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# Nitrosylsulfuric acid in the synthesis of 5-chloroisoxazoles from 1,1-dichlorocyclopropanes

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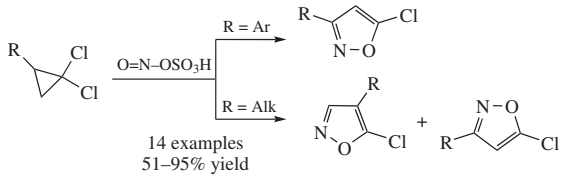
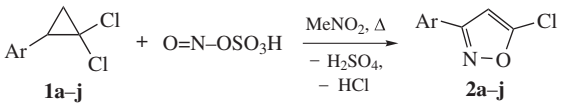
**Nitrosylsulfuric acid is shown to be a usable reagent for the synthesis of 5-chloroisoxazoles from readily available 1,1-dichlorocyclopropanes *via* nitrosation–heterocyclization reaction. A cytotoxicity of some of the prepared 5-chloroisoxazoles towards MCF7, A549, HEK293T and VA13 cell lines was evaluated.**




For several decades now isoxazoles have been in the spotlight of bioorganic and medicinal chemistry due to their valuable biological properties.[1,2] Therefore, development of new synthetic methodologies for preparation of isoxazoles is still topical.[3–6] The nitrosation–heterocyclization reaction of 1,1-dihalocyclopropanes affording substituted 5-haloisoxazoles[7] is a remarkable transformation. On the other hand, 1,1-dihalocyclopropanes are extremely available compounds but they demonstrate relatively low reactivity. Nitrosation of 1,1-dihalocyclopropanes is a rare example of their functionalization, which requires further detailed study.

In continuation of our work on the synthesis of isoxazole derivatives from 1,1-dihalocyclopropanes,[8,9] we concentrated our efforts on the search for alternative reaction conditions using other readily available and inexpensive nitrosating reagents.[10] In this work we have suggested a new procedure for the synthesis of 5-chloroisoxazoles using available and inexpensive nitrosylsulfuric acid which has some obvious advantages in comparison with other nitrosating reagents.[11,12]

We have found that the reaction between 2-aryl-1,1-dichlorocyclopropanes **1a–j** and nitrosylsulfuric acid affords substituted 3-aryl-5-chloroisoxazoles **2a–j** in good-to-excellent yields (Scheme 1, Table 1, *cf.* ref. 13).† The reaction proceeded with excellent chemo- and high regioselectivity giving 3-aryl-5-chloroisoxazoles **2a–j** only. Conversion of compounds **1** and the yields




**1a–j** **2a–j**

**a** Ar = Ph
**b** Ar = 4-$ClC_6H_4$
**c** Ar = 3-$ClC_6H_4$
**d** Ar = 3-$BrC_6H_4$
**e** Ar = 3-$O_2NC_6H_4$
**f** Ar = 2-$O_2NC_6H_4$
**g** Ar = 4-$O_2NC_6H_4$
**h** Ar = 4-$BrC_6H_4$
**i** Ar = 4-$FC_6H_4$
**j** Ar = 3-Br-4-$MeC_6H_3$

**Scheme 1**

of products **2** strongly depend on the reaction temperature and the ratio of the reactants. Raising the temperature facilitates the reaction (entries 1–4), the optimal temperature being 70–75 °C. An excess of nitrosylsulfuric acid accelerates nitrosation of the

**Table 1** Nitrosation of 2-aryl-1,1-dichlorocyclopropanes **1a–j** and 2-alkyl-1,1-dichlorocyclopropanes **3a–d** with nitrosylsulfuric acid in nitromethane.

| Entry | Starting compound | Equiv. $NO^+$ | *T*/°C | *t*/h | Conversion (%) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | 2.5 | 20 | 48 | 37 | **2a** | 37 |
| 2 | **1a** | 2.5 | 50 | 3 | 53 | **2a** | 53 |
| 3 | **1a** | 2.5 | 70–75 | 2 | 80 | **2a** | 80 (67) |
| 4 | **1a** | 2.5 | 70–75 | 3 | 100 | **2a** | 100 (77) |
| 5 | **1b** | 1.5 | 70–75 | 5 | 54 | **2b** | 54 |
| 6 | **1b** | 2.5 | 75 | 2 | 55 | **2b** | 55 |
| 7 | **1b** | 2.5 | 70–75 | 3 | 100 | **2b** | 100 (95) |
| 8 | **1c** | 1.5 | 70–75 | 5 | 63 | **2c** | 63 |
| 9 | **1c** | 5.0 | 65–70 | 2 | 100 | **2c** | 100 (90) |
| 10 | **1d** | 3.0 | 75 | 4 | 100 | **2d** | 100 (95) |
| 11 | **1e** | 2.7 | 70–75 | 3 | 100 | **2e** | 100 (85) |
| 12 | **1f** | 2.7 | 70–75 | 3 | 95 | **2f** | 95 (92) |
| 13 | **1g** | 2.7 | 70–75 | 3 | 100 | **2g** | 100 (93) |
| 14 | **1h** | 3.0 | 75 | 4 | 100 | **2h** | 100 (90) |
| 15 | **1i** | 2.4 | 65–70 | 3 | 100 | **2i** | 100 (56) |
| 16 | **1j** | 2.5 | 20 | 20[b] | 100 | **2j** | 100 (72) |
| 17 | **3a** | 2.0 | 70 | 3 | 100 | **4a** + **5a** (1.2 : 1) | (60)[c] |
| 18 | **3b** | 3.0 | 70 | 6 | 100 | **4b** + **5b** (1.2 : 1) | (80)[c] |
| 19 | **3c** | 2.0 | 75 | 10 | 68[d] | **4c** + **5c** (1.1 : 1) | (51)[c] |
| 20 | **3d** | 3.0 | 70 | 3 | 60 | **4d** + **5d** (1.1 : 1) | (50)[c] |
| 21 | **3d** | 2.5 | 75 | 10 | 70[d] | **4d** + **5d** (1.1 : 1) | (64)[c] |

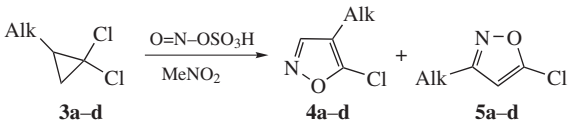
[a] Isolated yields are given in parentheses. [b] Nitration of the benzene ring of the newly formed isoxazole **2j** occurred at elevated temperatures. [c] Overall isolated yields. [d] At greater amount of $O=N–OSO_3H$ or longer reaction time yields of crude product are lower.

† *General procedure for the synthesis of 5-chloroisoxazoles*. A reaction vessel with a magnetic stirrer was charged with reactants in the following sequence: $NOHSO_4$ (3 mmol), nitromethane (3 ml) and the corresponding 1,1-dichlorocyclopropane (1 mmol), then closed with a joint stopper, and placed in a thermostatic bath. The reaction mixture was vigorously stirred and heated gradually from room temperature up to 70–75 °C and then kept at 70–75 °C for 3–4 h. Afterwards, the resulting mixture was passed through a layer of $SiO_2$ (40/60), the latter was additionally washed with chloroform (3×5 ml). The filtrate was evaporated under reduced pressure to afford the crude product which was recrystallized from ethanol or purified by column chromatography (Silica gel 40/60, ethyl acetate–light petroleum, 1:10). The $^1H$ and $^{13}C$ NMR spectra of isoxazoles **2a–i**, **4b**,**c** and **5b**,**c** were as described elsewhere.[14–16]

cyclopropane ring. The equal conversions of cyclopropane **1b** were achieved using a 1.5 molar excess of nitrosylsulfuric acid for 5 h or a 2.5 molar excess of nitrosylsulfuric acid for 2 h (entries 5, 6). Nitrosation of cyclopropane **1c** with 5 molar excess of nitrosylsulfuric acid for 2 h afforded a nearly quantitative yield of the corresponding isoxazole **2c**, whereas its conversion at 1.5 molar excess of nitrosylsulfuric acid for a longer reaction time (5 h) was only 63% (entries 8, 9). The minimum reaction time needed for full conversion of arylated 1,1-dichlorocyclopropanes **1a–i** at 75 °C and with a 2.5–3.0-fold molar excess of nitrosylsulfuric acid was 3–4 h (see, *e.g.*, entries 3 and 4, 6 and 7). Note that dichloromethane, chloroform, or ethyl acetate were not appropriate solvents for this process, as no conversion of 1,1-dichlorocyclopropanes was observed in those cases.

To evaluate the scope and limitations of the procedure, we also performed nitrosation of 2-alkyl-1,1-dichlorocyclopropanes **3a–d**. In these cases, mixtures of regioisomeric 4-alkyl- and 3-alkyl-5-chloroisoxazoles **4a–d** and **5a–d**, respectively, were obtained in good overall yields (Scheme 2). The isomers were isolated by column chromatography.‡ For alkyl substituted 1,1-dichlorocyclopropanes **3a–d**, nitrosation–heterocyclization reactions proceeded less vigorously and required longer times for their completion (see Table 1, entries 17–21). According to Table 1, the alkyl chain length slightly influences the isomer ratios, however conversion of the starting materials was slightly decreased with the elongation of the aliphatic substituent. The mechanism of the reaction was reported elsewhere.[10,16]

To further demonstrate the utility of 5-chloroisoxazoles, we tested some of them for cytotoxicity against the MCF7 (human breast




**3a–d** **4a–d** **5a–d**

**a** Alk = Pr **c** Alk = hexyl
**b** Alk = Bu **d** Alk = heptyl

**Scheme 2**

*3-(3-Bromo-4-methylphenyl)-5-chloroisoxazole* **2j**. Yellowish solid, mp 63 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 2.41 (s, 3H, Me), 6.41 (s, 1H, HC=CCl), 7.27 (d, 1H, Ar, $^3J$ 7.7 Hz), 7.54 (d, 1H, Ar, $^3J$ 7.7 Hz), 7.88 (s, 1H, Ar). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$: 22.9 (Me), 99.5 ($HC_{is}$), 125.3 ($CH_{Ar}$), 125.4 (CBr), 127.4 ($C_{Ar}$), 130.3 ($CH_{Ar}$), 131.3 ($CH_{Ar}$), 140.6 (*C*Me), 155.3 (C–O), 162.8 (C=N). HRMS [M+H]$^+$, *m/z*: 271.9471, 273.9449, 275.9416 (calc. for $C_{10}H_8BrClNO^+$, *m/z*: 271.9472, 273.9452, 275.9422).

‡ *5-Chloro-4-propylisoxazole* **4a**. Colorless liquid, $R_f$ 0.52 (EtOAc–light petroleum, 1 : 7). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.94 (t, 3H, Me, $^3J$ 7.3 Hz), 1.57 (m, 2H, $CH_2$), 2.36 (t, 2H, $CH_2$, $^3J$ 7.5 Hz), 8.16 (s, 1H, HC=N). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$: 13.5, 22.3, 24.0, 113.9 ($C_{is}$), 150.9 (O–C–Cl), 152.8 (HC=N). MS (EI) *m/z* (%): 145 (M$^+$, 81), 116 (M$^+$ – Et, 100), 81 (M$^+$ – Et – Cl, 96), 51 (M$^+$ – Et – Cl – NO, 58).

*5-Chloro-3-propylisoxazole* **5a**. Colorless liquid, $R_f$ 0.78 (EtOAc – light petroleum, 1 : 7). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.99 (t, 3H, Me, $^3J$ 7.3 Hz), 1.69 (m, 2H, $CH_2$), 2.63 (t, 2H, $CH_2$, $^3J$ 7.6 Hz), 6.03 (s, 1H, HC=CCl). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$: 13.6, 21.3, 28.3, 101.0 ($HC_{is}$), 152.2 (O–C–Cl), 166.1 (C=N).

*5-Chloro-4-heptylisoxazole* **4d**. Colorless liquid, $R_f$ 0.46 (EtOAc – light petroleum, 1 : 10). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.90 (t, 3H, Me, $^3J$ 7.0 Hz), 1.32 (m, 8H, $CH_2$), 1.56 (m, 2H, $CH_2$), 2.39 (t, 2H, $CH_2$, $^3J$ 7.6 Hz), 8.17 (s, 1H, HC=N). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$: 14.0, 22.0, 22.6, 28.9 (2$CH_2$), 29.0, 31.7, 114.1 ($C_{is}$), 150.9 (O–C–Cl), 152.8 (HC=N). Found (for a mixture of isomers **4d** and **5d**, %): C, 59.47; H, 7.91; N, 7.20. Calc. for $C_{10}H_{16}ClNO$ (%): C, 59.55; H, 8.00; N 6.94.

*5-Chloro-3-heptylisoxazole* **5d**. Colorless liquid, $R_f$ 0.58 (EtOAc – light petroleum, 1 : 10). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.89 (t, 3H, Me, $^3J$ 7.0 Hz), 1.32 (m, 8H, 4$CH_2$), 1.65 (m, 2H, $CH_2$), 2.64 (t, 2H, $CH_2$, $^3J$ 7.6 Hz), 6.03 (s, HC=CCl). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$: 14.0, 22.6, 26.4, 27.9, 28.9, 29.0, 31.7, 101.0 ($HC_{is}$), 154.2 (O–C–Cl), 166.3 (C=N).

**Table 2** *In vitro* cytotoxicity ($IC_{50}$/μM) of chloroisoxazoles **2a**,**d**,**e**,**g** compared to Doxorubicin.

| Compound | A549 | HEK293T | MCF7 | VA13 |
|---|---|---|---|---|
| **2a** | 36.12±12.85 | 7.55±3.71 | 22.75±7.79 | 21.80±4.42 |
| **2d** | 24.17±1.37 | 5.36±2.06 | 18.4±8.01 | 22.48±2.27 |
| **2e** | 45.73±12.76 | 5.61±0.42 | 11.59±6.4 | 41.03±10.17 |
| **2g** | 180.14±164.51 | 13.15±8.95 | 21.77±2.13 | 89.00±7.26 |
| Doxorubicin | not analyzed | 0.13±0.04 | 0.13±0.06 | 0.52±0.28 |

adenocarcinoma), A549 (human lung carcinoma), HEK293T (human embryonic kidney), and VA13 (SV40 transformed embryonal lung fibroblasts) cell lines in accordance with the standard MTT method.[17] Doxorubicin was used as the reference (Table 2). Among the tested compounds, isoxazoles **2d**,**e** exhibited moderate cytotoxicities towards investigated cell lines. The higher cytotoxicity was shown for HEK293T cells. Furthermore, isoxazole **2e** revealed some selectivity between low growth rate (VA13) and high growth rate cell lines (A549, HEK293T, MCF7) in comparison with the other isoxazoles.

In conclusion, the new procedure reported here provides an access to 5-chloroisoxazoles from *gem*-dichlorocyclopropanes and nitrosylsulfuric acid *via* a nitrosation–heterocyclization sequence. It is advantageous for delivering chemical purity and good-to-excellent yields of the desired products in combination with short reaction times and ready availability of the starting materials. The synthesized 5-chloroisoxazoles **2d**,**e** demonstrated moderate cytotoxicity towards MCF7, A549, HEK293T and VA13 cell lines.

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## References

1 A. Sysak and B. Obmin´ska-Mrukowicz, *Eur. J. Med. Chem.*, 2017, **137**, 292.
2 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845.
3 M. V. Andreev, A. S. Medvedeva, L. I. Larina and M. M. Demina, *Mendeleev Commun.*, 2017, **27**, 175.
4 D. L. Obydennov, L. R. Khammatova and V. Ya. Sosnovskikh, *Mendeleev Commun.*, 2017, **27**, 172.
5 D. A. Vasilenko, E. B. Averina, N. A. Zefirov, B. Wobith, Yu. K. Grishin, V. B. Rybakov, O. N. Zefirova, T. S. Kuznetsova, S. A. Kuznetsov and N. S. Zefirov, *Mendeleev Commun.*, 2017, **27**, 228.
6 A. V. Galenko, A. F. Khlebnikov, M. S. Novikov, V. V. Pakalnis and N. V. Rostovskii, *Russ. Chem. Rev.*, 2015, **84**, 335.
7 S. T. Lin, S. H. Kuo and F. M. Yang, *J. Org. Chem.*, 1997, **62**, 5229.
8 O. B. Bondarenko, A. A. Vinogradov, P. A. Danilov, S. N. Nikolaeva, A. Yu. Gavrilova and N. V. Zyk, *Tetrahedron Lett.*, 2015, **56**, 6577.
9 O. B. Bondarenko, M. R. Baimuratov, Yu. N. Klimochkin, and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2017, **66**, 376 (*Izv. Akad. Nauk, Ser. Khim.*, 2017, 376).
10 O. B. Bondarenko, A. Yu. Gavrilova, D. S. Murodov, N. V. Zyk and N. S. Zefirov, *Mendeleev Commun.*, 2011, **21**, 188.
11 G. A. Olah, G. K. S. Prakash, Q. Wang and X.-Y. Li, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. Paquette, John Wiley & Sons, Ltd., New York, 1995, vol. 6, p. 3771.
12 O. B. Bondarenko, A. I. Komarov, L. I. Kuznetsova, S. N. Nikolaeva, A. Yu. Gavrilova and N. V. Zyk, *Russ. Chem. Bull., Int. Ed.*, 2018, **67**, 517 (*Izv. Akad. Nauk, Ser. Khim.*, 2018, 517).
13 O. B. Bondarenko and N. V. Zyk, *RF Patent 2637927*, 2017.
14 O. B. Bondarenko, A. Yu. Gavrilova, D. S. Murodov, N. V. Zyk and N. S. Zefirov, *Russ. J. Org. Chem.*, 2013, **49**, 186 (*Zh. Org. Khim.*, 2013, **49**, 198).
15 U. Velaparthi, S. Kumaravel, A. M. S. S. Karuppiah, S. H. Maheshwarappa, C. R. Rachamreddy, M. D. Wittman and H. Liu, *Patent WO 2015/195880*, 2015.
16 N. V. Zyk, O. B. Bondarenko, A. Yu. Gavrilova, A. O. Chizhov and N. S. Zefirov, *Russ. Chem. Bull., Int. Ed.*, 2011, **60**, 328 (*Izv. Akad. Nauk, Ser. Khim.*, 2011, 321).
17 T. Mosmann, *J. Immunol. Methods*, 1983, **65**, 55.

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