Synthesis and Spectral Properties of New 6-Methoxy-3-(2'-thienyl)-1,2-benzisoxazole and its Isomeric Benzoxazole

Martine Varache-Béranger, Alain Nuhrich and Guy Devaux [1]

Laboratoire de Pharmacie chimique et Chimie thérapeutique
U.E.R. des Sciences pharmaceutiques, Université de Bordeaux II, 3, place de la Victoire,
33076 Bordeaux Cedex, France

Françoise Duboudin

Laboratoire de Chimie organique et organométallique (UA 35), Université de Bordeaux I,
351, cours de la Libération,
33405 Talence Cedex, France

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6-Methoxy-3-(2'-thienyl)-1,2-benzisoxazole has been prepared simultaneously with 6-methoxy-2-(2'-thienyl)-1,3-benzoxazole. The spectral data of these new compounds have been discussed. Mass spectroscopy has proved to be a valid tool in the structural characterization of these isomers and ^{13}C nmr spectrometry confirmed their structures.

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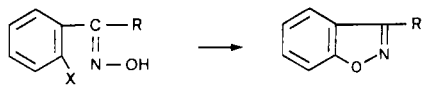
In order to prepare new compounds with pharmacological application, we attempted to synthesize the 6-methoxy-3-(2'-thienyl)-1,2-benzisoxazole. Most methods for the synthesis of 1,2-benzisoxazoles are based on ring closure reactions of benzene derivatives, which contain a chain -C-N-O- in position *ortho* to a group X capable of being eliminated. The most generally used method consists in the cyclisation of *ortho* substituted aromatic oximes [2] (Scheme I).

Scheme I



X: F, Cl, Br, I, NO_2, OH, OCH_3

For our synthesis, the route shown in Scheme II was worked up [3]. The (2-hydroxy-4-methoxyphenyl)-2-thienyl methanone oxime (**2**) was prepared by the reaction of the thienyl methanone **1** with hydroxylamine hydrochloride and sodium hydroxide in aqueous alcoholic solvent. Compound **2** was treated with acetic anhydride, then with sodium hydride in *N,N*-dimethylformamide solution. In contrast with the expected result, we have obtained two different products, **4** and **5** which have been isolated by hplc.

The study of the ir and the ^1H nmr spectra did not allow us to establish the structure of compounds **4** and **5**, but it confirmed the presence of a methoxy aromatic ring and a thiophene ring in the two molecules.

Mass Spectra.

These structures were identified by the fragmentation pattern in their mass spectra.

The mass spectra of **4** (Figure 1) and **5** (Figure 2) showed some common features. They exhibited an intense molecular ion (base peak, m/z = 231) and the same sulfur isotopic ratio of sulfur atom. These two spectral data showed that derivatives **4** and **5** were isomeric compounds with only one sulfur atom.

Therefore we supposed that the structural difference occurred at the intermediate ring.

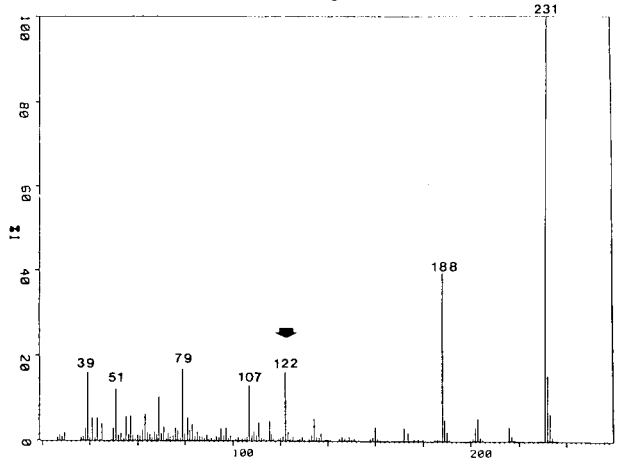


Figure 1. Mass spectrum of **4**.

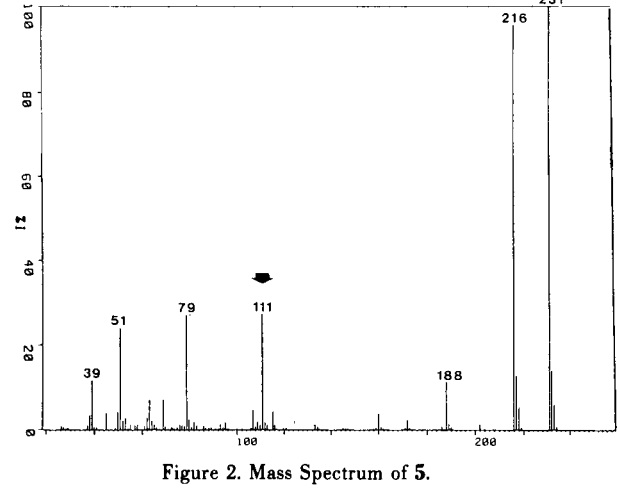
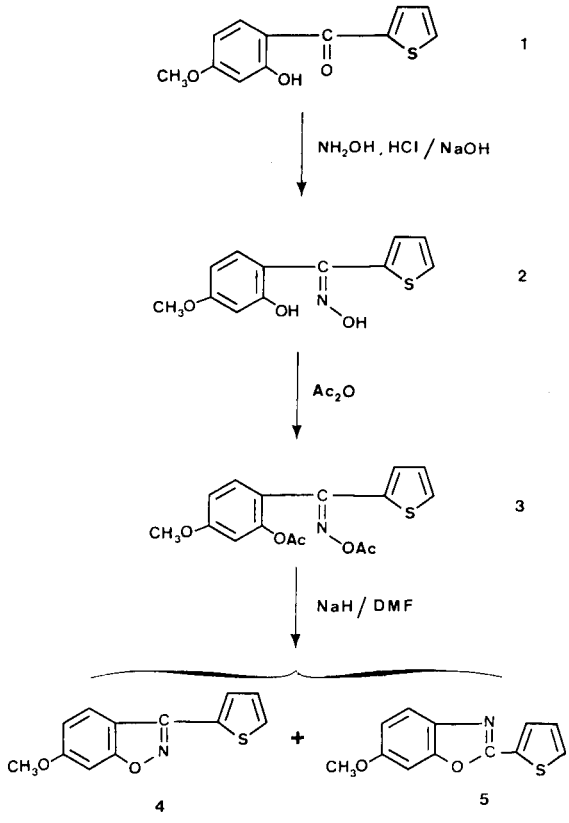


Figure 2. Mass Spectrum of **5**.

Scheme II



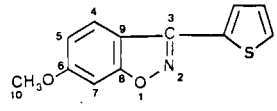
Fragment ions at m/z = 216 and 188 resulted from expulsions of a methyl radical and of a carbonyl group from the molecular ion. The presence of radical ions (Scheme III) at m/z = 122 and 109 showed the cleavage of the oxygen-nitrogen bond characteristic of isoxazoles [4] [5] and confirmed the structure of the expected benzisoxazole **4**.

In a similar manner (Figure 2) the peaks at m/z = 216 and 188 are attributed to the loss of a methyl radical and a carbonyl group, from the molecular ion, respectively. But contrary to what has been observed on derivative **4**, the peak at m/z = 216 is of very high intensity. This reflected the stability of this fragment (which could take a mesomeric quinonic structure) (Scheme IV) under electron impact, which resulted from the 1-4 position of the nitrogen atom and the methoxy group on the benzenic ring.

On the one hand, the absence of the peak at m/z = 122 characteristic of an isoxazole ring, on the other hand, the presence of a new peak at m/z = 111, which was in accor-

Table I

^{13}C NMR Chemical Shifts in δ, ppm and Assignments for Compound **4** and 1,2-Benzisoxazole (**6**)



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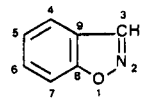
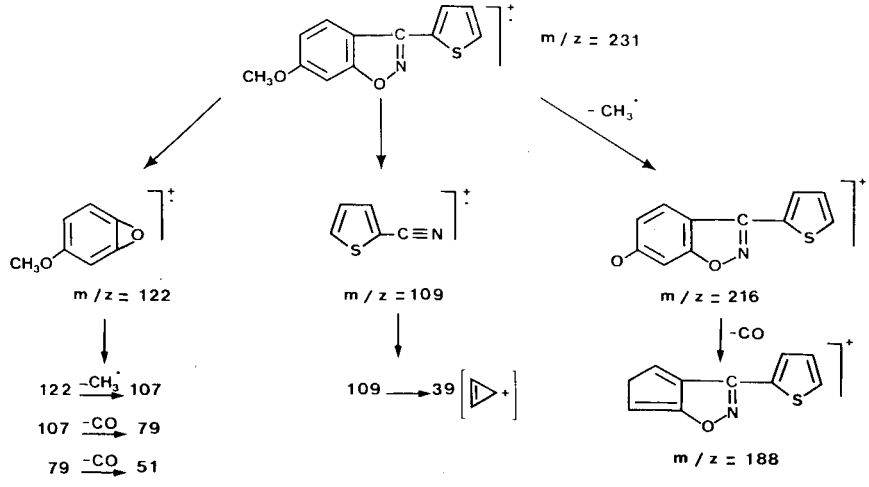


6

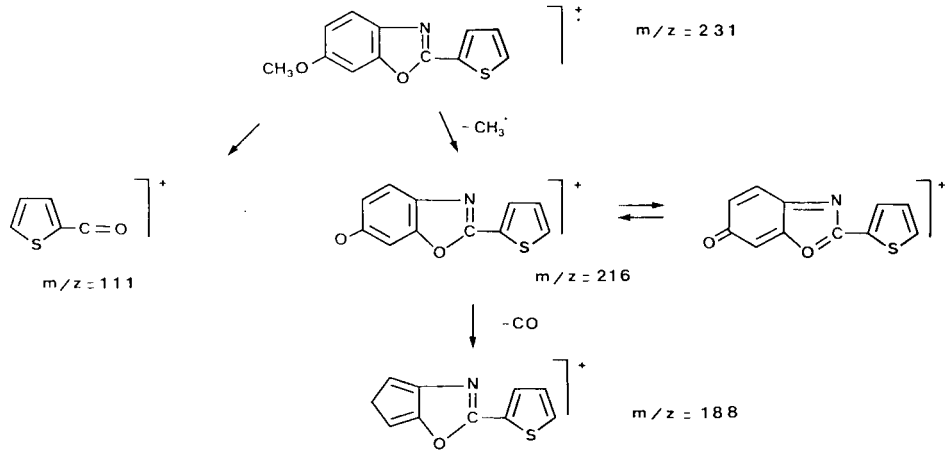
	Measured δ [a]	Predicted δ [b]	
C_3	152.1	—	147.1 [c]
C_4	122.2	125.3	124.3 [c]
C_5	114.9	108.6	123.0 [c]
C_6	162.4	161.5	130.1 [c]
C_7	92.9	95.5	109.9 [c]
C_8	165.8	163.7	162.7 [c]
C_9	113.4	114.2	122.2 [c]
C_{10}	55.9		

[a] Thiophene absorptions 127.9 - 127.9 - 128.1 - 130.2. [b] δ Calculated using the increment rule [9b]. [c] Data from ref [7].

Scheme III. Proposed pathways for the fragmentation of **4**.



Scheme IV. Proposed pathways for the fragmentation of **5**.



dance with a thenoyle ion proved the existence of an oxazolic ring [6] in compound **5**.

^{13}C NMR Spectra.

Final characterization of compounds **4** and **5** was based upon assignments of their ^{13}C nmr spectra. The ^{13}C chemical shift data and assignments of the various carbons of compounds **4** and 1,2-benzisoxazole (**6**) were collected in Table I.

These assignments were realized by comparison with the data reported for the simpler compound **6** [7] [8] and the thiophene ring system [9a] using proton broadband decoupling spectra information.

The methoxy substituted carbon-6 resonance of compound **4** (162.4 ppm) was shifted downfield of the characteristic carbon-6 chemical shift of the parent **6** in accord with substituent effects [9b].

The presence of this typical electron donor group induced also two great variations of shift in the *ortho* and *para* positions. The chemical shifts of carbons-5 and -7 at 114.9 and 92.9 ppm, respectively, showed an upfield shift. Likewise, the chemical shift for carbon-9 was shielded (113.4 ppm).

In Table II, the chemical shifts of compound **5** were compared with benzoxazole (**7**) [10] [11]. In the same manner, the chemical shift for carbon-6 was deshielded by the electron donor methoxy group whereas the chemical shifts of carbons-5 and -7 were shielded. Correspondingly, the shielded carbon-9 resonated at 135.6 ppm.

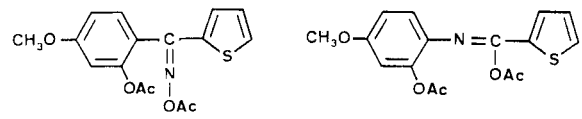
The structures of the isomers **4** and **5**, already indicated by the mass spectra, have been confirmed by a ^{13}C nmr study.

In order to explain the benzoxazole **5** formation, we have undertaken a spectroscopic study of the acetyl derivative **3** which was formed during the acetic anhydride treatment of the oxime.

The ^{1}H nmr spectrum was compatible with a diacetate structure whose purity has been controlled by hplc.

Two isomers **A** and **B** were possible (Scheme V).

Scheme V



A B

The ^{13}C nmr spectroscopy study confirmed the structure **A**. As can be seen from the data in Table III, the quaternary carbon-1 in compound **3** was shown at 119.9 ppm. This chemical shift was similar to the value of the corresponding carbon in benzisoxazole derivatives **4** and **6** (113.4 and 122.2 ppm respectively) (Table I).

Contrarily, it appeared that carbon-1 in compound **3** was more shielded relative to the corresponding carbons in compounds **5** and **7** (Table II).

Accordingly, some litterature data [12] showed a similar chemical shift for carbon-1 of 2,4-dimethoxyacetophenone (**8**) (121.0 ppm).

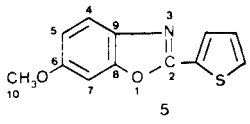
These results were in accordance with the oxime acetate structure A which was cyclized in our experimental conditions to give product **4**.

In order to explain the major product **5** formation, we had thought to a benzisoxazole (**4**) rearrangement as shown in litterature data [13]. But treatment of pure benzisoxazole (**4**) with sodium hydride-dimethylformamide in the same experimental conditions did not give the isomer **5**.

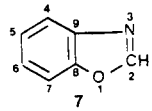
Therefore these observations suggested that the oxime acetate (**3**) was partially converted to imine form during treatment with sodium hydride-dimethylformamide according to a Beckmann type rearrangement in mildly basic conditions [14] [15] followed by ring closure. These considerations led us to propose the reaction pathway shown in Scheme VI.

Table II

^{13}C NMR Chemical Shifts in δ, ppm and Assignments for Compound **5** and benzoxazole (**7**)



5



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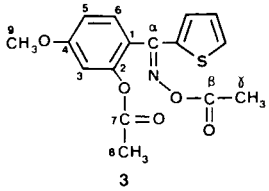
	Measured [a]	Predicted δ [b]	
C_2	151.3	—	152.6 [c]
C_4	119.7	121.5	120.5 [c]
C_5	112.9	111.0	125.4 [c]
C_6	158.3	155.9	124.4 [c]
C_7	95.5	96.4	110.8 [c]
C_8	158.4	151.0	150.0 [c]
C_9	135.6	132.3	140.1 [c]
C_{10}	55.9		

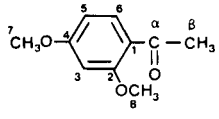
[a] Thiophene absorptions 128.2 - 129.2 - 129.6 - 129.9. [b] δ Calculated using the increment rule [9b]. [c] Data from refs [10] [11].

Table III

^{13}C NMR Chemical Shifts in δ, ppm and Assignments for Compound **3** and 2,4-Dimethoxyacetophenone (**8**)



3



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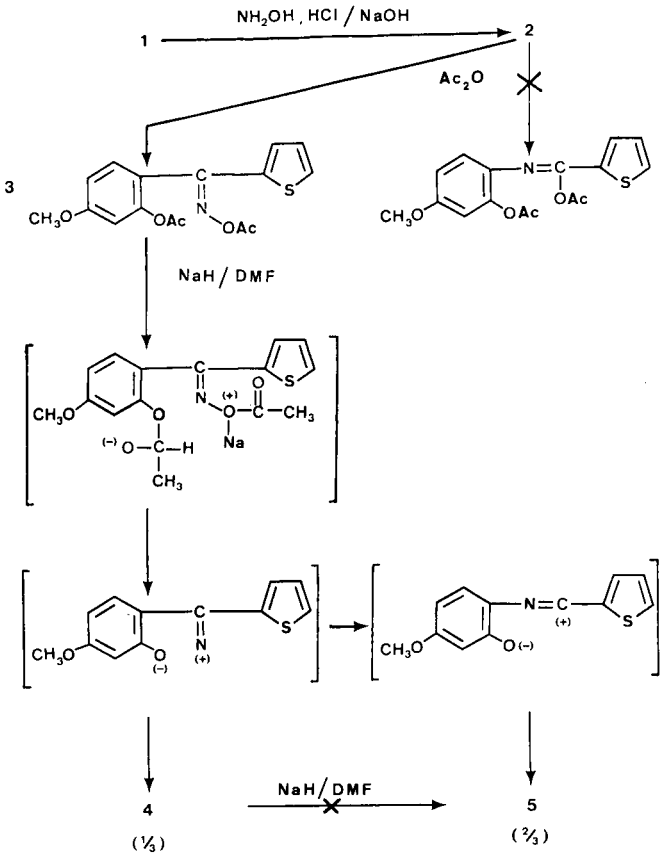
	3			8	
C_1	119.9	C_α 150.2	C_1	121.0 [b]	C_α 197.2 [b]
C_2	161.7	C_β 167.9	C_2	161.2 [b]	C_β 31.8 [b]
C_3	109.3	C_γ 20.2	C_3	98.2 [b]	
C_4	154.3		C_4	164.7 [b]	
C_5	111.7	Thiophene absorptions [a]	C_5	105.4 [b]	
C_6	126.4		C_6	132.5 [b]	
C_7	168.8		C_7	55.4 [b]	
C_8	20.7		C_8	55.4 [b]	
C_9	55.8				

[a] 131.6 - 132.1 - 133.1 - 135.2. [b] Data from ref [12].

EXPERIMENTAL

Melting points were taken using a Köfler melting point apparatus and were uncorrected. Ultraviolet spectra were measured in 95% ethanol with an Unicam Model SP 1800 spectrophotometer. Infrared spectra were run on a Beckman Model Aculab 1 spectrophotometer as potassium bromide pellets. The ^1H nmr spectra were recorded on a 60 MHz Varian Model EM 360 L spectrometer; ^{13}C nmr spectra were measured with a 62.9 MHz BRUKER AC 250 spectrometer in deuteriochloroform as solvent; off resonance and DEPT spectra were recorded. Chemical shifts were measured in ppm (δ) using tetramethylsilane as internal reference. The mass spectra were obtained on an A.E.I. MS 12 spectrometer with a 16F data system. Samples were analysed by a direct insertion probe at an ionization voltage of 70 eV with a source temperature of 220°. Preparative chromatography was performed using Waters Preparative LC System 500A liquid chromatograph. Elemental analyses were performed by the Service Central d'Analyse du C.N.R.S [Vernaison (Rhône) - France].

Scheme VI



(2-Hydroxy-4-methoxyphenyl)-2-thienylmethanone Oxime (**2**).

To a stirred solution of 3.55 g (15.0 mmoles) of (2-hydroxy-4-methoxyphenyl)-2-thienylmethanone (**1**) [16] in 50 ml of an ethanol-water mixture (75:25) was added successively 1.39 g (20.0 mmoles) of hydroxylamine hydrochloride and 6 g (150.0 mmoles) of sodium hydroxide portionwise over 10 minutes. The reaction mixture was heated at reflux for 30 minutes and after cooling poured into water. Neutralization with concentrated hydrochloric acid produced a brown oil which was extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel eluting with dichloromethane-ethyl acetate (95:5). Recrystallization from hexane-dichloromethane (95:5) gave 2.43 g (65%) of **2**, mp 100°; ir: 3350, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.78 (s, 3H), 6.32 to 7.80 (m, 6H), 9.62 (s, 1H), 11.82 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62; S, 12.86. Found: C, 57.76; H, 4.28; N, 5.37; S, 12.51.

(2-Acetoxy-4-methoxyphenyl)-2-thienylmethanone Oxime Acetate (**3**).

A stirred solution of 2.49 g (10.0 mmoles) of **2** in 100 ml of acetic anhydride was heated at 90° for 1 hour. The reaction mixture was allowed to stir at room temperature for 18 hours, and then poured into 200 ml of water. Following an hour hydrolysing, the reaction mixture was made neutral by adding aqueous sodium hydroxide (10%), then extracted with dichloromethane. The organic solution was washed with saturated aqueous sodium hydrogen carbonate, then with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate-hexane (60:40) as eluent, and the obtained solid was recrystallized from cyclohexane to give 1.50 g (45%) of **3** as white crystals, mp 112°; ir: 1775, 1760, 1615, 1580 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.98 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 6.75 to 7.75 (m, 6H); ^{13}C nmr: δ off resonance results 20.2 (CH_3), 20.7 (CH_3), 55.8 (CH_3), 109.3 (CH), 111.7 (CH), 119.9 (C), 126.4 (CH), 131.6 (C), 132.1 (CH), 133.1 (CH), 135.2 (CH), 150.2 (C), 154.3 (C), 161.7 (C), 167.9 (C), 168.8 (C).

Anal. Calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.53; N, 4.20; S, 9.62. Found: C, 57.67; H, 4.48; N, 4.11; S, 9.35.

6-Methoxy-3-(2'-thienyl)-1,2-benzisoxazole (**4**) and 6-Methoxy-2-(2'-thienyl)-1,3-benzoxazole (**5**).

To a solution of 1.66 g (5 mmoles) of **3** in 50 ml of dimethylformamide, 200 mg (5 mmoles) of sodium hydride (60% dispersion in mineral oil) was added with ice-cooling at 0°. The resulting mixture was stirred at room temperature for 4 hours, poured into 500 ml of ice-cold water, and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate and with water. After drying over anhydrous sodium sulfate, the ethyl acetate was evaporated *in vacuo*. High performance liquid chromatography on Waters prep-pak silica cartridge using hexane-dichloromethane eluent (60:40) afforded two crystalline products. The first one was recrystallized from cyclohexane to yield 0.24 g (21%) of **4**, mp 97°; uv: λ max (ε) 217 (12000), 254 (14500), 296 (15600) nm; ir: 1620, 1600, 1555, 1450, 1435, 1285 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 3.85 (s, 3H), 6.80 to 7.95 (m, 6H); ^{13}C nmr: δ off resonance results 55.9 (CH_3), 92.9 (CH), 113.4 (C), 114.9 (CH), 122.2 (CH), 127.9 (2 CH), 128.1 (CH), 130.2 (C), 152.1 (C), 162.4 (C), 165.8 (C); ms: (70 eV) m/z (%), 231 (100), 216 (3), 188 (39), 122 (17), 107 (13), 79 (17), 69 (10), 51 (12), 39 (16).

Anal. Calcd. for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.05; S, 13.86. Found: C, 62.24; H, 3.86; N, 6.01; S, 13.74.

Recrystallization of the second product from hexane furnished 0.50 g (43%) of **5**, mp 74°; uv: λ max (ε), 326 (27400) nm; ir: 1615, 1580, 1490, 1320 cm^{-1}; ^1H nmr (carbon tetrachloride): δ 3.85 (s, 3H), 6.80 to 7.95 (m, 6H); ^{13}C nmr: δ off resonance results 55.9 (CH_3), 95.5 (CH), 112.9 (CH), 119.7 (CH), 128.2 (CH), 129.2 (CH), 129.6 (CH), 129.9 (C), 135.6 (C), 151.3 (C), 158.3 (C), 158.4 (C); ms: (70 eV) m/z (%), 231 (100), 216 (96), 188 (11), 111 (27), 79 (27), 51 (24), 39 (11).

Anal. Calcd. for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.05; S, 13.86. Found: C, 62.11; H, 3.86; N, 5.79; S, 13.25.

Acknowledgements.

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