A Convenient Procedure for Transformation of Tertiary Cyclopropanols into 5-Substituted Isoxazoles

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Abstract: Tertiary cyclopropanols, when treated with an excess of amyl nitrite at room temperature, are smoothly converted into dimeric β-nitrosoketones. Heating the methanolic solutions of the latter under reflux gives 5-substituted isoxazoles in good yields.

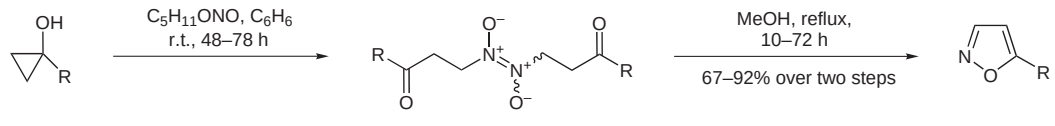
Key words: cyclopropanols, nitrosation, β-nitrosoketones, isoxazoles, isoxazolines

Substituted cyclopropanols can be easily prepared by a number of procedures, including the reductive cyclopropanation of esters with dialkoxytitanacyclopropane reagents,[1,2] desilylation of cyclopropanol silyl ethers,[3,4] alkylation of cyclopropanone hemiacetals,[5] reductive cyclization of β-halogeno ketones[6] as well as using some other methods.[7] Synthetic applications of these compounds are based mainly on the C^1–C^2 or C^1–C^3 cyclopropane ring-opening reactions.[7] In many cases, the conversion of cyclopropanols or their derivatives into alkyl ketones, α,β-unsaturated ketones, 2-substituted alkyl halides, as well as to some other compounds, occurs in a highly selective manner, and has a considerable preparative value.[7,8]

At the end of 1960s, De Puy and co-workers[9] observed a remarkably high activity of cyclopropyl nitrites in the reactions involving homolytic cleavage of the N–O bond, which proceeded at temperatures 100–250 °C lower than for nitrites not associated with a cyclopropyl ring. These transformations proceeded via opening of the cyclopropane ring and resulted in formation of dimeric β-nitrosoketones or 5-hydroxy-Δ^2-isoxazolines. Also, β-nitrosoketones were reported to be transformed into isoxazoles upon standing or with some heating.[9b] Since the cleavage of the N–O bond in isoxazoles is widely used for the preparation of various 1,3-bifunctional compounds including some natural products,[10] the transformation of cyclopropanols **1** into isoxazoles **3** via β-nitrosoketones **2** has a substantial synthetic potential. At the same time, the procedure proposed for the generation of cyclopropyl nitrites by treating cyclopropanols with nitrosyl chloride (NOCl) in the presence of pyridine[9b] has some significant disadvantages. First, a careful control of the reagent added is required because an excess of NOCl was found to cause decomposition of cyclopropyl nitrite. Furthermore, the decomposition of cyclopropyl nitrites may also be induced by pyridine hydrochloride, which must be removed by low-temperature filtration. It should also be noted that the protocol for the conversion of β-nitrosoketones into the respective isoxazoles[9b] was not described in detail.

Here, we report a simple and efficient experimental procedure resulting in transformation of cyclopropanols **1** into isoxazoles **3** via β-nitrosoketones **2** (Scheme 1). We found that keeping the mixture, composed of monosubstituted cyclopropanol **1a**–**g**,[11] an excess of freshly prepared amyl nitrite,[12] and small amount of benzene at room temperature for two to three days yielded dimeric β-nitrosoketones **2a**–**g** almost quantitatively (as was determined by ^{1}H NMR). After the removal of benzene and excess of amyl nitrite under reduced pressure crystalline compounds **2a**–**d** were isolated as mixtures of *Z* and *E* isomers.[13] Under these conditions monosubstituted cyclopropanols bearing alkyl (see Table 1, entries 1 and 2), aryl (entry 4), alkenyl (entry 5), halogenalkyl (entry 3), alkoxyalkyl (entries 6 and 7) substituents were converted into β-nitrosoketones **2** in high yields, whereas 1,2-disubstituted cyclopropanol **1h** gave the corresponding product only in a poor yield (entry 8).

The transformation of β-nitrosoketones **2** to isoxazoles **3** proceeded clearly in methanolic solutions heated under reflux for two to three days (Scheme 1) and the products were isolated in good yields. In order to avoid transacetalization, the cyclization of nitroso compound **2g** was carried out under reflux in ethanol. Although the reaction was



1 **2** **3**

Scheme 1

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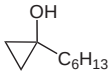
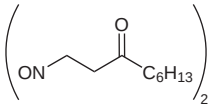
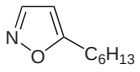
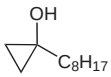
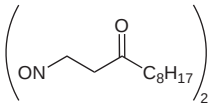
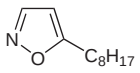
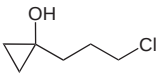
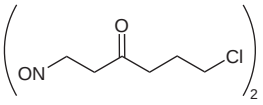
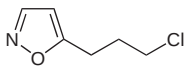
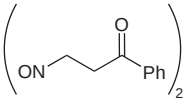
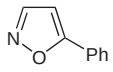
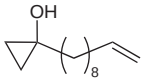
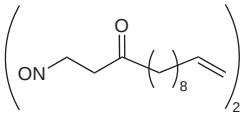
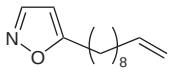
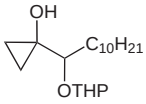
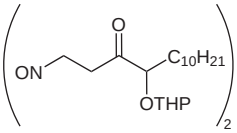
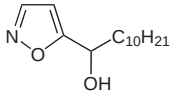
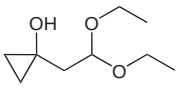
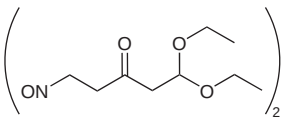
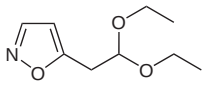
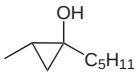
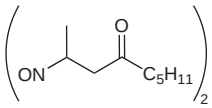
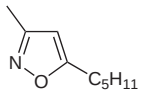
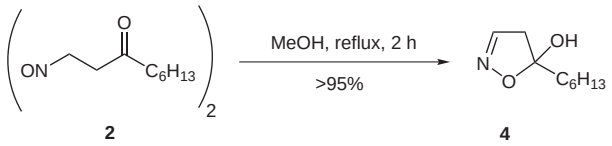
Table 1 The Conversion of Cyclopropanols **1** to β-Nitrosoketones **2** and 5-Substituted Isoxazoles **3**

Entry	Cyclopropanol	β-Nitrosoketone[a–c]	Yield (%)[d]	Isoxazole[e,f]	Yield (%)[g]
1	 **1a**	 **2a**	68	 **3a**	91
2	 **1b**	 **2b**	77	 **3b**	92
3	 **1c**	 **2c**	79	 **3c**	85
4	 **1d**	 **2d**	62	 **3d**	80
5	 **1e**	 **2e**	>90[h]	 **3e**	84
6	 **1f**	 **2f**	>90[h]	 **3f**	68
7	 **1g**	 **2g**	>90[h]	 **3g**	67[i]
8	 **1h**	 **2h**	~33[h]	 **3h**	36[h]

[a] Typical procedure for the preparation of β-nitrosoketones **2** was followed. See ref.[14] for details.
[b] For selected data of β-nitrosoketones **2**, see ref.[15]
[c] Products, as indicated by IR, are dimers.[15,16]
[d] Isolated yields of crystalline compounds (mixture of *Z* and *E* isomers).
[e] Typical procedure for the transformation of b-nitrosoketones **2** to isoxazoles **3** was followed. For details, see ref.[17]
[f] For selected data of isoxazoles **3**, see ref.[18]
[g] Isolated yields of isoxazoles **3** after distillation or column chromatography on silica gel.
[h] Determined by ^{1}H NMR spectra.
[i] Cyclization was carried out in EtOH.

completed after ten hours in this case, the use of ethanol for cyclization of nitroso compound **2a** led to a mixture of isoxazole **3a** and 5-ethoxy-5-hexyl-Δ^2-isoxazoline.

The conversion of β-nitrosoketones **2** into isoxazoles **3** proceeded via the intermediate formation of 5-hydroxy-Δ^2-isoxazolines **4** that could be isolated as individual compounds after a brief reflux of nitroso compounds **2** in methanol. Thus, 5-hexyl-5-hydroxy-Δ^2-isoxazoline **4**[19] was isolated in an almost quantitative yield after heating a methanolic solution of nitrosoketone **2a** under reflux for two hours and subsequent removal of the solvent in vacuo (Scheme 2).



Scheme 2

In conclusion, a simple and efficient procedure has been developed to prepare 5-substituted isoxazoles from easily available tertiary cyclopropanols by treating the latter with freshly prepared amyl nitrite and subsequent heating of methanolic solutions of the β-nitrosoketones formed.

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(11) Cyclopropanols **1a**–**h** were synthesized by the reductive cyclopropanation of the corresponding esters with ethylmagnesium bromide (compounds **1a**–**g**) or propylmagnesium bromide (**1h**) in the presence of titanium(IV) isopropoxide (see ref. 1).

(12) Utilization of amyl nitrite that was stored in a refrigerator for more than two weeks led to a significant reduction of the reaction rate and to a decrease in the yields of products.

(13) After crystallization from MeOH pure *E* isomer was obtained.

(14) **Preparation of β-Nitrosoketones 2; Typical Procedure**: Freshly prepared amyl nitrite (17 mL, 124 mmol) was added at 5 °C under Ar atmosphere to a solution of **1a** (4.9 g, 31 mmol) in anhyd benzene (5 mL) in one portion. The mixture was stirred for 3 h and was kept at r.t. until the reaction was completed as monitored by TLC (2–3 d, see ref. 20). The mixture was concentrated in vacuo and was used for the preparation of isoxazoles without further purification. In order to obtain solid samples of **2a** (as a mixture of *Z* and *E* isomers), the residue was diluted with petroleum ether, cooled and the crystals were filtered off. Single *E* isomer of **2a** (3.45 g, 20.2 mmol, 65%) was obtained by the crystallization from hot MeOH as a yellowish solid (mp 86–87 °C).

(15) Analytical data of selected nitrosoketones **2**.
2a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.8 Hz, 3 H), 1.18–1.30 (m, 6 H), 1.49–1.59 (m, 2 H), 2.44 (t, *J* = 7.4 Hz, 2 H), 2.90 (t, *J* = 6.2 Hz, 2 H), 4.40 (t, *J* = 6.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.84, 22.31, 23.41, 28.64, 31.39, 36.40, 42.74, 53.48, 206.63. IR (CCl_4): 1722, 1371, 1250 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_2$ (171.24): C, 63.13; H, 10.01. Found: C, 63.28; H, 9.75.
2c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04–2.13 (m, 2 H), 2.72 (t, *J* = 7.0 Hz, 2 H), 2.97 (t, *J* = 6.1 Hz, 2 H), 3.58 (t, *J* = 6.2 Hz, 2 H), 4.47 (t, *J* = 6.1 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.10, 36.69, 39.44, 44.21, 53.60, 205.58. IR (CCl_4): 1720, 1370, 1247 cm^{-1}. Anal. Calcd for $C_6H_{10}ClNO_2$ (163.61): C, 44.05; H, 6.16. Found: C, 43.90; H, 5.89.

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(17) **Preparation of Isoxazoles; Typical Procedure**: Crude β-nitrosoketone **2a**, prepared from **1e** (4.9 g, 31 mmol) and amyl nitrite (17.0 mL, 124 mmol) as described above (see ref. 14) was diluted with anhyd MeOH (45 mL). The solution was heated under reflux until TLC indicated that no β-nitrosoketone **2a** and intermediate isoxazoline **4a** remained (2–3 days, see ref. 20). After removal of the solvent under reduced pressure, the isoxazole **3a** was isolated by column chromatography (SiO_2, PE–EtOAc as eluent) as a yellowish oil (4.4 g, 91%).

(18) Analytical data of selected isoxazoles **3**.
3c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.22 (m, 2 H), 2.97 (t, *J* = 7.4 Hz, 2 H), 3.57 (t, *J* = 6.3 Hz, 2 H), 6.03–6.05 (m, 1 H), 8.14–8.17 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.70, 30.14, 43.54, 100.58, 150.22, 170.93. IR (CCl_4): 1606 cm^{-1}. Anal. Calcd for C_6H_8ClNO (145.59): C, 49.50; H, 5.54. Found: C, 49.33; H, 5.75.
3e: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.40 (m, 10 H), 1.65–1.73 (m, 2 H), 1.99–2.06 (m, 2 H), 2.76 (t, *J* = 7.7 Hz, 2 H), 4.92 (ddt, J_1 = 10.2 Hz, J_2 = 2.2 Hz, J_3 = 1.1 Hz, 1 H), 4.98 (ddt, J_1 = 16.9 Hz, J_2 = 2.2 Hz, J_3 = 1.5 Hz, 1 H), 5.80 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1 H), 5.95–5.97 (m, 1 H), 8.12–8.14 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.49, 27.49, 28.83, 28.98, 28.99, 29.11, 29.24, 33.73, 99.76, 114.13, 139.10, 150.12, 173.02. IR (CCl_4): 3079, 1640, 1593 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$ (207.32): C, 75.32; H, 10.21. Found: C, 75.59; H, 10.02.
3g: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.0 Hz, 6 H), 3.09 (d, *J* = 5.7 Hz, 2 H), 3.29 (dq, J_1 = 9.4 Hz, J_2 = 7.0 Hz, 2 H), 3.66 (dq, J_1 = 9.4 Hz, J_2 = 7.0 Hz, 2 H), 4.78 (t, *J* = 5.7 Hz, 1 H), 6.09 (d, *J* = 1.6 Hz, 1 H), 8.14 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.06, 31.92, 61.91, 100.18, 101.56, 150.19, 168.18. IR (CCl_4): 2874, 1734, 1597, 1125, 1064 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_3$ (185.22): C, 58.36; H, 8.16. Found: C, 58.60; H, 8.01.

(19) Analytical data of **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.22–1.53 (m, 8 H), 1.82–1.97 (m, 2 H), 2.89 (dd, J_1 = 18.4 Hz, J_2 = 1.3 Hz, 1 H), 2.92 (dd, J_1 = 18.4 Hz, J_2 = 1.6 Hz, 1 H), 3.10 (br s, 1 H), 7.20–7.23 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.97, 22.44, 24.60, 29.13, 31.58, 37.95, 44.86, 106.61, 147.16. IR (CCl_4): 3598, 3395, 1722, 1601 cm^{-1}. Anal. Calcd for $C_9H_{17}NO_2$ (171.24): C, 63.13; H, 10.01. Found: C, 63.28; H, 9.75.

(20) The reaction proceeded less smoothly under elevated temperatures or in the presence of acidic or basic catalysts.