

Coumarin as Dipolarophile towards  
3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide  
Clara Baldoli, Fabio Gioffreda and Gaetano Zecchi\*

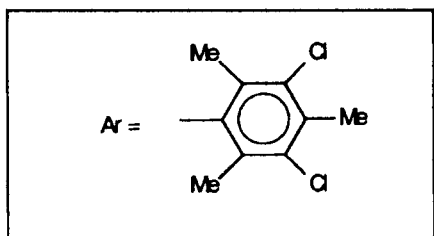
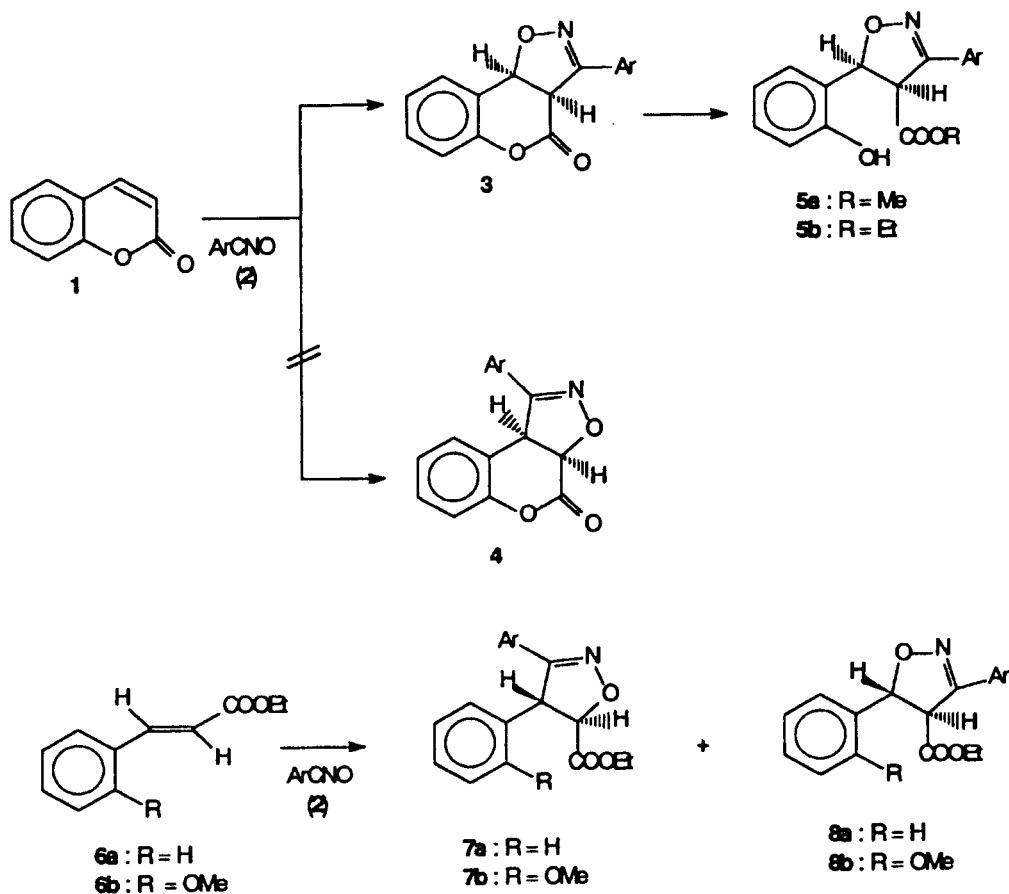
Dipartimento di Chimica Organica e Industriale and Centro C.N.R., Via Golgi 19, 20133 Milano, Italy  
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The reaction of coumarin with the title nitrile oxide gives a single regioisomer in high yield. This result is compared with the dipolarophilic behavior of cinnamic acid esters.

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In spite of the enormous body of literature dealing with 1,3-dipolar cycloadditions [1,2], little has been reported about the use of coumarins as dipolarophiles [3-6]. This is surprising since 1,3-dipolar cycloadditions to the ethyl-

enic bond of the coumarin system could provide a versatile entry to annulated coumarins, a class of compounds including several natural products such as warfarins, aflatoxins and coumestans [7]. In the light of these considera-



tions, we studied the reaction of the parent coumarin **1** with the nitrile oxide **2**.

By reacting equimolar amounts of **1** and **2** in dioxane solution at room temperature, we obtained the single cycloadduct **3** in 80% yield. The choice between the two regioisomeric structures **3** and **4** followed from NOE experiments. In fact, upon irradiation of the most deshielded aromatic proton, the intensity of the doublet at 6.08 ppm was increased, while no change was detected on the doublet at 4.70 ppm. The observed coupling constant of the isoxazolinic protons (10.4 Hz) fits well to the literature data for the *cis* relationship in 4,5-disubstituted 4,5-dihydroisoxazoles [8]. Treatment of **3** with boron trifluoride in alcohols led to the corresponding hydrox-esters **5**.

The regioselective and stereoselective course of the above cycloaddition represents a valuable feature from the synthetic point of view. This is clear if one considers that the reaction of alkyl (*o*-methoxy)cinnamates **6** with the nitrile oxide **2** furnished a 1:1 mixture of the regioisomeric products **7** and **8**, both of which exhibit a *trans* configuration at the 4 and 5 positions of the isoxazole ring.

Taking into account the dipole moment of the coumarin and the properties of its frontier orbitals [3,9-11], it can be argued that both coulombic and overlap terms of the interaction energy work to drive the oxygen of the dipole towards the 4-carbon of **1**, so determining a full regioselectivity which is not shared by nitrile oxide cycloadditions to cinnamic acid esters.

## EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are not corrected. The ir spectra were taken on a Perkin-Elmer 377 spectrophotometer. The nmr spectra were recorded on a 300 Bruker instrument; chemical shifts are given in ppm from tetramethylsilane; coupling constants are given in Hz. Mass spectra were measured on a VG70EQ apparatus.

Compound **2** was prepared according to the literature method [12].

### Reaction of Coumarin **1** with Nitrile Oxide **2**.

A solution of **1** (3 mmoles) and **2** (3 mmoles) in dioxane (9 ml) was left at room temperature for 72 hours. The solvent was removed and the residue was recrystallized from benzene to give 3-(3,5-dichloro-2,4,6-trimethylphenyl)-3a,9b-dihydro-4-oxo[1]benzopyrano[3,4-*d*]isoxazole **3** (80%), mp 160°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.20 (6H, s), 2.51 (3H, s), 4.70 (1H, d, J = 10.4), 6.08 (1H, d, J = 10.4), 6.79 (1H, dd, J = 8 and 2), 7.3-7.4 (2H, m), 7.63 (1H, dd, J = 8 and 2); ms: m/z 375 (M<sup>+</sup>).

*Anal.* Calcd for C<sub>19</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>3</sub>: C, 60.60; H, 4.02; N, 3.72. Found: C, 60.89; H, 3.95; N, 3.76.

### Reaction of Compound **3** with Boron Trifluoride in Methanol.

A solution of **3** (1 mmole) in methanol (3 ml) was treated with boron trifluoride ethyl etherate (0.2 ml) and stirred at room temperature for 48 hours. The resulting mixture was evaporated to dryness and the residue was recrystallized from methanol to give 3-(3,5-dichloro-2,4,6-trimethylphenyl)-5-(2-hydroxyphenyl)-4,5-dihydroisoxazole-4-carboxylic acid methyl ester **5a** (51%), mp 199°; ir (nujol): ν 3415, 1725 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 2.39 (6H, s), 2.51 (3H, s), 3.20 (3H, s), 4.59 (1H, d, J = 10.7), 5.82 (1H, br s), 6.21 (1H, d, J = 10.7), 6.78 (1H, dd, J = 8 and 2), 7.0-7.2 (2H, m), 7.41 (1H, dd, J = 8 and 2); ms: m/z 407 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>20</sub>H<sub>19</sub>Cl<sub>2</sub>NO<sub>4</sub>: C, 58.83; H, 4.69; N, 3.43. Found: C, 58.70; H, 4.91; N, 3.31.

### Reaction of Compound **3** with Boron Trifluoride in Ethanol.

Following the same procedure as described in the preceding preparation, compound **3** gave the ethyl ester **5b** (48%), mp 203° (from ethanol); ir (nujol): ν 3425, 1720 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 0.78 (3H, t, J = 7), 2.45 (6H, s), 2.53 (3H, s), 3.70 (2H, m), 4.53 (1H, d, J = 10.8), 5.84 (1H, br s), 6.22 (1H, d, J = 10.8), 6.80 (1H, dd, J = 8 and 2), 6.9-7.2 (2H, m), 7.42 (1H, dd, J = 8 and 2); ms: m/z 421 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>4</sub>: C, 59.72; H, 5.01; N, 3.32. Found: C, 59.58; H, 4.98; N, 3.51.

### Reaction of Compound **6a** with Nitrile Oxide **2**.

A solution of **6a** (1 mmole) and **2** (1 mmole) in dioxane (3 ml) was left at room temperature for 72 hours. The solvent was removed and the residue was chromatographed on a silica gel column by eluting with dichloromethane-light petroleum (3:1). The first fractions gave the cycloadduct **8a** (38%), mp 132° (from hexane); ir (nujol): 1750 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 0.98 (3H, t, J = 7), 2.23 (6H, s), 2.53 (3H, s), 4.05 (2H, m), 4.24 (1H, d, J = 9.0), 6.17 (1H, d, J = 9.0), 7.2-7.6 (5H, m); ms: m/z 405 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>: C, 62.07; H, 5.21; N, 3.45. Found: C, 62.10; H, 5.39; N, 3.25.

Subsequent fractions contained the cycloadduct **7a** (36%), mp 146° (from hexane); ir (nujol): ν 1750 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.35 (3H, t, J = 7), 2.00 (6H, s), 2.47 (3H, s), 4.32 (2H, m), 4.72 (1H, d, J = 4.1), 5.39 (1H, d, J = 4.1), 7.0-7.4 (5H, m); ms: m/z 405 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>: C, 62.07; H, 5.21; N, 3.45. Found: C, 61.91; H, 5.07; N, 3.53.

### Reaction of Compound **6b** with Nitrile Oxide **2**.

A solution of **6b** (1 mmole) and **2** (1 mmole) in dioxane (3 ml) was left at room temperature for 72 hours. After removal of the solvent, the residue was chromatographed on a silica gel column by eluting with dichloromethane-light petroleum (2:1). First fractions contained the cycloadduct **8b** (43%), mp 114° (from hexane); ir (nujol): ν 1750 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.05 (3H, t, J = 7), 2.21 (6H, s), 2.52 (3H, s), 3.83 (3H, s), 4.09 (2H, m), 4.22 (1H, d, J = 8.4), 6.29 (1H, d, J = 8.4), 6.92 (1H, dd, J = 7.5 and 1.5), 7.1-7.3 (2H, m), 7.51 (1H, dd, J = 7.5 and 1.5); ms: m/z 435 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>22</sub>H<sub>23</sub>Cl<sub>2</sub>NO<sub>4</sub>: C, 60.56; H, 5.31; N, 3.21. Found: C, 60.39; H, 5.55; N, 3.35.

Subsequent fractions furnished the cycloadduct **7b** (45%), mp 135° (from hexane); ir (nujol):  $\nu$  1750  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.32 (3H, t,  $J = 7$ ), 2.18 (6H, s), 2.42 (3H, s), 3.41 (3H, s), 4.32 (2H, m), 5.34, 5.39 (2H, AB,  $J = 4.8$ ), 6.71 (1H, dd,  $J = 7.5$  and 1.5), 6.9-7.3 (3H, m); ms:  $m/z$  435 ( $M^+$ ).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{NO}_4$ : C, 60.56; H, 5.31; N, 3.21. Found: C, 60.78; H, 5.18; N, 3.40.

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