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# Synthesis of 4,5-Dihydroisoxazoles from Arylcyclopropanes and Nitrosyl Chloride

**O. B. Bondarenko, A. Yu. Gavrilova, L. G. Saginova, and N. V. Zyk**

*Faculty of Chemistry, Moscow State University, Vorob'evy gory, Moscow, 119899 Russia*
*e-mail: bondarenko@org.chem.msu.ru*

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**Abstract**—Arylcyclopropanes readily react with nitrosyl chloride in liquid sulfur dioxide to give the corresponding 5-aryl-4,5-dihydroisoxazoles in good yield. The reaction is most selective at –40 to –50°C; at higher temperature, the contribution of side processes becomes appreciable. The complete conversion of arylcyclopropanes containing donor substituents is attained with the use of 1.5 equiv of nitrosyl chloride, while the rate of the transformation of compounds with nonactivated aromatic rings considerably increases on raising the molar ratio NOCl–arylcyclopropane.

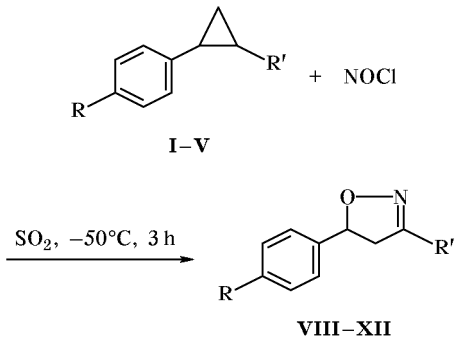
Dihydroisoxazole moiety is widely used in the synthesis of biologically active and natural compounds [1]. Dihydroisoxazole ring remains unchanged in many organic reactions, thus making it possible to modify side chains. In addition, latent difunctional character of the heteroring provides the possibility for generation of a variety of functional groups in the final stages of synthetic sequences.

There are several radically different approaches to construction of a dihydroisoxazole ring. The most general approach is based on 1,3-dipolar cycloaddition of nitrile oxides generated by various methods to unsaturated compounds [2]. Only a few examples have been reported on the synthesis of dihydroisoxazoles from arylcyclopropanes by the action of nitrosating agents. The latter were sodium nitrite in the presence of trifluoroacetic acid [3], nitrosonium tetrafluoroborate, and nitrogen(II) oxide (under irradiation) [4]. Undoubtedly, search for new nitrosating agents is important from the viewpoint of extending the scope of application of the above reaction and its synthetic potential.

The present communication describes a preparative route to 5-aryl-4,5-dihydroisoxazoles from aryl- and 1,2-diarylcyclopropanes and nitrosyl chloride. It should be noted that we have found no published data on the use of nitrosyl chloride for nitrosation of arylcyclopropanes.

As starting compounds we used *trans*-1,2-diphenylcyclopropane (**I**), *trans*-1,2-bis(4-fluorophenyl)cyclopropane (**II**), *trans*-1,2-bis(4-methoxyphenyl)cyclopropane (**III**), *trans*-1-(4-methoxyphenyl)-2-phenylcyclopropane (**IV**), phenylcyclopropane (**V**), nitrophenylcyclopropane (**VI**, a mixture of *ortho* and *para* isomers at a ratio of 4 : 1), and 4-acetylphenylcyclopropane (**VII**). We found that nitrosyl chloride readily adds to aryl- and 1,2-diarylcyclopropanes in liquid sulfur dioxide to afford, respectively, 5-aryl- and 3,5-diaryl-4,5-dihydroisoxazoles **VIII**–**XII** in high yield (Scheme 1).

**Scheme 1.**




**I**, **VIII**, R = H, R′ = Ph; **II**, **IX**, R = F, R′ = 4-$FC_6H_4$; **III**, **X**, R = OMe, R′ = 4-$MeOC_6H_4$; **IV**, **XI**, R = OMe, R′ = Ph; **V**, **XII**, R = R′ = H.

In the reaction of 1,2-diphenylcyclopropane (**I**) with 5 equiv of nitrosyl chloride, the substrate conversion attained 100% in 3 h at –50°C. The product, 3,5-diphenyl-4,5-dihydroisoxazole (**VIII**) was obtained in 82% yield (Table 1). With methylene

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**Table 1.** Reaction of 1,2-diphenylcyclopropane (**I**) with nitrosyl chloride in different solvents

| Solvent | ε | **I**-to-NOCl molar ratio | Temperature, °C | Time, h | Yield, % | | |
|---|---|---|---|---|---|---|---|
| | | | | | **VIII** | 1,3-dichloro-1,3-diarylpropane | **I** |
| $SO_2$ | 13.8 | 1:5 | –50 | 3 | 82 | 8 | – |
| $CH_2Cl_2$ | 9.1 | 1:4 | 0 | 3 | 9 | 6 | 80 |
| Ether | 4.2 | 1:5 | 0 | 4 | – | – | 98 |
| Ether[a] | 4.2 | 1:5 | 0 | 3 | – | 18 | 75 |

[a] The substrate was 1,2-bis(4-methoxyphenyl)cyclopropane (**III**).

chloride as solvent, the yield of the target product sharply decreased: After 3 h at 0°C, the yield of **VIII** was as low as 9%; 6% of 1,3-diphenyl-1,3-dichloropropane was formed; and 80% of initial cyclopropane **I** was recovered from the reaction mixture. No reaction at all occurred in diethyl ether. Under analogous conditions, more reactive 1,2-bis(4-methoxyphenyl)-cyclopropane (**III**) was not converted into dihydroisoxazole: From the reaction mixture we isolated only the corresponding 1,3-dichloride and initial cyclopropane **III**.

It was presumed [3] that nitrosation of arylcyclopropanes is an electrophilic process. In fact, increase in the solvent polarity is likely to favor polarization of nitrosyl chloride molecule and generation of active electrophilic species. Liquid sulfur dioxide turned out to be the most appropriate solvent for the reaction of arylcyclopropanes with nitrosyl chloride.

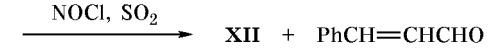
With the goal of finding optimal temperature conditions, we performed a series of experiments with phenylcyclopropane (**V**): at –40, –20, and 0°C. The results are summarized in Table 2. Apart from 5-phenyl-4,5-dihydroisoxazole (**XII**), a small amount of cinnamaldehyde was obtained (Scheme 2). The data in Table 2 show that at a **V**-to-NOCl ratio equal to 1:2, the conversion of compound **V** was about 50% in 2 h, regardless of the temperature. The reaction was most selective at –40°C; however, the yield of 5-phenyl-4,5-dihydroisoxazole (**XII**) did not exceed 38%, while the remaining 57% of **V** was recovered from the reaction mixture. The conversion increased at higher temperature, but the process was accompanied by partial tarring and the yield of cinnamaldehyde increased.

**Table 2.** Effect of temperature and reactant ratio on the yield of 5-phenyl-4,5-dihydroisoxazole (**XII**) and selectivity of the reaction in liquid sulfur dioxide

| **V**:NOCl, mol/mol | Temperature, °C | Time, h | Yield, % | | |
|---|---|---|---|---|---|
| | | | **V** | cinnamaldehyde | **XII** |
| 1:2 | 0–5[a] | 2 | 30 | 5 | 32 |
| 1:2 | –20 | 2 | 30 | 8 | 40 |
| 1:2 | –40 | 2 | 57 | – | 38 |
| 1:5 | –40 | 3 | – | 10 | 69 |

[a] The reaction at 0°C was accompanied by considerable tarring.

**Scheme 2.**




In order to maintain the reaction selectivity and simultaneously increase the conversion of initial hydrocarbon **V**, the reaction was carried out at –40 to –50°C using 5 equiv of nitrosyl chloride. In this case we isolated 69% of 5-phenyl-4,5-dihydroisoxazole (**XII**), but 10% of cinnamaldehyde was also obtained; no other products were detected in the reaction mixture. Analogous temperature dependences were observed in the series of diarylcyclopropanes. When the reaction mixture was quickly warmed up to room temperature, the fraction of the corresponding 1,3-dichloro derivatives increased, and appreciable tarring occurred (Table 3). Thus the optimal temperature ensuring the maximal selectivity is –40 to –50°C.

We also tried to elucidate the effect of electronic factors on the reaction under study. For this purpose, we compared the behavior of arylcyclopropanes containing donor (compounds **III** and **IV**) and acceptor substituents (**VI**, **VII**) in the aromatic ring (Table 3). As follows from the data given in Tables 2 and 3, diarylcyclopropanes are more reactive toward nitrosyl chloride than compound **V** despite the presence in the former of bulky substituents. These data indicate that the reaction of arylcyclopropanes with nitrosyl chloride depends only slightly on the steric factor

**Table 3.** Effect of temperature and reactant ratio on the yield of dihydroisoxazoles

| Comp. no. | Temperature, °C | Cyclopropane : NOCl, mol/mol | Time, h | Yield, % | |
|---|---|---|---|---|---|
| | | | | isoxazole | 1,3-diaryl-1,3-dichloropropane |
| **I** | 20 | 1 : 2 | 10 | 67 | 10 |
| | –50 to –40 | 1 : 5 | 3 | 82 | 8 |
| | – | – | – | – | – |
| **II** | 20 | 1 : 2 | 10 | 64 | 16 |
| | –50 to –40 | 1 : 5 | 3 | 86 | 9 |
| | – | – | – | – | – |
| **III** | 20 | 1 : 2 | 1.5 | 30 | 60 |
| | –50 to –40 | 1 : 5 | 3 | 6 | 60 |
| | –50 to –40 | 1 : 1.5 | 3.5 | 87 | 8 |
| **IV** | 20 | 1 : 2 | 1.5 | 73 | 22 |
| | –50 to –40 | 1 : 5 | 3 | 42 | 48 |
| | –50 to –40 | 1 : 1.5 | 3.5 | 85 | 8 |
| **VI**[a] | –50 to –40 | 1 : 5 | 3 | – | – |
| **VII**[b] | 20 | 1 : 1.5 | 20 | Traces | – |

[a] 100% of initial phenylcyclopropane **VI** was recovered.
[b] 95% of initial phenylcyclopropane **VII** was recovered.

but is governed by electronic requirements. Donor substituents in the aromatic ring favor successful reaction. However, as the number of donor substituents increases (compounds **III** and **IV**), the yield of 1,3-dichlorides as by-products increases. In the reaction of cyclopropane **III** with 5 equiv of nitrosyl chloride, the corresponding 1,3-dichloride was the only product. Acceptor substituents in the aromatic ring deactivate the small ring so strongly that 4-acetylphenylcyclopropane (**VI**) failed to react with nitrosyl chloride under standard conditions (Table 3). When the reaction of nitrophenylcyclopropane (**VII**) with nitrosyl chloride was performed at room temperature over a period of 24 h, the $^1$H NMR spectrum of the reaction mixture contained signals of 5-(2-nitrophenyl)-4,5-dihydroisoxazole whose intensity did not exceed 5% of those of initial cyclopropane **VII**.

## EXPERIMENTAL

The $^1$H and $^{13}$C NMR spectra were recorded on a Varian XR-400 instrument in $CDCl_3$ using HMDS as internal reference. The melting points were determined in an open capillary.

**General procedure for the synthesis of dihydroisoxazoles from arylcyclopropanes and nitrosyl chloride.** An ampule was charged with 0.003 mol of arylcyclopropane and cooled to –60°C, and a required amount of NOCl as a solution in methylene chloride and 8–10 ml of liquid sulfur dioxide were added. The ampule was sealed, allowed to warm up to a specified temperature, shaken until the mixture became homogeneous, and kept for a required time at that temperature. The ampule was then opened, the solution was carefully evaporated, and 20 ml of methylene chloride was added. The organic layer was neutralized with a solution of sodium carbonate and washed with water, the aqueous phase was treated with methylene chloride, and the combined organic extracts were dried over sodium sulfate. The solvent was evaporated, and the product was purified by recrystallization or column chromatography. The melting points of the isolated dihydroisoxazoles and their spectral parameters, as well as the $^1$H NMR spectra of 1,3-diaryl-1,3-dichlorocyclopropanes and cinnamaldehyde, were consistent with those reported previously [3, 5].

**3,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazole (IX)** was synthesized from 0.23 g (0.001 mol) of cyclopropane **II** and 0.32 g (0.005 mol) of NOCl in methylene chloride at –50°C (reaction time 3 h). Recrystallization from ethanol gave 0.22 g (86%) of the product with mp 111.5°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.26 d.d (1H, $CH_2$, $^2J$ = 16.9, $^3J$ = 8.2), 3.73 d.d (1H, $CH_2$, $^2J$ = 16.9, $^3J$ = 11.0), 5.71 d.d (1H, CHO, $^3J$ = 11.0, $^3J$ = 8.2), 7.06 m (4H, $H_{arom}$), 7.34 m (2H, $H_{arom}$), 7.66 m (2H, $H_{arom}$). $^{13}$C NMR spectrum, $\delta_C$, ppm (*J*, Hz): 43.25 ($CH_2$), 82.04

(CHO), 115.71 d (*m*-CF, $^3J_{CF}$ = 22.8), 115.93 d (*m*-CF, $^3J_{CF}$ = 22.3), 125.61 d (*p*-CF, $^4J_{CF}$ = 4.2), 127.65 d (*o*-CF, $^2J_{CF}$ = 7.9), 128.68 d (*o*-CF, $^2J_{CF}$ = 8.5), 136.53 d (*p*-CF, $^4J_{CF}$ = 4.1), 155.14 (C=N), 162.62 d (CF, $^1J_{CF}$ = 246.6), 163.82 d (CF, $^1J_{CF}$ = 251.1). Found, %: C 69.24; H 4.23; N 5.31. $C_{15}H_{11}F_2NO$. Calculated, %: C 69.50; H 4.25; N 5.41.

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