Photochemical synthesis of 4(5)-nitro-2-arylimidazoles

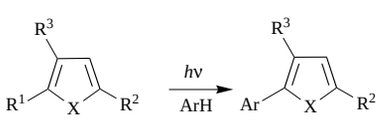
Maurizio D'Auria,* Eliana De Luca, Giacomo Mauriello and Rocco Racioppi

Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

The irradiation at $\lambda > 300$ nm of 4(5)-nitro-2-iodoimidazole in acetonitrile in the presence of benzene gives the corresponding 2-phenyl substituted derivative. The same behaviour has been observed using *m*-xylene and thienyl derivatives. While the yields are nearly quantitative for benzene, *m*-xylene and thiophene as the aromatic partner of the imidazole derivative, the yields decrease to 50% when 2-methyl- and 2-chloro-thiophene are used as reagents. The compounds obtained by coupling of 4(5)-nitro-2-iodoimidazole and *m*-xylene, thiophene, 2-methylthiophene and 2-chlorothiophene have not been reported before. The observed behaviour can be explained on the basis of the previous reported data on the mechanism of the photochemical arylation of halogenothiophene.

During the last three decades nitroimidazoles as a class of compounds have attracted much attention. They have been used in therapy against amoebic, trichomonal, giardial and anaerobic bacterial infections, as antabuse agents,[1] and as hypoxic cell radiosensitizers in cancer therapy.[2] Imidazole derivatives, bearing both a phenyl and a nitro group, have been described as biologically active compounds showing anti-protozoic activity.[3,4]

We reported earlier that a photochemical procedure can be used in order to obtain aryl substituted furan, thiophene and pyrrole derivatives bearing an electron-withdrawing group starting from the corresponding halogeno substituted compounds (Scheme 1).[5–13] To our knowledge the photochemical



1 **2**

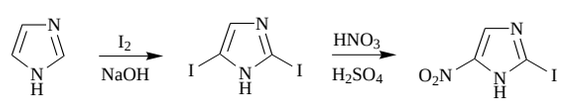
a X = O, R^1 = Br, R^2 = COR, R^3 = H
b X = O, R^1 = I, R^2 = COR, R^3 = H
c X = S, R^1 = Br, R^2 = COR, R^3 = H
d X = S, R^1 = I, R^2 = COR, R^3 = H
e X = S, R^1 = I, R^2 = CO_2R, R^3 = H
f X = S, R^1 = I, R^2 = NO_2, R^3 = H
g X = NH, R^1 = I, R^2 = CHO, R^3 = I

Scheme 1

arylation of halogenoimidazoles has not been described before. Considering the biological properties of the products, we tested the possibility of carrying out the photochemical arylation of halogeno substituted nitroimidazoles.

Results and discussion

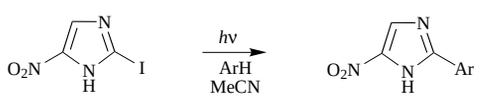
The starting material used in our experiments, 4(5)-nitro-2-iodoimidazole **5**, was prepared according to a described procedure starting from 2,5-diiodoimidazole.[14] 2,5-Diiodoimidazole was synthesized from imidazole in the presence of iodine in a basic medium (Scheme 2).[15] Compound **5** showed peaks in the UV spectrum (EtOH) at 314 (log ε 3.86), 236 (log ε 3.68) and 212 nm (log ε 4.05).



3 **4** **5**

Scheme 2

Compound **5** in acetonitrile was irradiated in the presence of an aromatic or heteroaromatic compound with a 125 W high-pressure mercury arc surrounded by a Pyrex water-jacket. After variable irradiation times (see Table 1), the mixture was evaporated and the crude product was chromatographed on silica gel. Elution with diethyl ether gave the pure products **6** (Scheme 3, Table 1).



5 **6**

Scheme 3

We obtained high yields of the corresponding 2-aryl or heteroaryl substituted derivatives. The yields are nearly quantitative when aromatic compounds are used (Table 1, entries 1 and 2), but less (*ca.* 50%) when substituted thiophenes are used (Table 1, entries 4 and 5). Probably, this behaviour is the result of the intrinsic instability of some thiophene derivatives when irradiated.

These results are the first to study the photochemical behaviour of such nitroimidazole derivatives, until now, only the photochemical replacement of the nitro group with cyano being known.[2] Further, in our work we observed no photoisomerisation, as described for other imidazole derivatives.[16]

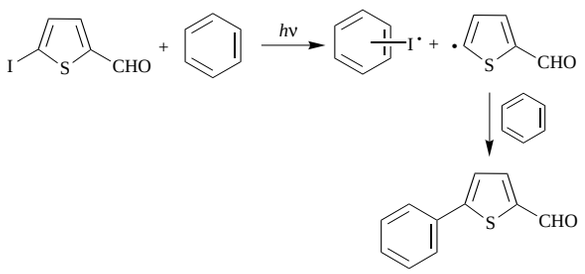
The mechanism of the photoarylation of halogenothiophenes has been investigated.[17] Our studies showed that the excitation of the substrate leads to a n,π* triplet state, but that this excited state is unable to induce dissociation of the carbon–iodine bond. This assertion was supported by the fact that generation of the n,π* triplet state by sensitisation with chrysene failed to produce any coupling products. Thus, probably the reaction occurs in a higher excited (π,σ*, n,σ* or σ,σ*) triplet state mainly localised on the carbon–iodine bond. Furthermore, the interaction between this triplet state of the substrate and aromatic compounds leads to the homolytic cleavage of the C–I bond with the formation of both the radical and a complex between the aromatic compound and the halogen atom. The formation of this complex was demonstrated by the presence of a short-lived transient with $\lambda_{max} = 510$ nm showing second-order decay kinetics and a half-life of *ca.* 0.4 μs in laser flash photolysis. The thienyl radical thus formed reacts rapidly with the aromatic compound to form the corresponding arylation product (Scheme 4).[17]

We found also that this radical can evolve giving the dehalogenation product or the arylation product. The dehalogenation

Table 1 Photochemical arylation of 5(4)-nitro-2-iodoimidazole

Entry	ArH	Irradiation time (h)	Product	Ar	Yields (%)[a]
1	Benzene	4.25	**6a**	Phenyl	94
2	*m*-Xylene	4	**6b**	2,4-Dimethylphenyl	98
3	Thiophene	4.75	**6c**	2-Thienyl	98
4	2-Methylthiophene	1.45	**6d**	2-(5-Methylthienyl)	53
5	2-Chlorothiophene	2	**6e**	2-(5-Chlorothienyl)	51

[a] All the yields refer to isolated chromatographically pure compounds.



Scheme 4

can be observed in thiophene and pyrrole derivatives as well as in aromatic compounds.[11,13,18,19] We showed that the difference [$\Delta\Delta H_f(S_0 \rightarrow D_0)$] between the heat of formation of the radical deriving from the homolytic cleavage of the C–Hal bond and the heat of formation of the substrates can be a useful parameter to explain the observed behaviour. This difference represents the fraction of the absorbed photochemical energy ($S_0 \rightarrow S_1$) that was not dissipated during the process. If this energy is low the only reaction allowed is the photoarylation, while, if the energy is higher than 55 kcal mol^{-1}, the dehalogenation, that involves a higher transition state energy than the photoarylation, becomes predominant. Above, we reported that irradiation of compound **5** gave only the arylation product and we tested our previously described hypothesis on this substrate. The calculated value for $\Delta\Delta H_f(S_0 \rightarrow D_0)$, calculated by using a semiempirical method (PM3),[20] was 43 kcal mol^{-1}, in agreement with the absence of the dehalogenation.

In conclusion, we have shown that (1) the irradiation of a halogeno substituted imidazole in the presence of aromatic compounds can give the corresponding aryl derivatives; (2) this process allows us to obtain in a very simple way compounds both with interesting biological properties and never described before.

Experimental

Mass spectra were obtained with a Hewlett-Packard 5971 mass selective detector on a Hewlett-Packard 5890 gas chromatograph. Gas chromatographic analyses were obtained by using an OV-1 capillary column in the range 70–250 °C (20 °C min^{-1}). A Cary 2300 spectrophotometer was used for the UV spectra. ^1H and ^{13}C NMR spectra were recorded with Bruker 300 AM instrument. Elemental analyses were obtained with a Carlo Erba Elemental Analyser 1106; *J* values given in Hz.

Photochemical arylation of 4(5)-nitro-2-iodoimidazole

General procedure. 4(5)-Nitro-2-iodoimidazole (0.17 mmol) was dissolved in acetonitrile (10 cm^3) in the presence of an aromatic or heteroaromatic compound (3 cm^3). The mixture was outgassed with nitrogen for 1 h and then irradiated with a 125 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After a variable irradiation time (Table 1), the mixture was evaporated and the crude product was chromatographed on silica gel. Elution with hexane removed the iodine, while elution with diethyl ether gave the pure products **6**.

4(5)-Nitro-2-phenylimidazole 6a. $\delta_H([^2H_6]$-DMSO) 7.83 (s, 1 H), 7.60 (m, 2 H) and 7.44 (m, 3 H); *m/z* 190 (14%), 189 (M^+, 100), 136 (11), 133 (13), 132 (15), 119 (21), 116 (16), 105 (14), 104 (42), 103 (16), 91 (10), 90 (10), 89 (75), 77 (35), 76 (13), 63 (16), 55 (13) and 51 (13) (Found: C, 57.2; H, 3.6; N, 22.1. $C_9H_7N_3O_2$ requires C, 57.14; H, 3.73; N, 22.21%).

4(5)-Nitro-2-(2,4-dimethylphenyl)imidazole 6b. $\delta_H([^2H_6]$-DMSO) 8.32 (s, 1 H), 7.65 (d, 1 H, *J* 8), 7.60 (s, 1 H), 7.53 (d, 1 H, *J* 8), 2.75 (s, 3 H) and 2.40 (s, 3 H); *m/z* 217 (M^+, 35%), 201 (16), 200 (100), 199 (13), 187 (15), 186 (39), 185 (15), 183 (18), 182 (16), 173 (21), 172 (21), 171 (16), 170 (20), 169 (13), 160 (16), 159 (12), 158 (20), 157 (14), 156 (12), 155 (15), 147 (11), 146 (59), 145 (34), 144 (21), 143 (32), 142 (26), 134 (12), 133 (15), 132 (29), 131 (22), 130 (36), 128 (11), 118 (26), 117 (43), 116 (36), 115 (45), 105 (13), 104 (14), 103 (21), 102 (16), 91 (25), 89 (15), 79 (12), 78 (15), 77 (27), 76 (10), 65 (12), 63 (13) and 51 (12) (Found: C, 60.8; H, 5.2; N, 19.4. $C_{11}H_{11}N_3O_2$ requires C, 60.82; H, 5.10; N, 19.34%).

4(5)-Nitro-2-(2-thienyl)imidazole 6c. $\delta_H([^2H_6]$-DMSO) 7.92 (s, 1H), 7.80 (d, 2 H, *J* 5) and 7.22 (dd, 1 H, $J_1 = J_2 = 5$); *m/z* 195 (M^+, 100%), 165 (23), 137 (21), 127 (30), 126 (22), 122 (42), 110 (23), 109 (61), 95 (52) and 69 (30) (Found: C, 42.9; H, 2.5; N, 21.4; S, 16.5. $C_7H_5N_3O_2S$ requires C, 43.07; H, 2.58; N, 21.53; S, 16.42%).

4(5)-Nitro-2-(5-methyl-2-thienyl)imidazole 6d. $\delta_H([^2H_6]$-DMSO) 7.25 (s, 1 H), 7.03 (d, 1 H, *J* 5), 6.30 (d, 1 H, *J* 5) and 1.90 (s, 3 H); *m/z* 210 (11%), 209 (M^+, 100), 179 (11), 152 (10), 136 (19), 124 (34), 122 (11), 109 (32), 97 (11) and 69 (15) (Found: C, 46.0; H, 3.6; N, 20.0; S, 15.3. $C_8H_7N_3O_2S$ requires C, 45.93; H, 3.37; N, 20.08; S, 15.32%).

4(5)-Nitro-2-(5-chloro-2-thienyl)imidazole 6e. $\delta_H([^2H_6]$-DMSO) 8.00 (s, 1 H), 7.69 (d, 1 H, *J* 5) and 7.28 (d, 1 H, *J* 5) (Found: C, 36.6; H, 2.0; N, 18.2; S, 13.9. $C_7H_4ClN_3O_2S$ requires C, 36.61; H, 1.76; N, 18.30; S, 13.96%).

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Paper 7/05654K
Received 4*th August* 1997
Accepted 6*th October* 1997