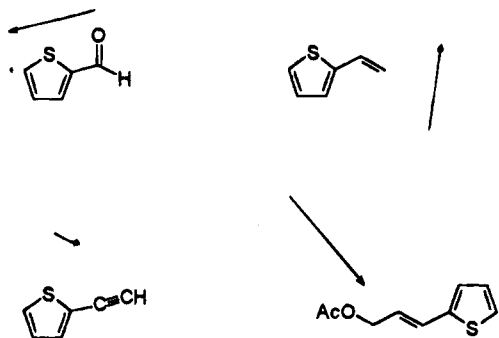
Table 4. Total Energy (kcal mol⁻¹) of Reactants and Radical Intermediates Involved in the Reactions Depicted in Scheme 3

entry	reactants			radical intermediates						difference ^a		
	17	2-ethenylthiophene	10b	8b	19	20	21	22	23	24	A	B
1	-27469	-24075			-55178	-54953					3634	3409
2			-23408				-54514	-54360			3637	3483
3				-50144					-80090	-79538	2485	1925

^a Differences between the total energy of reactants and the total energy of each radical intermediate. The values are reported in kcal mol⁻¹. A is the difference between the energy of reactants and 19, 21, and 23, respectively; B is the difference between the energy of reactants and 20, 22, and 24, respectively.

Table 5. Dipole Moments of Selected Compounds

compound	μ (D)
thiophene-2-carbaldehyde 5-radical	1.655
2-ethenylthiophene	1.450
2-ethynylthiophene	0.472
2-(3-acetoxy-1-propenyl)thiophene	2.058

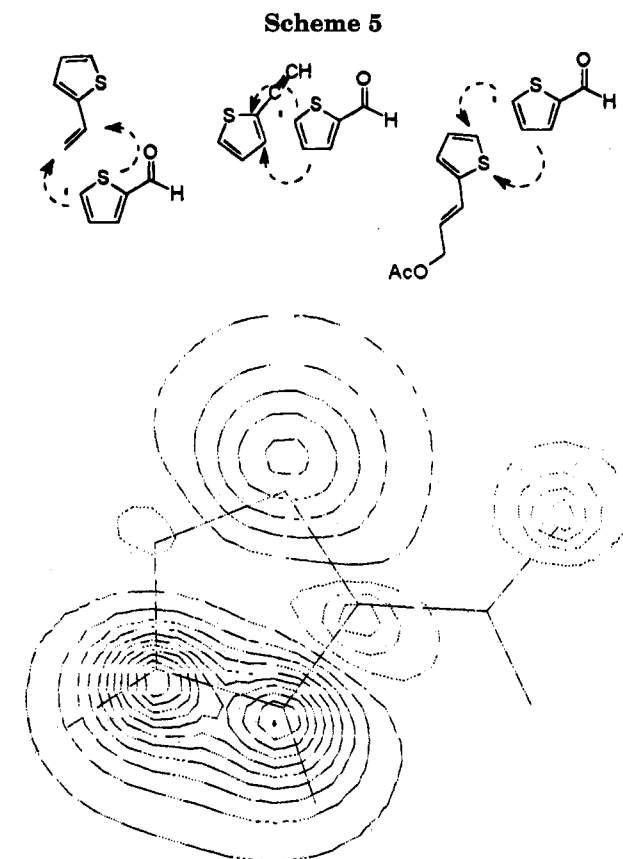
Scheme 4

calculated the total energy of 17 showing that it was -27469 kcal mol⁻¹. Furthermore, in Table 4 we reported also the total energy of both the arylalkenes (2-ethenylthiophene and 2-(3-acetoxy-1-propenyl)thiophene) and arylalkyne (2-ethynylthiophene) involved in this study. We can see that there is a clear difference between the total energy of the reactants and that of the radical intermediates. Then, the conversion of 17 into 19-24 is a very fast reaction, that is independent of the different stabilities of 19-24.

The reaction of the radical 17 with arylalkenes and arylalkynes is clearly under kinetic control, and the regiochemical behavior of these reactions must be due to the way that 17 approaches and interacts with these substrates. For this reason we calculated the dipole moments of the radical 17 and of 2-ethenylthiophene, 2-ethynylthiophene, and 2-(3-acetoxy-1-propenyl)thiophene (Table 5). The direction of the dipoles are collected in Scheme 4.¹⁶

These data can be used to explore some aspects of the regiochemical control of the reaction assuming that 17 can approach the arylalkenes or arylalkynes on different parallel planes. In fact, in order to obtain an approach with opposite dipole moments we have to assume the situation depicted in Scheme 5.

In order to explain the observed regiochemistry we have to consider the SOMO of 17, too (Figure 2). In the case of 2-vinylthiophene the alignment of the dipoles induces a steric situation where only the superposition between C-5 and C-6 of the substrate and the C-S bond is possible. The best superposition can be obtained considering the SOMO of 17 and the LUMO of 2-ethenylthiophene (Table 3). This orbital interaction allows only the reaction on the double bond.

**Figure 2. SOMO of radical 17.**

ylthiophene (Table 3). This orbital interaction allows only the reaction on the double bond.

When 2-ethynylthiophene is used as substrate another possible explanation can be offered. 2-Ethynylthiophene shows a very low dipole moment, and this datum can be in agreement with the hypothesis that, in this case, the approach of 17 to the substrate is randomized. Then, the attack on C-1 and C-6 can depend on the charge density on these atoms. The charge density on these atoms is -0.44 and -0.19, respectively. To test this hypothesis we have calculated the dipole moment for phenylacetylene using the same method. We used phenylacetylene because, while 2-thienylacetylene gave a mixture of products deriving from the attack of 17 on both the triple bond and the thiophene ring, this substrate gave only the product deriving from the attack on triple bond.¹ Phenylacetylene showed a dipole moment $\mu = 0.142$ D. This value is lower than the one showed by 2-ethynylthiophene, and the above described hypothesis is not able to explain the observed regiochemical results.

Another hypothesis is depicted in Scheme 5. In this case, the approach of the reactants can be obtained with an angle of ca. 70° between them and under such

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conditions that only the interaction between C-3 and C-4 of 2-ethynylthiophene and the C-S bond is possible. In fact, the SOMO-LUMO superposition also in this case gave the best results. In this case, the radical position is nearly equidistant between the reaction sites C-1 and C-6, and the radical **17** can react with both positions depending on the charge density distribution.

In a previous paper we reported also that the regiochemical behavior of the photochemical coupling between haloheterocyclic derivatives and 2-ethynylthiophene can be changed working at different concentrations.¹ In particular we found that, working at very low reagent concentrations, the regiochemistry of the reaction changed, giving the coupling product at the alkyne as the main product. These results were explained in that paper, on the basis of an electron transfer mechanism. However, we have seen that that mechanistic hypothesis is not involved in this type of reaction.¹⁰ On the basis of the above reported data, we can formulate only a hypothesis to explain this behavior. We have seen that photochemical coupling reactions occur *via* the interaction of the radical **17** with a molecule of the substrate. Working at very low reagent concentrations, probably the only possible interaction is between **17** and the iodine-substrate complex. This change in the nature of the reagent could justify the different regiochemistry. Unfortunately, we do not have the instruments to verify it.

When **8b** is used as substrate the situation is as depicted in Scheme 5. Also in this case the allowed approach between **17** and **8b** can occur in such a way that only superposition between the C-1-S bond of **8b** and the C-C bond of **17** is possible. Also in this case the best superposition is obtained between the SOMO of **17** and the LUMO of **8b**. In this steric situation only the reaction on the thiophene ring is possible.

It is noteworthy that the orbital superposition occurs only between the SOMO of radical **17** and the LUMO of the substrates. In fact, on the basis of the presence of an electron-withdrawing substituent on the substrate **17**, we expected a behavior typical of electrophilic radicals that interact with the HOMO of the other reagent. In this case, the electron-withdrawing substituent probably cannot compensate for the π -excessive character of the thienyl ring, and the radical behaves as a nucleophilic radical.

On the basis of these data we can formulate the following conclusions: electrochemical properties could be used to estimate the capability of aromatic compounds to give complexes with a halogen atom and then to allow the photochemical coupling between haloheterocyclic derivatives and both arylalkenes and arylalkynes. On the other hand, the direction and the size of the dipole moments of the molecules used as partners of haloheterocyclic compounds allow us to predict the regiochemical behavior of the reaction.

Experimental Section

Starting Materials. 2-Ethynylthiophene was prepared from thiophene-2-carbaldehyde by reaction with carbon tetrabromide and triphenylphosphine in methylene chloride and subsequent reaction of the dibromoalkene with MeLi and then water.¹⁷ 3-(2-Furyl)acrylic acid was converted into the methyl ester by reaction of the corresponding acyl chloride¹⁸ with

MeOH in the presence of pyridine.¹⁹ 2-(3-Acetoxy-1-propenyl)thiophene was obtained by reduction of 3-(2-thienyl)acrylic acid with LiAlH₄ and acetylation of the product. 2-(3-Acetoxy-1-propynyl)thiophene was obtained through reduction with diisobutylaluminum hydride of ethyl 3-(2-thienyl)propionate to give 3-(2-thienyl)allylic alcohol.²⁰ Acetylation of the product gave 2-(3-acetoxy-1-propynyl)thiophene. Ethyl 3-(2-thienyl)propionate was prepared from thiophene-2-carboxylic acid that was converted into the corresponding acyl chloride which upon treatment with (ethoxycarbonylmethylene)phosphorane gave the corresponding betaine. Thermolysis of this betaine gave ethyl 3-(2-thienyl)propionate.²¹

2-Ethynylthiophene: bp 44–46 °C/15 mmHg; ¹H NMR (CDCl₃) δ 7.22 (m, 2 H), 6.93 (dd, 1 H, $J_1 = 4.0$ Hz, $J_2 = 5.1$ Hz), 3.13 ppm (s, 1 H).

(E)-Methyl 3-(2-furyl)acrylate: bp 114–116 °C/18 mmHg (lit.,²² 114–115 °C/16 mmHg); ¹H NMR (CDCl₃) δ 7.50 (m, 1 H), 7.10 (d, 1 H, $J = 16$ Hz), 6.59 (d, 1 H, $J = 4$ Hz), 6.44 (dd, 1 H, $J_1 = 2$ Hz, $J_2 = 4$ Hz), 6.29 (d, 1 H, $J = 16$ Hz), and 3.77 ppm (s, 3 H); IR ν_{\max} 1720, 1645, 1560, 1485, 1435, 1390, 1310, 1275, 1260, 1210, 1200, 1168, 1075, 1040, 1020, 970, 930, 883, 860, 818, 750, 730, 680 cm⁻¹; MS m/z 152.

2-(3-Acetoxy-1-propenyl)thiophene: ¹H NMR (CDCl₃) δ 7.16 (d, 1 H, $J = 5$ Hz), 6.95 (dd, 2 H, $J_1 = 4$ Hz, $J_2 = 3$ Hz), 6.09 (dt, 1 H, $J_1 = 16$ Hz, $J_2 = 6.5$ Hz), 4.66 (d, 2 H, $J = 6.5$ Hz), 2.07 ppm (s, 3 H); IR ν_{\max} 1734, 1380, 1363, 1232, 1230, 1041, 1024, 956, 756, 700 cm⁻¹; MS m/z 184 (5%), 183 (10), 182 (100), 140 (53), 139 (79), 123 (81), 122 (35), 121 (52), 11 (74), 98 (15), 97 (19), 96 (11), 84 (25), 79 (21), 78 (17), 77 (23), 65 (11).

3-(2-Thienyl)prop-2-yn-1-ol: ¹H NMR (CDCl₃) δ 7.24 (dd, 1 H, $J_1 = 5$ Hz, $J_2 = 1$ Hz), 7.19 (dd, 1 H, $J_1 = 4$ Hz, $J_2 = 1$ Hz), 6.95 (dd, 1 H, $J_1 = 5$ Hz, $J_2 = 4$ Hz), 4.48 (s, 2 H), 1.93 ppm (1 H, bs); IR ν_{\max} 2225, 1421, 1357, 1265, 1190, 1080, 1045, 1020, 847, 832, 702 cm⁻¹.

2-(3-Acetoxy-1-propynyl)thiophene: ¹H NMR (CDCl₃) δ 7.26 (dd, 1 H, $J_1 = 5$ Hz, $J_2 = 1$ Hz), 7.23 (dd, 1 H, $J_1 = 4$ Hz, $J_2 = 1$ Hz), 6.95 (dd, 1 H, $J_1 = 5$ Hz, $J_2 = 4$ Hz), 4.89 (s, 2 H), 2.10 (s, 3 H); IR ν_{\max} 2230, 1741, 1426, 1375, 1359, 1223, 1196, 1118, 1026, 849, 705 cm⁻¹.

Voltammograms. All the voltammograms were performed by an Amel Model 433A (Amel, Milan, Italy) polarograph (operating potentiostatically) controlled by a Model 30 PS/2 IBM personal computer. As a stationary working electrode, a homemade platinum microelectrode (spherically shaped) was used, while a platinum ring and Ag, AgCl/LiCl_{sat} (in acetonitrile) were, respectively, used as counter and reference electrode.²³ The voltammetric experiments were carried out in acetonitrile containing NaClO₄ (0.1 M) as supporting electrolyte. All the voltammograms [linear sweep (LS) and differential pulse (DP)] were recorded scanning the potential between 0 and 3 V with a scan rate of 50 and 100 nV s⁻¹. Furthermore, 50 mV of pulse height, 50 ms of pulse duration and 8 ms of sampling time were used in differential pulse voltammetric experiments. All the experiments were performed at room temperature (ca. 20 °C) on 25 mL of solution. The solutions to be processed were at first bubbled with nitrogen for few seconds in order to prevent the contact with either oxygen and air humidity.

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