

## SYNTHESIS OF ISOXAZOLO[4,5-d]PYRIMIDINONES, AND THEIR ISOMERIZATION INTO OXAZOLO[4,5-d]PYRIMIDINONES ON FLASH VACUUM PYROLYSIS

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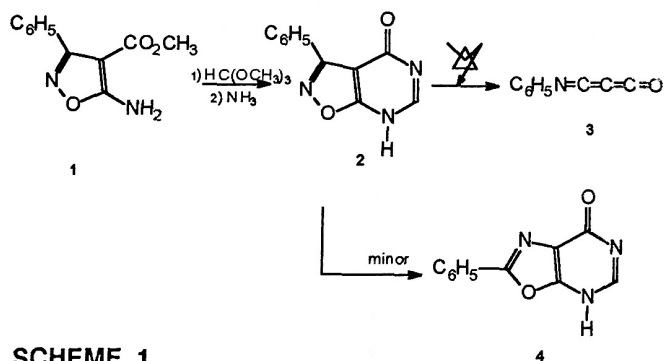
*Dedicated to Professor Jacques Nasielski (ULB) on the occasion of his retirement*

### ABSTRACT

A series of new 3-phenylisoxazolo[4,5-d]pyrimidinones **5a-d** were prepared from 5-aminoisoxazole-4-carboxylic acid esters. Upon flash-vacuum pyrolysis, these heterocycles are isomerized into hitherto unreported 2-phenyloxazolo[4,5-d]pyrimidinones **8a-d**.

### INTRODUCTION

PYRIMIDINES fused to five or six membered rings have been the subject of numerous works.<sup>1</sup> The general access to these molecules frequently involves the construction of the pyrimidine ring starting with properly substituted heterocycles. Thus, transformation of 5-amino-4-methoxycarbonyl-3-phenylisoxazole [**1**] into 3-phenylisoxazolo[5,4-d]pyrimidinone [**2**] is readily completed by reaction with methyl orthoformate followed by cyclisation with ammonia (Scheme 1).<sup>2</sup>



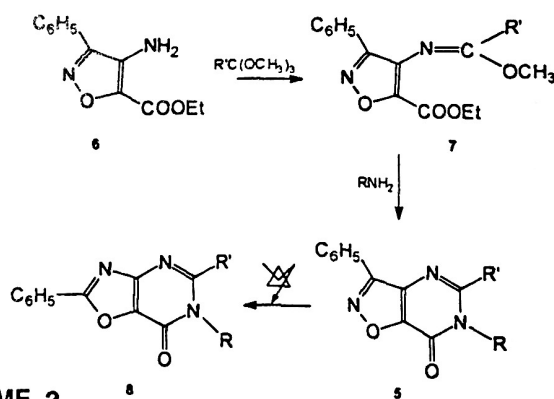
SCHEME 1.

We have recently shown that these pyrimidinones constitute an interesting source of a new class of heterocumulenes. For instance, **2** upon flash vacuum pyrolysis (FVP) at ca. 700°C loses  $\text{HN}=\text{C}=\text{O}$  and  $\text{HCN}$  producing phenyliminopropadienone,  $\text{PhN}=\text{C}=\text{C}=\text{C}=\text{O}$  [**3**].<sup>3</sup> Isomerization of the isoxazole **2** into the fused oxazole **4** was also observed to a lesser extent. These unexpected results prompted us to investigate the behaviour upon short contact time FVP conditions of a closely related system, the 3-phenylisoxazolo[4,5-d]pyrimidinones **5a-d**.

### RESULTS

#### Preparation of 3-phenylisoxazolo[4,5-d]pyrimidinones **5a-d**

These new pyrimidinones **5a-d** were prepared by a two step reaction sequence similar to the sequence described in Scheme 1 starting with ethyl 3-phenyl-4-aminoisoxazole-5-carboxylate [**6**] (Scheme 2). The intermediate imidates **7a-d** were not isolated; they are nevertheless stable enough to be identified spectroscopically. The imidates were cyclized with ammonia, methylamine or aniline in dry boiling methanol. Reaction conditions and physical data of the pyrimidinones **5a-d** are collected in Table 1.



SCHEME 2.

#### Flash-vacuum pyrolysis of the pyrimidinones **5a-d**

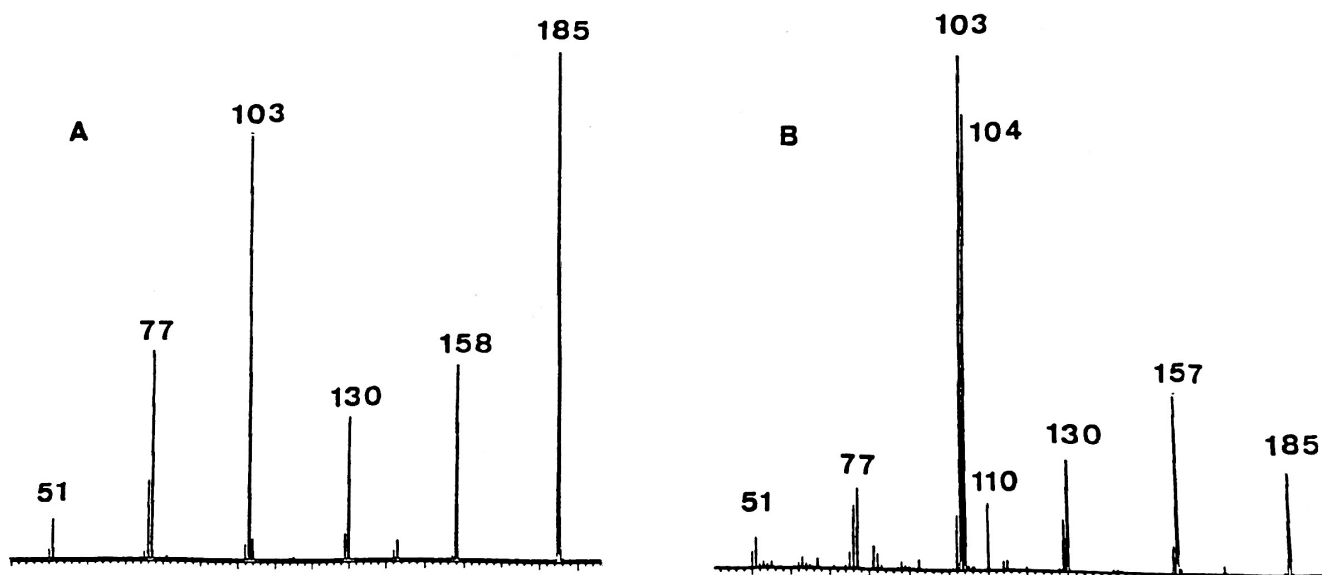
Short contact time FVP has been applied to **5a-d** in a 700-800°C temperature range, real-time analysis of the pyrolyzates being performed by mass spectrometry (MS) and tandem mass spectrometry (MS/MS).<sup>4</sup> The data collected in Table 2 clearly show that the mass spectra are strongly modified when FVP precedes ionization; the molecular ion peaks remain nevertheless very intense in all cases. That isomerization has occurred

**TABLE 1.**  
Reaction conditions and physical data for 3-phenylisoxazolo[4,5-d]pyrimidinones **5a-d**.

Pyrimidinones	R	R'	Reaction time (hours)	Yield (%)	m.p. (°C)	300 MHz RMN [DMSO-d <sub>6</sub> , δ]	HRMS
<b>5a</b>	H	H	2.5	81	279	13.4-12.4 (1H, broad, NH); 8.45-8.35 (3H, m, $\phi$ , C <sub>5</sub> H); 7.75-7.65 (3H, m, $\phi$ )	213.0530
<b>5b</b>	CH <sub>3</sub>	H	0.5	85	230	8.7 (1H, s, C <sub>5</sub> H); 8.45-8.35 (2H, m, $\phi$ ); 7.75-7.65 (3H, m, $\phi$ ); 3.7 (3H, s, CH <sub>3</sub> )	227.0687
<b>5c</b>	C <sub>6</sub> H <sub>5</sub>	H	8	62	198-199	8.65 (1H, s, C <sub>5</sub> H); 8.45-8.35 (2H, m, $\phi$ ); 7.75-7.6 (8H, m, $\phi$ , $\phi$ )	289.0852
<b>5d</b>	CH <sub>3</sub>	CH <sub>3</sub>	1.5	73	177-170	8.45-8.35 (2H, m, $\phi$ ); 7.75-7.65 (3H, m, $\phi$ ); 3.7 (3H, s, CH <sub>3</sub> ); 2.6 (3H, s, C <sub>5</sub> -CH <sub>3</sub> )	241.0856

**TABLE 2.**  
EI (70 eV) mass spectra of pyrimidinones **5a-d** at 200°C (a) and after FVP at 700°C (b).  
Eight more intense peaks indicated.

Compounds		m/z (relative abundance)							
<b>5a</b>	(a)	213(100)	185(40)	158(21)	130(31)	104(32)	103(78)	77 (48)	51(32)
	(b)	(100)	(6)	(1)	(10)	(41)	(58)	(26)	(16)
<b>5b</b>	(a)	227 (76)	199(18)	198(11)	103(23)	77(30)	51(17)	42(100)	
	(b)	(88)	(4)	(1)	(60)	(23)	(11)	(100)	
<b>5c</b>	(a)	289 (84)	261(29)	260(23)	129(28)	104(72)	103(39)	77(100)	51(49)
	(b)	(100)	(10)	(8)	(23)	(68)	(64)	(92)	(46)
<b>5d</b>	(a)	241 (66)	213(15)	143(9)	103(11)	82(18)	77(22)	56(100)	51(20)
	(b)	(73)	(7)	(1)	(20)	(27)	(25)	(100)	(20)



**FIG. 1.**  
Evolution of the CA(O<sub>2</sub>) spectrum of the molecular ions of the isoxazolopyrimidinone **5a** upon flash-vacuum pyrolysis (A = 200° and B = 700°).

is indicated by MS/MS experiments. FIG. 1 shows the resolved collisional activation (CA) spectrum of mass-selected molecular ions of 5a ( $m/z$  213) before and after FVP. The signal at  $m/z$  158 being quantitatively replaced by a peak at  $m/z$  157, the  $m/z$  213 ions do not correspond anymore to 5a<sup>+</sup> ions. A small, but significant peak at  $m/z$  110 (loss of benzonitrile) also characterizes the isomerization product; it is worth noting that this behaviour was also observed for 4<sup>+</sup> ions.<sup>3</sup> The thermally induced isomerization of some isoxazoles into oxazoles being moreover already mentioned in some instances in the literature,<sup>5</sup> we propose that 5a has been isomerized into the hitherto unreported 2-phenyl-oxazolo-[4,5-d]pyrimidinone [8a] upon FVP.

### Semi-preparative FVP results

Further confirmation of the thermal production of 8a has been provided by semi-preparative experiments which have allowed the isolation of enough material to characterize the oxazole by NMR (FIG. 2) and IR spectroscopies. As predicted by mass spectrometry, argon matrix isolation has not allowed the detection of  $\text{PhN}=\text{C}=\text{C}=\text{O}$  3 by FTIR. The very strong IR absorption at  $2247\text{ cm}^{-1}$  observed<sup>3b</sup> during the FVP of 2 was indeed not observed for 5a ( $750^\circ\text{C}$ ,  $10^{-3}$  torr).

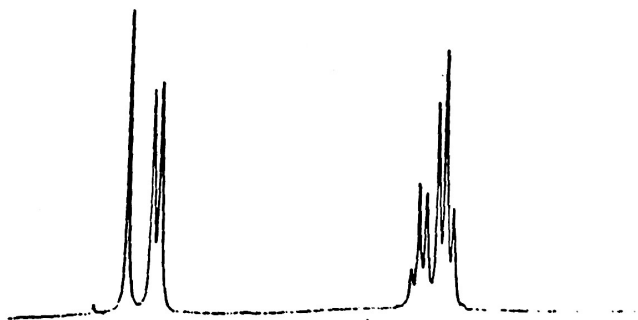


FIG. 2.

500 MHz PMR spectrum of the oxazolopyrimidinone 8a.

### EXPERIMENTAL

The electron impact mass spectra were recorded with a VG Analytical AutoSpec 6F mass spectrometer of EBEBE geometry (E stands for electric sector, B for magnetic sector) operating at an accelerating voltage of 8 kV.<sup>6</sup> In the CA experiment described in FIG. 1, a homogeneous beam of ions was selected with the first three sectors, and submitted to collisional activation with oxygen (80% transmittance); the resulting fragment ions were recorded by a linked scanning of the last three sectors.

The flash-vacuum pyrolysis device installed in the ion source housing of the spectrometer consists of a quartz tube (50 mm length, 3 mm internal diameter) equipped with a tantalum wiring and reflectors.<sup>7</sup> Semi-preparative pyrolyses were performed by using a similar device (alumina instead of quartz) installed in a stainless steel

housing evacuated with a 150 l/min diffusion pump.<sup>8</sup> The pyrolyzates were collected on a liquid nitrogen cooled receptor and rapidly dissolved in methanol before reaching room temperature.

PMR spectra have been recorded on Varian EM36L (60 MHz), Bruker AMX 300 (300 MHz) and Bruker AMX 500 (500 MHz) spectrometers. IR spectra were recorded on a Perkin Elmer 1760 FTIR spectrometer.

#### Ethyl-3-phenyl-4-(methoxymethylidene)aminoisoxazole-5-carboxylate 7 ( $R'=H$ )

2 mmol of ethyl 3-phenyl-4-aminoisoxazole-5-carboxylate<sup>9</sup> and 8 ml of trimethylorthoformate were refluxed during 4 hours in the presence of a catalytic (0.5 ml) amount of acetic anhydride. After removing the excess of orthoester, the imideate 7 ( $R'=H$ ) was isolated as an oil. 60 MHz PMR [ $\text{DMSO}-d_6$ ,  $\delta$  (ppm)] : 8.2 (1H, s, CH), 8-7.8 (2H, m, Ph), 7.6-7.4 (3H, m, Ph), 4.3 (2H, q,  $\text{OCH}_2$ ), 3.9 (3H, s,  $\text{OCH}_3$ ), 1.2 (3H, t,  $\text{CH}_3$ ).

#### Ethyl-3-phenyl-(methoxyethylidene)aminoisoxazole-5-carboxylate 7 ( $R'=CH_3$ )

This imideate was obtained similarly using trimethyl orthoacetate. 60 MHz PMR : 7.9-7.7 (2H, m, Ph), 7.6-7.4 (3H, m, Ph), 4.2 (2H, q,  $\text{OCH}_2$ ), 3.8 (3H, s,  $\text{OCH}_3$ ), 1.8 (3H, s,  $\text{CH}_3$ ), 1.2 (3H, t,  $\text{CH}_3$ ).

#### 3-phenylisoxazolo[4,5-d]pyrimidine-7-ones 5 (General method)

A mixture of an imideate 7 ( $R'=H$  or  $\text{CH}_3$ ) and a primary aliphatic or aromatic amine was refluxed in 10 ml of dry methanol. The pyrimidones which precipitate during the reflux were collected by filtration and recrystallized in methanol (reaction characteristics and physical data are given in Table 1). Eleven other pyrimidinones have been prepared using this procedure; 5 ( $R/R'$ ) : H/n-propyl, H/i-propyl, H/n-butyl, H/i-butyl, H/s-butyl, H/t-butyl, H/o-tolyl, H/p-tolyl, methyl/n-propyl, methyl/n-butyl, methyl/i-butyl (Physical data available upon request).

#### 2-phenylloxazolo[4,5-d]pyrimidine-7-one 8a

10 mg portions of the isoxazolopyrimidinone 5a were vaporized through the alumina furnace heated at ca.  $700^\circ\text{C}$  at a pressure of ca.  $10^{-5}$  torr. The experiment was repeated until sufficient material was collected for spectroscopic identification. The oxazolopyrimidinone 8a was purified by column chromatography (Silica, methylene chloride) followed by recrystallization in methanol (m.p.  $231-235^\circ$ ). 500 MHz PMR [ $\text{DMSO}-d_6$ , (ppm)] : 8.23 (1H, s, CH), 8.17 (2H, d, Ph), 7.69 (1H, t, Ph), 7.61 (2H, t, Ph); HRMS : 213,0539; IR ( $\text{KBr}$ ,  $\text{cm}^{-1}$ ) : 1780, 1715.

### ACKNOWLEDGMENT

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