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Short communication

Synthesis of 5-fluoro- and 5-bromoalkylisoxazoles *via* nitrosation of 1,1-dihalocyclopropanes with sulfur trioxide activated nitrosyl chloride

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ABSTRACT

A method for the synthesis of 5-fluoro- and 5-bromoalkylisoxazoles *via* nitrosation of alkylated *gem*-dihalocyclopropanes with a nitrosyl chloride sulfur trioxide adduct has been developed. In the case of bromofluorocyclopropanes the reaction proceeded with excellent chemoselectivity thus providing exclusively 5-fluoroisoxazoles.

1. Introduction

Isoxazole derivatives every year find more wide application as objects for pharmacological investigations. Some of them exhibit antibacterial, antiasthmatic, antirheumatic and other pharmacological activities and are active principle of some drugs different in their function (Arava, Bextra, Marplan, Sulfafurazole) [1]. On the other hand many fluorinated organic compounds exhibit unique biological properties [2] and are indicated by medicinal chemistry for clinical use [3]. The combination of isoxazole moiety with fluorine atom in one structure may results in the appearance of specific biological activity, as, for example, in the case of Risperidone (antipsychotic) (Fig. 1). Thus, fluorine-substituted isoxazoles are very attractive targets.

Our literature search revealed that there has been only one report on the synthesis of 5-fluoroisoxazoles [4], and in one case, 5-fluoroisoxazole was occasionally obtained as a by-product in extremely poor yield [5]. In addition, recent attempts to synthesize 5-fluoroisoxazoles *via* nitrosation of 1-bromo-1-fluorocyclopropanes with nitrosonium tetrafluoroborate were unsuccessful [6]. In previous paper [7] we have reported on the nitrosation of alkyl substituted 1,1-dichlorocyclopropanes with sulfur trioxide activated nitrosyl chloride providing an access to alkylated
5-chloroisoxazoles. In this work we have extended the scope of this reaction on alkylated bromofluoro- and *gem*-dibromocyclopropanes aiming at the synthesis of 5-fluoro- and 5-bromoisoxazoles.

Bromoisoxazoles are promising precursors for some transition-metal-catalyzed cross-coupling reactions (Suzuki-Miyaura, Stille, Hiyama) [8] which provide a route for new heterocyclic structures. There are few reports in the literature for the synthesis of alkyl substituted 5-bromoisoxazoles. They have been synthesized *via* the intramolecular cycloaddition reaction of an *in situ* generated nitrile oxide fragment to a brominated triple bond [8c], as well as by the reaction of phosphorous oxybromide with isoxazolones [8e]. The last reaction was realized mainly for arylated substrates [9]. Both methods are characterized by moderate yields of 5-bromoisoxazoles. Thus, a convenient preparative method for the production of 5-fluoro- and 5-bromoisoxazoles is still required, and the nitrosation-heterocyclization reaction reported here will serve as a good addition to the known procedures.

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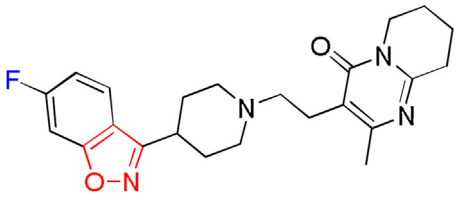
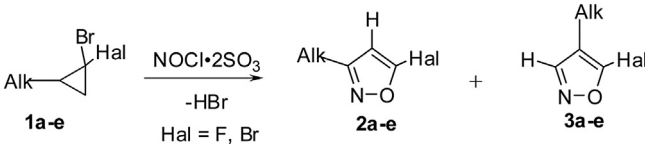


Fig. 1. Risperidone.

2. Results and discussion

In this work we demonstrate that nitrosation of 2-alkyl-1, 1-dibromocyclopropanes **1a-c** with a nitrosyl chloride sulfur trioxide adduct carried out in agreement with the protocol published elsewhere [7] ensured full conversion of the starting material within 20 h and afforded isoxazoles as a mixture of two regioisomers: 3-alkyl- **2a-c** and 4-alkyl-5-bromoisoxazoles **3a-c** in 73–94% overall yields (Table 1).



We next studied the nitrosation of 2-alkyl-1-bromo-1-fluorocyclopropanes **1d**,**e** under the same reaction conditions and found that the yields of the corresponding 5-fluoroisoxazoles **2d**,**e** and **3d**,**e** were rather moderate. The reaction was accompanied with noticeable polymerization. As the reactivity of bromofluorocyclopropanes was higher than that of dibromocyclopropanes we conducted the reaction under milder conditions (-20 – 0 °C). We also changed the solvent to the more polar nitromethane. Under these conditions the overall yields of 5-fluoroisoxazoles were 49 and 53% for butyl- (**2d,3d**) and hexyl- (**2e,3e**) substituents, respectively (Table 1).

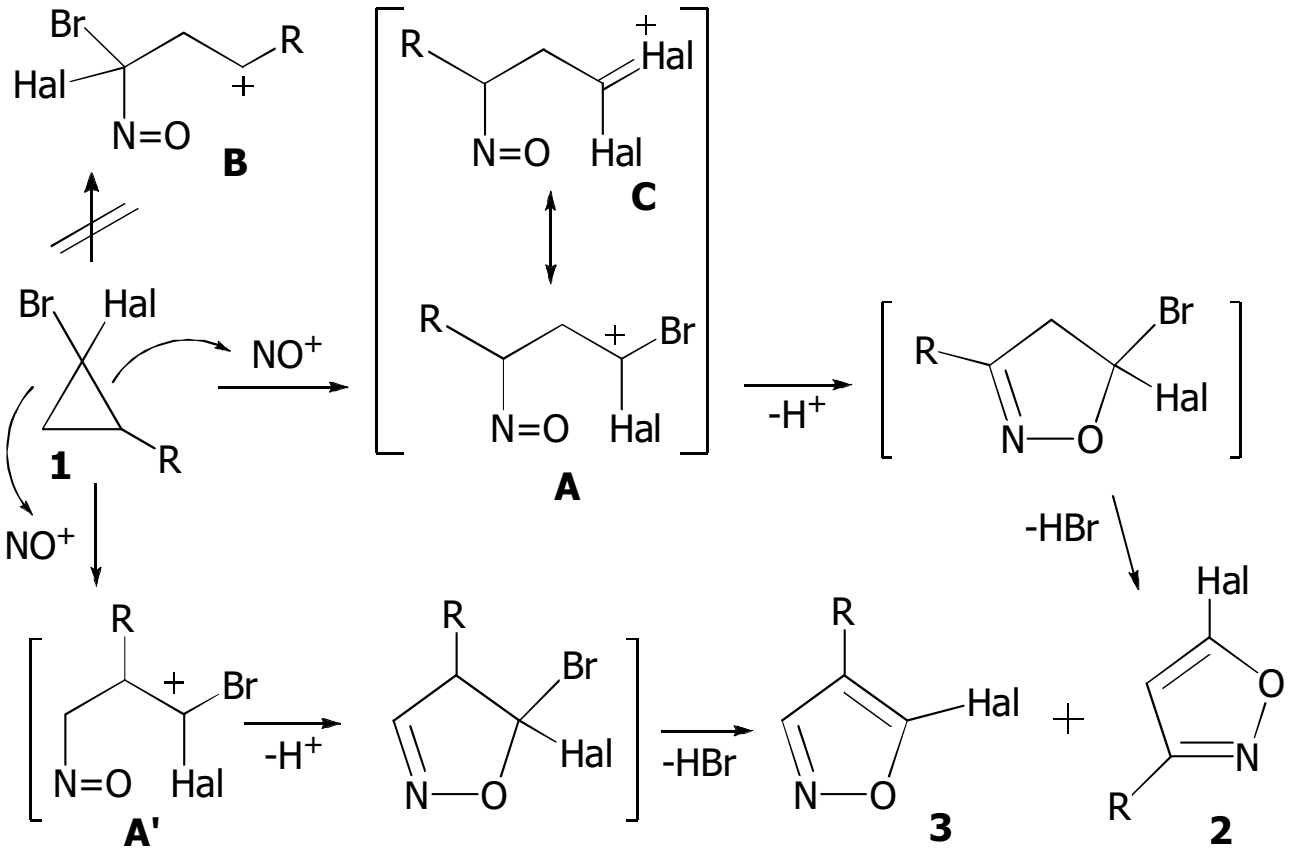
Table 1
The nitrosation of 1,1-dihalocyclopropanes **1a–e** with a nitrosyl chloride sulfur trioxide adduct.

Comp.	Hal	*R*	Solv	*T* (°C)	τ, h	**2**:**3** ratio[a]	Yield (%)[b]
1a	Br	*n*-Bu	CH_2Cl_2	20	20	1:1.8	73
1b	Br	*n*-Pent	CH_2Cl_2	20	24	1:1.8	80
1c	Br	*n*-Hex	CH_2Cl_2	20	24	1:1.8	94
1d	F	*n*-Bu	CH_3NO_2	−20–0	45	1:1	49
1e	F	*n*-Hex	CH_3NO_2	−20–0	45	1:1	53

[a] The isomers ratio was determined from the ^{1}H NMR spectra of the resultant mixtures.
[b] Isolated chromatographic yields.

Transformation of 1,1-dihalocyclopropanes **1a-e** to 5-haloisoxazoles **2a-e** and **3a-e** can be viewed as an electrophylic nitrosation-heterocyclization reaction proceeding through the initial attack of the NO^+ cation at the cyclopropane ring and the formation of dihalomethyl cations **A**,**A'**. The alternative regiochemistry of the initial attack of the electrophile leading to the cation **B** was shown to be unlikely because of its less stability (~7 kcal/mol) in ratio to the cation **A** [6]. The latter can be stabilized by two halogen atoms (structure **C**) (Scheme 1).

The regioisomers were separated by column chromatography and uniquely assigned to the spectral data [10]. In the ^{1}H NMR spectra of isoxazoles **2a-c** the H atom of the heterocycle absorbs in the region characteristic for the H-4: its signal appears as a narrow singlet at δ 6.15 ppm. The ^{13}C NMR spectra exhibit a set of signals of



Scheme 1. Possible Reaction Pathway.