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Synthesis of new 1,2,4-oxadiazolidin-3-ones by cycloaddition of 2-alkyl-3-aryloxaziridines with chlorosulfonylisocyanate

Jamil Kraïem,[a] Laurent Grosvalet,[b] Monique Perrin[b] and Béchir Ben Hassine[a,*]

[a]*Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, Faculté des Sciences de Monastir, Avenue de l'environnement, 5019 Monastir, Tunisia*

[b]*Laboratoire de Cristallographie, CNRS UPRES A 5078, Reconnaissance et Organisation Moléculaire, Université Claude Bernard Lion 1, Bâi. 201, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*

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Abstract—2-Alkyl-4-chlorosulfonyl-5-aryl-1,2,4-oxadiazolidin-3-ones **5** were prepared via cycloaddition of 2-alkyl-3-aryloxaziridines **3** with chlorosulfonylisocyanate. The structure of **5** was proved by a crystal X-ray analysis. Hydrolysis of **5** in the presence of triethylamine afforded 2-alkyl-5-aryl-1,2,4-oxadiazolidin-3-ones **6**. © 2001 Elsevier Science Ltd. All rights reserved.

1,2,4-Oxadiazolidin-3-ones, first reported in 1957 by Lopresti et al.,[1] represent a class of biologically active heterocycles.[1–5] However, only a few methods of synthesis of these compounds have been reported,[1,3,6–8] in which carbamonyl chlorides, hydroxyureas and α-bromoisocyanates are often employed as starting materials. Del'tsova et al.[8] have shown that cycloaddition of the fluorinated oxaziridine **1** with the *n*-heptafluoropropylisocyanate occurs with cleavage of the C–N bond of the oxaziridine ring and leads to the corresponding 1,2,4-oxadiazolidin-3-one **2**. These authors have described only one example. In fact, cycloaddition of oxaziridines with isocyanates does not appear to be a general procedure for preparation of 1,2,4-oxadiazolidin-3-ones. Indeed, Agawa et al.[9] have previously reported cycloaddition of 2-alkyl-3-aryloxaziridines **3** with phenylisocyanate, which proceeds with cleavage of the C–O bond of the oxaziridine ring to give the corresponding 1,2,4-oxadiazolidin-5-ones **4**.

Chlorosulfonylisocyanate (CSI), discovered by Graf,[10] is an heterocumulene of exceptional reactivity.[11] Until now, no reaction of this compound with oxaziridines has been reported.

Herein, we describe a facile synthesis of new 1,2,4-oxadiazolidin-3-ones by cycloaddition of CSI with a variety of 2-alkyl-3-aryloxaziridines **3a–h**. The latter were prepared via oxidation of the corresponding imines with the benzonitrile–hydrogen peroxide system,[12] and were obtained exclusively in the (E) isomeric form. Adducts **5a–h** were obtained in good yields (Table 1) by refluxing oxaziridines **3a–h** with CSI in CH_2Cl_2[13] (Scheme 1). The reaction was completed within 30 min and no significant by-products were observed. These compounds were stable at room temperature for several months without any significant decomposition. The cleavage of the chlorosulfonyl group was carried out by

Table 1. Synthesis of 2-alkyl-4-chlorosulfonyl-5-aryl-1,2,4-oxadiazolidin-3-ones **5a–h**

Entry	Product	R	X	Isolated yields (%)	Mp (°C)
1	**5a**	*t*Bu	H	75	86–88
2	**5b**	*t*Bu	4-Cl	67	82–84
3	**5c**	*t*Bu	4-Me	68	72–74
4	**5d**	*i*Pr	H	69	68–70
5	**5e**	*i*Pr	4-Me	62	63–65
6	**5f**	*c*-C_6H_{11}	H	82	114–116
7	**5g**	*c*-C_6H_{11}	4-Me	70	110–112
8	**5h**	*c*-C_6H_{11}	2-Me	78	105–107

* Corresponding author. E-mail: bechir.benhassine@fsm.rnu.tn

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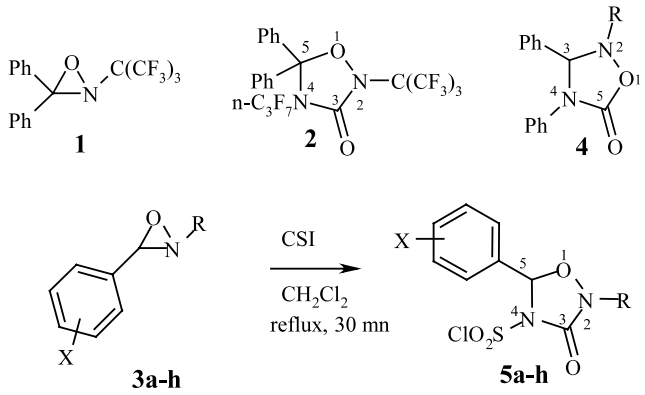

Scheme 1.

hydrolysis of oxadiazolidinones **5a**–**e** in the presence of triethylamine at room temperature[14] (Scheme 2). This reaction afforded 2-alkyl-5-aryl-1,2,4-oxadiazolidin-3-ones **6a**–**e** in high yields (Table 2).

From a mechanistic point of view, oxaziridines **3a**–**h** undergo cycloaddition with CSI, which involves selective cleavage of the C–N bond of the oxaziridine ring (Scheme 3), and appears to be similar to Del'tsova cycloaddition reaction, rather than of Agawa et al. This result was proved by the X-ray analysis[15] of the adduct cited in entry 4, which was identified as 2-alkyl-4-chlorosulfonyl-5-phenyl-1,2,4-oxadiazolidin-3-one (**5d**) (Fig. 1).

To conclude, cycloaddition of 2-alkyl-3-aryloxaziridines with CSI afforded new 1,2,4-oxadiazolidin-3-ones. These compounds represent a new class of 1,2,4-oxadiazolidin-3-ones, since the reactivity of the chlorosulfonyl group linked to the N-4 atom of the cycle permit the anticipation of several applications of these compounds in synthetic organic chemistry. On the other hand, it will be more interesting to prepare the first example of chiral 1,2,4-oxadiazolidin-3-ones from optically pure oxaziridines.[12]

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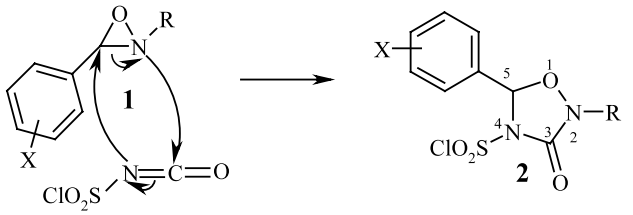
Table 2. Synthesis of 2-alkyl-5-aryl-1,2,4-oxadiazolidin-3-ones **6a**–**e**

6a–e	R	X	Isolated yields (%)	Mp (°C)
6a	*t*Bu	H	92	145–147
6b	*t*Bu	4-Cl	88	144–146
6c	*t*Bu	4-Me	88	173–176
6d	*i*Pr	H	77	102–104
6e	*i*Pr	4-Me	82	108–110



Scheme 3.

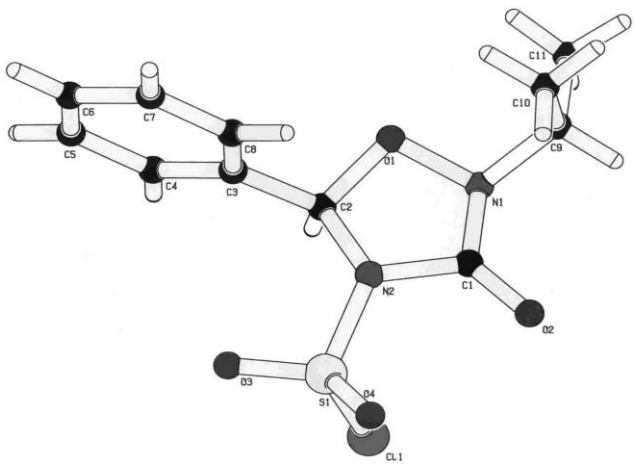
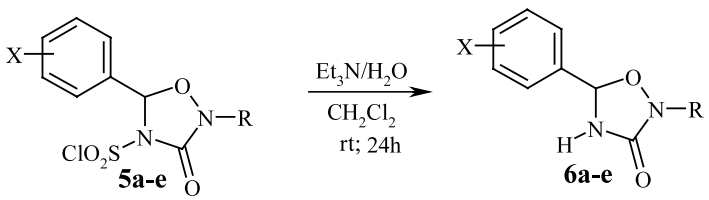


Figure 1. X-Ray structure of **5d**.



Scheme 2.

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13. Typical procedure for the synthesis of **5a–h**. To a stirred solution of oxaziridine (10 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over 5 min a solution of CSI (11 mmol) in 10 mL of CH_2Cl_2 via syringe. The reaction mixture was refluxed for 30 min under argon. At that time, all of the oxaziridine was consumed. After cooling the mixture to room temperature, the solvent was removed on a rotary evaporator and the crude product was purified by flash chromatography (SiO_2; cyclohexane–ethyl acetate 95:5). Characteristics of compounds **5a–h** are given as follows.
Compound **5a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62–7.49 (m, 5H), 6.30 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.36 (C=O), 132.17, 131.36, 128.79, 128.24, 90.52 (CH methine), 61.29, 26.39; IR (KBr) 1778 cm^{-1}; MS DCI/NH_3: 336 (M+NH_4^+). Anal. calcd for $C_{12}H_{15}ClN_2O_4S$: C, 45.21; H, 4.70; N, 8.79. Found: C, 44.90; H, 4.72; N, 8.72%.
Compound **5b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.45 (m, 4H), 6.28 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.15, 137.55, 130.73, 129.55, 129.16, 89.72, 61.41, 26.37; IR (KBr) 1778 cm^{-1}; MS DCI/NH_3: 370 (M+NH_4^+). Anal. calcd for $C_{12}H_{14}Cl_2N_2O_4S$: C, 40.79; H, 3.96; N, 7.93. Found: C, 41.12; H, 4.02; N, 7.99%.
Compound **5c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49–7.28 (m, 4H), 6.25 (s, 1H), 2.43 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.86, 142.18, 129.95, 129.78, 128.65, 91.10, 61.68, 26.88, 21.79; IR (KBr) 1778 cm^{-1}; MS DCI/NH_3: 350 (M+NH_4^+).
Compound **5d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.44 (m, 5H), 6.32 (s, 1H), 4.29–4.22 (h, 1H), 1.35 (d, 3H), 1.33 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.21, 131.96, 131.37, 128.75, 128.15, 91.06, 61.43, 18.82, 18.20; IR (KBr) 1780 cm^{-1}; MS DCI/NH_3: 322 (M+NH_4^+). Anal. calcd for $C_{11}H_{12}ClN_2O_4S$: C, 43.34; H, 4.26; N, 9.19. Found: C, 43.29; H, 4.31; N, 9.25%.
Compound **5e**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.31 (m, 4H), 6.30 (s, 1H), 4.33–4.24 (h, 1H), 2.43 (s, 3H), 1.37 (d, 3H), 1.35 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.41, 139.28, 129.70, 129.58, 128.49, 91.13, 61.24, 23.22, 18.52, 18.06; MS DCI/NH_3: 336 IR (KBr) 1766 cm^{-1}. (M+NH_4^+).
Compound **5f**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.52 (m, 5H), 6.34 (s, 1H), 3.98–3.81 (m, 1H), 1.91–1.20 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.12, 132.13, 131.38, 128.80, 128.17, 91.13, 58.53, 29.16, 28.49, 25.22, 24.87, 22.18; IR (KBr) 1761 cm^{-1}; MS DCI/NH_3: 362 (M+NH_4^+). Anal. calcd for $C_{14}H_{17}ClN_2O_4S$: C, 48.76; H, 4.93; N, 8.12. Found: C, 49.04; H, 5.03; N, 8.18%.
Compound **5g**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.28 (m, 4H), 6.29 (s, 1H), 3.93–3.86 (m, 1H), 2.43 (s, 3H), 1.96–1.14 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.23, 139.72, 131.29, 130.74, 129.45, 91.62, 60.32, 30.28, 29.49, 25.82, 24.99, 24.50, 20.05; IR (KBr) 1766 cm^{-1}; MS DCI/NH_3: 376 (M+NH_4^+).
Compound **5h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.25 (m, 4H), 6.55 (s, 1H), 3.97–3.85 (m, 1H), 2.53 (s, 3H), 2.05–1.14 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.24, 138.07, 131.25, 129.51, 128.80, 126.46, 89.36, 58.54, 29.37, 28.59, 25.31, 25.17, 24.93, 18.97; IR (KBr) 1772 cm^{-1}; MS DCI/NH_3: 376 (M+NH_4^+).
14. Typical procedure for synthesis of **6a–e**: To a stirred solution of 2-alkyl-4-chlorosulfonyl-5-aryl-1,2,4-oxadizolidin-3-one (5 mmol) in 20 mL of CH_2Cl_2 was added 7 mmol of triethylamine. After 15 min, 5 mL of water was added. The mixture was stirred for 24 h, washed with 200 mL of water and extracted with CH_2Cl_2. The organic layer was separated and dried ($MgSO_4$). Removal of the solvent gave the crude product, which was further purified by recrystallisation from ethanol–water. Characteristics of compounds **6a–e** are given as follows.
Compound **6a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58–7.47 (m, 5H), 6.14 (s, 1H at NH), 6.05 (s, 1H), 1.40 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.43, 136.72, 128.56, 127.10, 126.25, 84.46, 57.43, 24.80; IR (KBr) 3200, 1712; MS DCI/NH_3: 238 (M+NH_4^+), 221 (M+H^+).
Compound **6b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51–7.41 (m, 4H), 6.66 (s, 1H at NH), 6.03 (s, 1H), 1.37 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.15, 136.45, 134.58, 129.12, 129.07, 85.37, 59.61, 26.43; IR (KBr) 3230, 1708; MS DCI/NH_3: 271 (M+NH_4^+), 254 (M+H^+).
Compound **6c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.44 (m, 4H), 6.02 (s, 1H), 5.68 (s, 1H at NH), 2.41 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.87, 140.62, 132.48, 129.31, 127.75, 85.65, 59.31, 26.25, 21.23; IR (KBr) 3230, 1705; MS DCI/NH_3: 252 (M+NH_4^+), 235 (M+H^+).
Compound **6d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58–7.44 (m, 5H), 6.92 (s, 1H at NH), 6.10 (s, 1H), 4.00 (h, 1H), 1.27 (d, 3H), 1.24 (d, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.82, 135.25, 130.27, 128.50, 127.59, 86.36, 50.98, 19.23, 17.06; IR (KBr) 3234, 1705; MS DCI/NH_3: 224 (M+NH_4^+), 207 (M+H^+).
Compound **6e**: ^{1}H NMR (200, MHz): δ 7.47–2.24 (m, 5H), 6.07 (s, 1H), 6.00 (s, 1H at NH), 4.04 (h, 1H), 2.41 (s, 3H), 1.29 (d, 3H), 1.25 (d, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.12, 140.34, 132.13, 129.36, 127.76, 86.29, 51.13, 21.32, 19.42, 17.19; IR (KBr) 3201, 1708; MS DCI/NH_3: 238 (M+NH_4^+), 221 (M+H^+).
15. Crystal data for **5d**: $C_{11}H_{13}ClN_2O_4S$, $M=304.74$, crystal system monoclinic, space group C_2/c, $a=9.956(2)$, $b=19.908(4)$, $c=13.876(3)$ Å, $\alpha=90$, $\beta=96.53(3)$, $\gamma=90°$, $V=2732.5(10)$ Å^3, $Z=8$, $d_{calc}=1.482$ g/cm^3, $T=173(2)$ K, NONIUS Kappa diffractometer with a CCD detector, Mo Kα ($\lambda=0.71073$ Å), $\mu=0.443$ mm^{-1}, of 5276 measured data, 2962 were independent ($R_{int}=0.0304$), R_1 [$I>2\sigma(I)$] = 0.0376, wR_2 (all data) = 0.0985 and GOF = 1.033.