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New system for nitrosation of alkyl-substituted *gem*-dichlorocyclopropanes

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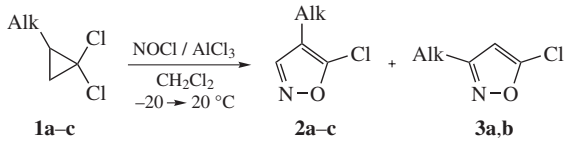
Treatment of alkyl-substituted *gem*-dichlorocyclopropanes with NOCl–$AlCl_3$ system affords alkyl-5-chloroisoxazoles.

gem-Dihalocyclopropanes play a noticeable role in organic synthesis foremost due to their exceptional availability.[1] Today they put together a really tremendous massive of organic compounds which differ by great structural variety; therefore, their application as synthons is very promising.[1(*c*),2] Earlier we have successfully applied an adduct of NOCl with sulfur trioxide as nitrosating reagent for transformation of alkyl-*gem*-dichlorocyclopropanes into alkyl-5-chloroisoxazoles.[3]

Note that isoxazole derivatives every year find more wide application as objects for pharmacological investigations. They exhibit antibacterial, antiasthmatic, and other pharmacological activities and are active principle of some drugs† different in their functions.[4]

Taking into account the practical value of isoxazoles we directed our efforts at searching for alternative conditions for nitrosation of alkyl-substituted *gem*-dichlorocyclopropanes. For this purpose we used here cheap and available reagents: nitrosyl chloride and aluminum chloride.

In fact, 2-alkyl-1,1-dichlorocyclopropanes **1a**,**b** under the action of nitrosyl chloride activated with aluminum chloride afford a mixture of regioisomeric 4-alkyl- **2a**,**b** and 3-alkyl-5-chloroisoxazoles **3a**,**b** in high yields (Scheme 1).‡



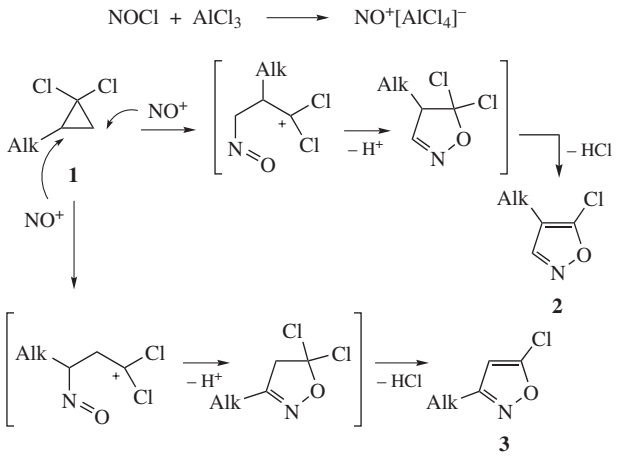
1a–c **2a–c** **3a**,**b**

a Alk = Bu, 93% (**2a** : **3a** = 1.3 : 1)
b Alk = hexyl, 90% (**2b** : **3b** = 1.4 : 1)
c Alk = Bn, 60% (**2c** only)

Scheme 1

† Arava (treatment: leflunomide which is a pyrimidine synthesis inhibitor indicated in adults for the treatment of active rheumatoid arthritis); Bextra (treatment: valdecoxib which is used for its anti-inflammatory, analgesic, and antipyretic activities in the management of osteoarthritis and for the treatment of dysmenorrhea or acute pain); Marplan (treatment: isocarboxazid which is effective in the treatment of major depression, dysthymic disorder and atypical depression and useful in the treatment of panic disorder and the phobic disorders); Sulfafurazole (a short-acting sulfonamide with antibacterial activity against a wide range of gram-negative and gram-positive organisms).[4]

‡ The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer with working frequencies of 400 and 100 MHz in $CDCl_3$ with TMS as an internal standard. The mass spectrum was registered on a Finnigan MAT SSQ 7000 GC-MS instrument equipped with 25 m quartz capillary OV-1 column in the electron-impact ionization mode at an ionization energy of 70 eV with temperature programming from 70 (2 min) to 280 °C (10 min) at a rate of 20 K min^{-1}. The melting point was measured in a block in an open capillary.



Scheme 2

The formation of isoxazoles **2**, **3** can be presented as outlined in Scheme 2.

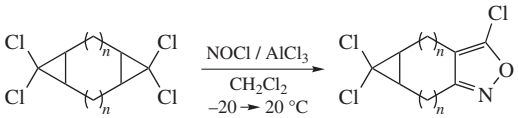
We have also studied the behaviour of 2-benzyl-1,1-dichlorocyclopropane **1c** under the suggested conditions of nitrosation. 2-Benzyl-1,1-dichlorocyclopropane **1c** is of certain interest, as on the one hand it can be classified as alkyl-substituted cyclopropane, and on the other hand it has an additional reaction site, benzene ring. Note, that the reaction of compound **1c** with the other previously known nitrosating reagents proceeds non-selectively. Thus, nitrosation of cyclopropane **1c** with sodium nitrite in trifluoroacetic acid is accompanied by nitration of the aromatic ring that results in the formation of a mixture of products.[5] The treatment of compound **1c** with complex $NOCl{\cdot}2SO_3$ leads, foremost, to sulfochlorination of the aromatic ring.[6] The excess of the reagent makes it possible to nitrosate the cyclopropane ring in the products of sulfochlorination affording isoxazolylarylsulfochlorides.

General procedure for preparing 5-chloroisoxazoles. A glass ampoule was loaded in sequence with 0.001 mol of $AlCl_3$ and cooled (–20 °C) solution of 0.002 mol of NOCl in 2 ml of dichloromethane, quickly closed with a joint stopper, and the mixture was vigorously stirred under ambient conditions for 0.5 h without any additional cooling. Then, the ampoule was placed into an ice bath, and 0.001 mol of corresponding alkyl-*gem*-dichlorocyclopropane was added, whereupon the ampoule was additionally cooled to –20 °C and sealed. The reaction mixture was stirred for 24 h being gradually heated to room temperature. Afterwards, the ampoule was opened, the resultant mixture was quenched with 1 M sodium bicarbonate solution and extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the products were isolated by chromatography (Silica gel 40/100, blend – ethyl acetate:light petroleum, 1:10). The ^1H and ^{13}C NMR spectra of isoxazoles **2a**,**b** and **3a**,**b** were as described elsewhere.[3]

The reaction of 2-benzyl-1,1-dichlorocyclopropane **1c** with nitrosyl chloride in the presence of aluminum chloride proceeded chemo- and regioselectively with the formation of 4-benzyl-5-chloroisoxazole **2c** (Scheme 1).§ The structure of compound **2c** was unambiguously proved based on its ^{1}H and ^{13}C NMR spectra and elemental analysis data.¶ The ^{1}H and ^{13}C NMR spectra of **2c** absolutely correlate with those of **2a** and **2b**. Thus, the ^{1}H NMR spectrum of isoxazole **2c** exhibits a narrow singlet in the field of C=N double bond at δ 8.13 ppm with intensity equal to one proton referred to hydrogen atom of heterocycle. The ^{13}C NMR spectrum contains a set of eight signals three of which at δ 113.4, 151.4, and 153.1 ppm are referred to isoxazole ring, the signals at δ 113.4 and 151.4 ppm belonging to tertiary carbon atoms and that in the field of C=N double bond (δ 153.1), to the carbon atom connected with hydrogen. These data confirm that benzyl substituent is located at C(4) carbon atom of the heterocycle.

Thus, in the case of 2-benzyl-1,1-dichlorocyclopropane **1c**, the suggested nitrosation system allows us to get the result which is impossible while using the other known nitrosating reagents.

By the example of biscyclopropanes **4a**,**b** we have shown that polycyclic *gem*-dichlorocyclopropanes can also be smoothly transformed into the corresponding isoxazoles **5a**,**b**.†† In both cases,



4a,**b**

a $n = 1$
b $n = 2$

5a, 90%
5b, 70%

Scheme 3

the reaction occurs with participation of only one of the cyclopropane rings (Scheme 3).

In summary, we have developed a chemoselective reagent system for transformation of alkyl-substituted *gem*-dichlorocyclopropanes into substituted 5-chloroisoxazoles in high yields.

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§ According to the ^{1}H NMR spectrum of the reaction mixture isoxazole **3c** was formed only in trace amounts (< 10%).

¶ **2c**: yield 60%. R_f 0.51 (ethyl acetate:light petroleum, 1:10). Red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 2H, CH_2Ph), 7.22 (dm, 2H, CH_{aryl}, ^3J 7.3 Hz), 7.29 (tt, 1H, CH_{aryl}, ^3J 7.3 Hz, ^4J 1.7 Hz), 7.37 (tt, 2H, CH_{aryl}, ^3J 7.3 Hz, ^4J 1.7 Hz), 8.13 (s, 1H, HC=N). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 28.4 (CH_2Ph), 113.4 (=C–Bn), 127.0 (C^4_{ar}H), 128.3 (2C_{ar}H), 128.9 (2C_{ar}H), 137.7 (C^1_{ar}H), 151.4 (=CCl), 153.1 (HC=N). Found (%): C, 61.88; H, 4.30; N, 7.07. Calc. for $C_{10}H_8ClNO$ (%): C, 62.02; H, 4.13; N, 7.24.

†† **5a**: yield 90%. R_f 0.37 (ethyl acetate:light petroleum, 1:7), mp 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.11 (dd, 1H, CH, ^3J 11.0 Hz, ^3J 7.7 Hz), 2.18 (dd, 1H, CH, ^3J 11.0 Hz, ^3J 7.3 Hz), 2.82 (d, 1H, CH_2, ^2J 17.7 Hz), 2.98 (dd, 1H, CH_2, ^2J 17.7 Hz, ^3J 7.7 Hz), 3.10 (d, 1H, CH_2, ^2J 18.6 Hz), 3.20 (dd, 1H, CH_2, ^2J 18.6 Hz, ^3J 7.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 14.7 (CH_2), 17.0 (CH_2), 25.0 (CH), 25.7 (CH), 63.2 (CCl_2), 107.0 (*C*=CCl), 149.2 (C=*C*Cl), 159.8 (C=N). MS (EI) *m*/*z* (I_{rel}, %): 237 (M^+, 10), 202 (M^+ – Cl, 11), 174 (M^+ – Cl – CO, 11), 166 (M^+ – Cl – HCl, 16), 138 (M^+ – Cl – HCl – CO, 28), 122 ($CH_2CHCHCCl_2^+$, 40), 109 ($CH_2CHCCl_2^+$, 100), 87 ($CH_2CHCHCCl^+$, 28), 51 (21). Found (%): C, 40.31; H, 2.46; N, 5.92. Calc. for $C_8H_6Cl_3NO$ (%): C, 40.25; H, 2.51; N, 5.87.

The ^{1}H and ^{13}C NMR spectra of isoxazole **5b** were as described elsewhere.[3]