Studies on Isocyanides and Related Compounds. An Unusual Synthesis of Imidazolyloxazolones

Ricardo Bossio, Stefano Marcaccini* and Roberto Pepino

CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, via Gino Capponi 9, I-50121 Firenze, Italy

Paola Paoli

Dipartimento di Energetica, Università di Firenze, via S. Marta 3, I-50139 Firenze, Italy

Received November 1, 1993

The reaction between ethyl (*Z*)-3-dimethylamino-2-isocyanoacrylate (**1**) and arenesulfenyl chlorides **6a-c** afforded the unexpected imidazolyloxazolones **7a-c**. The structure of compounds **7a-c** was in agreement with their ^{1}H nmr, ir and ms data and was confirmed by X-ray analysis of **7a**.

J. Heterocyclic Chem., **31**, 729 (1994).

In our continuing research on the synthesis of heterocyclic compounds from isocyanides [1], we reported two studies [2,3] on the behavior of ethyl (*Z*)-3-dimethylamino-2-isocyanoacrylate (**1**) towards acyl chlorides **2a,b** and sulfenyl chlorides **3a-c**. The reaction between **1** and chlorides **2a,b** and **3a-c** led to the formation of oxazolones **4a,b** and **5a-c** respectively.

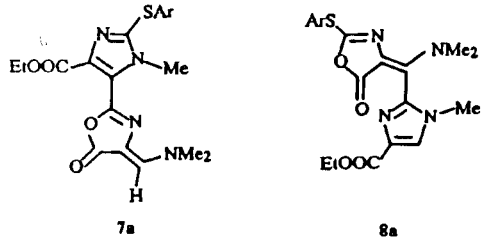
An attempt to prepare 2-phenylthio-4-dimethylaminomethyleneoxazol-5(4*H*)-one (structure **5**, Ar = C_6H_5) by reacting **1** with benzenesulfenyl chloride (**6a**) gave a reaction product with mp 148-149°, whose analytical and spectral data did not agree with the desired structure.

The analytical and mass spectral data for this compound suggested the following reaction stoichometry:

2 (**1**) + 2 PhSCl (**6a**) - PhSH - EtCl - MeCl

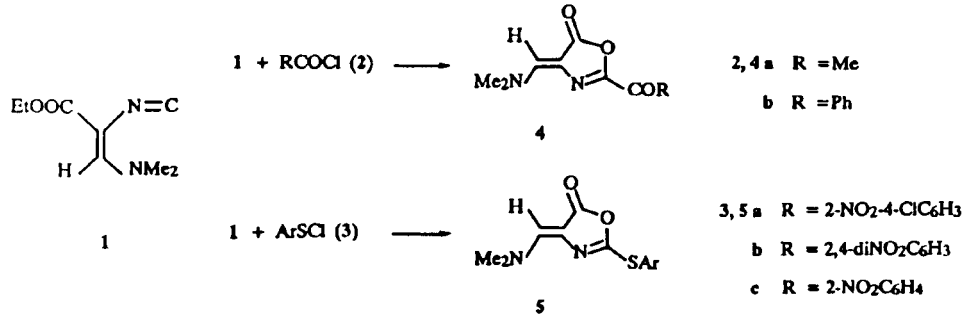
In the ^{1}H nmr spectrum of this compound a triplet signal at δ 1.36 and a quadruplet signal at δ 4.37 were detected, due to an ethoxycarbonyl group. Furthermore, three singlet signals were detected at δ 3.27, 3.52 and 3.74. These chemical shifts suggested the presence of three NCH_3 groups. A singlet signal, whose integral corresponds to one proton, was found at δ 7.21 and this suggested the presence of a deshielded proton. In addition, a multiplet signal at δ 7.23-7.30, whose integral corresponds to five protons, was detected in agreement with the presence of a phenyl group. In the ir spectrum three strong absorptions at 1740, 1724, and 1656 cm^{-1} were detected, in agreement with a lactone, an ester, and a C=N group, respectively. On the basis of the analytical and spectral data we hypothesized for this compound the following possible structures **7a** and **8a**. Since we considered the data in our possession as unsuitable for the determination of its structure, we performed an X-ray analysis that confirmed the structure **7a**. An analogous behavior was found by reacting **1** with 4-chlorobenzenesulfenyl chloride (**6b**) and 4-methylbenzene sulfenyl chloride (**6c**).

Scheme 2

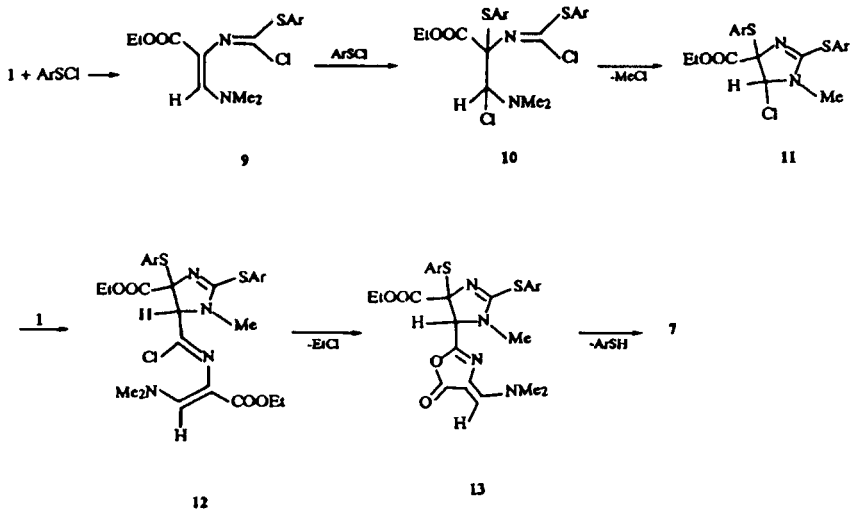


7a **8a**

Scheme 1



Scheme 3



1 + ArSCl → **7a-c** **6, 7** **a** Ar = C_6H_5

6a-c **b** Ar = 4-ClC_6H_4

c Ar = 4-$CH_3C_6H_4$

Thus, the reactivity of **1** towards sulfenyl chlorides **3** and **6** is totally different. Since compounds **3** bear a nitro group in *ortho* with respect to the SCl group the influence of steric effects on the reaction pathway can not be rejected *a priori*. Thus we performed a reaction between 4-nitrobenzenesulfenyl chloride and **1**. The reaction product was identified as 4-dimethylaminomethylene-2-(4-nitrophenylthio)oxazol-5(4*H*)-one (structure **5** Ar = 4-$NO_2C_6H_4$). This result led us to the conclusion that the different behavior depends upon the higher reactivity of sulfenyl chlorides **6** than **3**. A possible reaction pathway is reported below. The first attack of the sulfenyl chloride on the isocyano group of **1** is reasonable, on the basis of the well-stablished reactivity of sulfenyl chlorides towards isocyanides [4-6]. The formation of the adduct **10** can be explained on the basis of the high reactivity of sulfenyl chlorides towards enamines [7-9]. Since, in the reaction medium, the sulfenyl chloride is in lower concentration with respect to the start-

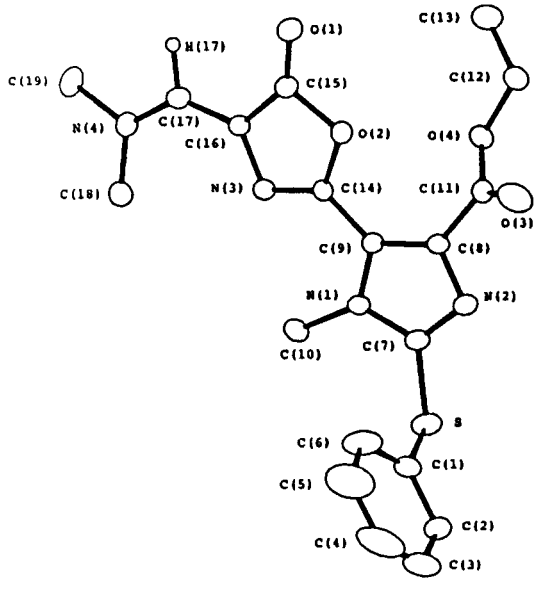


Figure. Structure of **7a** as determined by X-ray analysis.

Table 1

Positional Parameters (x10^4) and Equivalent Thermal Parameters (x10^3)

Atom	x/a	y/b	z/c	U
S	8019(1)	4203(2)	4362(1)	68(1)
N1	6404(3)	6017(6)	4641(2)	45(2)
N2	6519(3)	5415(6)	3437(2)	52(3)
N3	4754(3)	7734(5)	5294(2)	44(2)
N4	3715(3)	9022(6)	6646(2)	55(3)
O1	2780(3)	9729(5)	4297(2)	65(2)
O2	4150(2)	8290(5)	4109(2)	48(2)
O3	5287(3)	7136(8)	2250(2)	100(4)
O4	4139(2)	6094(5)	2892(2)	58(2)
C1	8874(4)	5821(8)	4238(3)	60(3)
C2	9753(4)	5278(11)	4045(3)	78(5)
C3	10461(5)	6478(17)	3979(4)	109(7)
C4	10299(7)	8177(17)	4070(6)	129(9)
C5	9424(7)	8702(12)	4262(7)	145(9)
C6	8705(4)	7532(9)	4356(5)	99(6)
C7	6935(3)	5271(7)	4125(3)	50(3)
C8	5678(3)	6241(6)	3507(3)	43(3)
C9	5590(3)	6638(6)	4245(3)	40(3)
C10	6667(4)	6059(8)	5452(3)	57(3)
C11	5027(4)	6572(7)	2814(3)	53(3)
C12	3414(4)	6533(10)	2277(3)	74(4)
C13	2480(5)	6564(10)	2576(4)	87(5)
C14	4854(3)	7541(6)	4595(2)	40(3)
C15	3489(3)	9017(7)	4574(3)	46(3)
C16	3904(3)	8672(7)	5313(3)	43(3)
C17	3448(3)	9154(7)	5925(3)	47(3)
C18	4640(4)	8396(8)	6953(3)	66(4)
C19	3049(4)	9465(10)	7195(3)	82(5)

ing isocyanide **1**, it is necessary to assume the adduct **9** to be more reactive than **1** towards **3**. The cyclization of the adduct **12**, formed through an electrophilic attack of **11** on **1** is closely similar to analogous reactions [2,3] and the elimination of thiol from **13** appears reasonable on the basis of the high conjugation of the final product **6**.

With regard to the ^{1}H nmr spectral data of **7a-c**, the singlet signal at about δ 5.70 was assigned to the methyl group in position 1 of the imidazole nucleus on the basis of the comparison of the spectra of compounds **7a-c** with those of compounds **5a-c** [3] and 4-dimethylaminomethylene-2-(4-nitrophenylthio)oxazol-5-(4*H*)-one (structure **5** Ar = 4-$NO_2C_6H_4$).

An examination of the geometrical features of compound **7a** showed the existence of an extended conjugation, involving the dimethylaminomethylene group and the imidazole ring through the oxazole nucleus. On the other hand, the ester group does not lie in the conjugation plane, probably on account of the repulsion between the O(2) and the oxygen atoms of the ester group itself.

Table 2

Bond Distances (A) and Angles (°)

S	-	C1		1.769(6)
S	-	C7		1.749(5)
N1	-	C7		1.374(7)
N1	-	C9		1.372(6)
N1	-	C10		1.467(6)
N2	-	C7		1.317(6)
N2	-	C8		1.360(6)
N3	-	C14		1.285(5)
N3	-	C16		1.402(6)
N4	-	C17		1.315(6)
N4	-	C18		1.444(7)
N4	-	C19		1.465(7)
O1	-	C15		1.203(6)
O2	-	C14		1.381(5)
O2	-	C15		1.425(6)
O3	-	C11		1.194(7)
O4	-	C11		1.321(6)
O4	-	C12		1.464(6)
C1	-	C2		1.379(8)
C1	-	C6		1.376(9)
C2	-	C3		1.377(13)
C3	-	C4		1.358(19)
C4	-	C5		1.368(15)
C5	-	C6		1.382(12)
C8	-	C9		1.378(7)
C8	-	C11		1.491(7)
C9	-	C14		1.444(6)
C12	-	C13		1.463(9)
C15	-	C16		1.421(7)
C16	-	C17		1.377(7)

Table 2 (continued)

C1	-	S	- C7	102.2(3)
C9	-	N1	- C10	128.4(4)
C7	-	N1	- C10	125.4(4)
C7	-	N1	- C9	106.2(4)
C7	-	N2	- C8	105.1(4)
C14	-	N3	- C16	105.1(4)
C18	-	N4	- C19	115.6(4)
C17	-	N4	- C19	120.4(4)
C17	-	N4	- C18	124.0(4)
C14	-	O2	- C15	105.3(4)
C11	-	O4	- C12	116.4(4)
S	-	C1	- C6	122.9(5)
S	-	C1	- C2	116.4(6)
C2	-	C1	- C6	120.6(6)
C1	-	C2	- C3	118.8(8)
C2	-	C3	- C4	121.4(7)
C3	-	C4	- C5	119.3(11)
C4	-	C5	- C6	121.0(9)
C1	-	C6	- C5	118.9(7)
N1	-	C7	- N2	112.1(4)
S	-	C7	- N2	124.2(4)
S	-	C7	- N1	123.6(4)
N2	-	C8	- C11	118.0(4)
N2	-	C8	- C9	110.9(4)
C9	-	C8	- C11	131.1(5)
N1	-	C9	- C8	105.6(4)
C8	-	C9	- C14	131.6(4)
N1	-	C9	- C14	122.7(3)
O4	-	C11	- C8	111.6(5)
O3	-	C11	- C8	124.0(5)
O3	-	C11	- O4	124.3(5)
O4	-	C12	- C13	107.8(5)
O2	-	C14	- C9	115.4(3)
N3	-	C14	- C9	129.3(4)
N3	-	C14	- O2	115.3(4)
O1	-	C15	- O2	120.0(5)
O2	-	C15	- C16	104.0(4)
O1	-	C15	- C16	136.0(5)
N3	-	C16	- C15	110.3(4)
C15	-	C16	- C17	120.9(4)
N3	-	C16	- C17	128.7(5)
N4	-	C17	- C16	130.9(5)

EXPERIMENTAL

Melting points were detemined in open capillary tubes with a Büchi 512 apparatus. Infrared spectra were recorded as potassium bromide pellets using a Perkin-Elmer 881 Infrared spectrophotometer. Proton nmr spectra were determined on a Varian Gemini 200 in deuteriochloroform saturated solutions. Elemental analyses for C, H and N were performed using a Perkin-Elmer 240 C Elemental analyzer. The molecular structure was determined by the X-ray diffraction using an Enraf-Nonius CAD4 automatic diffractometer. Mass spectra were measured on a Carlo Erba QMD 1000 apparatus operating with an activation energy of 70 eV. Compounds **1** [10], **6a** [11], **6b** [12] and **6c** [13] were prepared according to literature procedures.

General Procedure for the Reaction of Ethyl (*Z*)-3-Dimethylamino-2-isocyanoacrylate (**1**) with Arenesulfenyl Chlorides **6a-c**.

A solution of **6** (10 mmoles) in dichloromethane (10 ml) was slowly added to a well-stirred solution of **1** (1.68 g, 10 mmoles) in dichloromethane (40 ml), maintaining the temperature at −50°. The reaction mixture was allowed to stand overnight and then evaporated to dryness. The residue was recyrstallized from ethanol.

4-Dimethylaminomethylene-2-(2-phenylthio-4-ethoxycarbonyl-1-methylimidazol-5-yl)oxazol-5(4*H*)-one (**7a**).

This compound was obtained in 75% yield, mp 148-149°; ir: ν 1740, 1724, 1656 cm^{-1}; ^1H nmr: 1.35 (q, 3H, J = 7.2 Hz, CH_2CH_3), 3.27 (s, 3H, CH_3 dimethylamino), 3.52 (s, 3H, CH_3 dimethylamino), 3.74 (s, 3H, CH_3, on 1-imidazole position), 4.38 (q, 2H, J = 7.2 Hz, CH_2), 7.19 (s, 1H, vinyl proton), 7.23-7.30 (m, 5H, aromatic protons); ms: m/z 400 (M^+).

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.04; N, 13.99. Found: C, 57.15; H, 4.91; N, 14.07.

2-[2-(4-Chlorophenylthio)-4-ethoxycarbonyl-1-methylimidazol-5-yl]-4-dimethylaminomethyleneoxazol-5(4*H*)-one (**7b**).

This compound was obtained in 78% yield, mp 133-134°; ir: ν 1737, 1708, 1651 cm^{-1}; ^1H nmr: δ 1.35 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.28 (s, 3H, CH_3 dimethylamino), 3.52 (s, 3H, CH_3 dimethylamino), 3.75 (s, 3H, CH_3 on 1-imidazole position), 4.37 (q, 2H, J = 7.2 Hz, CH_2), 7.17-7.29 (m, 5H, aromatic and vinyl protons); ms: m/z 435 (M^+).

Anal. Calcd. for $C_{19}H_{19}ClN_4O_4S$: C, 52.48; H, 4.41; N, 12.88. Found: C, 52.60; H, 4.47; N, 12.71.

4-Dimethylaminomethylene-2-[2-(4-methylphenylthio)-4-ethoxycarbonyl-1-methylimidazol-5-yl]oxazol-5(4*H*)-one (**7c**).

This compound was obtained in 69% yield, mp 124-125°; ir: ν 1742, 1728, 1657 cm^{-1}; ^1H nmr: δ 1.35 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.30 (s, 3H, CH_3 toluene), 3.26 (s, 3H, CH_3 dimethylamino), 3.51 (s, 3H, CH_3 dimethylamino), 3.72 (s, 3H, CH_3 on 1-imidazole position), 4.36 (q, 2H, J = 7.2 Hz, CH_2), 7.07-7.26 (m, 5H, aromatic + vinyl protons); ms: m/z 414 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_4O_4S$: C, 57.96; H, 5.35; N, 13.52. Found: C, 57.81; H, 5.49; N, 13.69.

4-Dimethylaminomethylene-2-(4-nitrophenylthio)oxazol-5(4*H*)-one (Structure **5**, Ar = 4-$NO_2C_6H_4$).

This compound was prepared in 92% yield following the above procedure, by employing 4-nitrobenzenesulfenyl chloride in the place of compounds **6**, mp 141-142°; ir: ν 1762, 1634 cm^{-1}; ^1H nmr: δ 3.24 (s, 3H, CH_3 dimethylamino), 3.45 (s, 3H, CH_3 dimethylamino), 7.04 (s, 1H, vinyl proton), 7.59-8.21 (m, 4H, aromatic protons).

Anal. Calcd. for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33. Found: C, 49.26; H, 3.84; N, 14.19.

X-Ray Crystallographic Data for **7a**.

Crystals of $C_{19}H_{20}N_4O_4S$ were obtained from acetone. A single crystal of the appropriate size (0.8 x 0.6 x 0.3 mm) was employed. Determination of the cell parameters was performed by least squares refinement of 25 reflections. The compound crystallizes in the monoclinic system, space group $P2_1/n$ with a = 14.014(3), b = 7.804(6), c = 17.954(6) Å, β = 95.68(2)°; Z = 4; V = 1954(2) $Å^3$; m = 1.89 cm^{-1}; Dc = 1.36 g cm^{-3}; 3830 reflections were collected in the range $5 < 2\theta < 50°$, using MoKα radiation (λ = 0.71069 Å) θ-2θ scan mode. The structure was solved by direct methods of SIR88 [14] and refined by full-matrix least-squares to R = 0.060 and Rw = 0.064 ($w = 1/\sigma^2(F_o) + 0.0005 F_o^2$), by using the 1806 observed reflections having $I > 3\sigma(I)$ for 252 parameters refined. All non-hydrogen atoms were refined anisotropically, whereas the hydrogen atoms were refined in fixed positions with an overall isotropic temperature factor U of 0.05 $Å^2$. The fractional atomic coordinates and equivalent isotropic parameters for the individually refined atoms are reported in Table 1. Further data are available on request from the authors.

REFERENCES AND NOTES

[1a] R. Bossio, S. Marcaccini and R. Pepino, *Tetrahedron Letters*, **27**, 4643 (1986); [b] R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 935 (1990); [c] R. Bossio, S. Marcaccini, P. Paoli, R. Pepino and C. Polo, *Heterocycles*, **31**, 1855 (1990); [d] R. Bossio, S. Marcaccini and R. Pepino, *J. Chem. Res. (S)*, 331 (1991).

[2] R. Bossio, S. Marcaccini, R. Pepino, P. Paoli and C. Polo, *J. Heterocyclic Chem.*, **30**, 575 (1993).

[3] R. Bossio, S. Marcaccini and R. Pepino, *J. Chem. Res. (S)*, 1 (1993).

[4] E. Kühle, The Chemistry of the Sulfenic Acids, Georg Thieme Publishers, Stuttgart, 1973, p 57.

[5] A. J. Havlik and M. M. Wald, *J. Am. Chem. Soc.*, **77**, 5171 (1955).

[6] R. Bossio, S. Marcaccini and R. Pepino, *Heterocycles*, **24**, 2003 (1986).

[7] G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 798 (1964).

[8] R. Gompper and E. W. Elser, *Liebigs Ann. Chem.*, **725**, 73 (1969).

[9] R. Bossio, S. Marcaccini, R. Pepino, C. Polo and T. Torroba, *Heterocycles*, **29**, 1829 (1989).

[10] U. Schöllkopf, P. H. Porsch and H. H. Lau, *Liebigs Ann. Chem.*, 1444 (1979).

[11] H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

[12] M. B. Sparke, J. L. Cameron and N. Kharasch, *J. Am. Chem. Soc.*, **75**, 4907 (1953).

[13] H. Lecher, F. Holschneider, K. Köberle, W. Speer and P. Stöcklin, *Ber.*, **58**, 409 (1925).

[14] M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna and D. Viterbo, *J. Appl. Cryst.*, **22**, 389 (1989).