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Novel design of 3,8-diazabicyclo[3.2.1]octane framework in oxidative sulfonamidation of 1,5-hexadiene

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ABSTRACT

1,5-Hexadiene reacts with trifluoromethanesulfonamide in the oxidative system (*t*-BuOCl+NaI) to give *trans*-2,5-bis(iodomethyl)-1-(trifluoromethylsulfonyl)pyrrolidine **5** and 3,8-bis(trifluoromethylsulfonyl)-3,8-diazabicyclo[3.2.1]octane **6**. With arenesulfonamides $ArSO_2NH_2$ (Ar=Ph, Tol), the reaction stops at the formation of the trans and cis isomers of 2,5-bis(iodomethyl)-1-(arenesulfonyl)pyrrolidine **7** and **8** (1:1). The cis isomers of **7** and **8** do not undergo cyclization to the corresponding 3,8-disubstituted 3,8-diazabicyclo[3.2.1]octanes. The reaction with triflamide represents the first example of one-pot two-step route to 3,8-diazabicyclo[3.2.1]octane system.

1. Introduction

N,N′-Disubstituted 3,8-diazabicyclo[3.2.1]octanes (aza-analogs of tropane) are actively investigated as substitutes for the piperazine-based biologically active compounds with analgesic, antiarrhythmic, antitussive, antitumor, and antiproliferative activity;[1–5] these results are partly summarized in the recent review.[6] However, since their first multi-step syntheses by Cignarella et al. in 1960–1961,[2–7] small progress has been made in the methodology of construction of the 3,8-diazabicyclo[3.2.1]octane framework.[8] For example, the recently achieved diastereoselective synthesis of 3,8-diazabicyclo[3.2.1]octane-2-carboxylic acid included cyclization of the separately prepared pyrrolidine derivative followed by the reduction of the formed bicyclic adduct to the target product in eight steps from pyroglutamic acid.[9] An alternative synthetic strategy for the preparation of 3,8-diazabicyclo[3.2.1]octane derivatives elaborated by Joule et al. and ascending to the pioneering works by Katrizky[10] is to react 3-oxidopyraziniums with methyl acrylate or methacrylate.[11] The formation of substituted 3,8-bis(tosyl)-3,8-diazabicyclo[3.2.1]octanes in extremely low yields from the properly substituted 2-benzoyl-1,4-bis(tosyl)piperazines upon irradiation was also reported.[12] The yields are moderate and the substrates must be prepared in advance from commercially available reagents. To the best of our knowledge only two examples have been reported for the formation of 3,8-diazabicyclo[3.2.1]octan-2-one derivatives by intramolecular cyclization reaction, namely, from *N,N′*-diprotected 5-allyl-2-piperazinone in nine steps with total yield of 23%[13] and from 3-allyl-2-piperazinone in five steps with total yield of 32%.[14]

2. Results and discussion

There are no examples of one-pot construction of 3,8-diazabicyclo[3.2.1]octanes; neither are there examples of the triflyl derivatives of 3,8-diazabicyclo[3.2.1]octanes. In continuation of our systematic studies of triflamides[15] and, in particular, of oxidative triflamidation of alkenes and dienes,[16] we report here the reactions of 1,5-hexadiene **1** with trifluoromethanesulfonamide (triflamide) **2**, toluenesulfonamide (tosylamide) **3a**, benzenesulfonamide **3b**, and methanesulfonamide **4** in the presence of an oxidant. The reaction was carried out under mild conditions (MeCN solution, cooling) in the oxidative system (*t*-BuOCl+NaI). Two products were formed in the total isolated yield of 91%, which were separated by column chromatography and assigned as 2,5-bis(iodomethyl)-1-(trifluoromethylsulfonyl)pyrrolidine **5** and 3,8-bis(trifluoromethylsulfonyl)-3,8-diazabicyclo[3.2.1]octane **6**.

From ^{1}H NMR before separation the products **5** and **6** are formed in the ratio of 3:2. The ^{1}H NMR spectra of the two products have the

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same number of signals but differ in that the signals of **5** are broadened due to the flexibility of the five-membered ring, while for the rigid bicyclic structure of **6** they are more narrow and better resolved. The structure of product **6** was proved by the presence of the signals of two different CF_3 groups in the ^{13}C and ^{19}F NMR spectra and, finally, by X-ray analysis (Fig. 1).

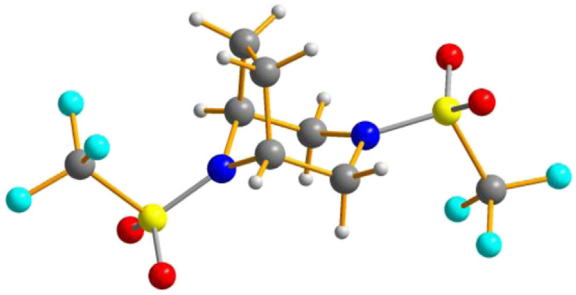


Fig. 1. X-ray structure of 3,8-bis(trifluoromethylsulfonyl)-3,8-diazabicyclo[3.2.1]octane **6**.

The formation of **6** is the first example of assembling the 3,8-diazabicyclo[3.2.1]octane framework in one-pot procedure. A priori, two mechanistic scenarios can be proposed for the formation of the product of bicyclization **6**, via the 2,5- (pathway A) or 1,6-cycloaddition (pathway B) to 1,5-hexadiene at the first step of the reaction (Scheme 2).

compound **5** to have the two iodomethyl groups trans to each other with respect to the heterocyclic ring (Fig. 2).

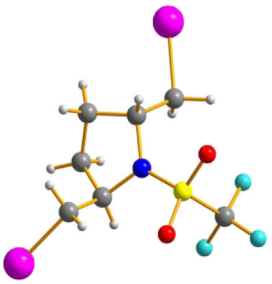
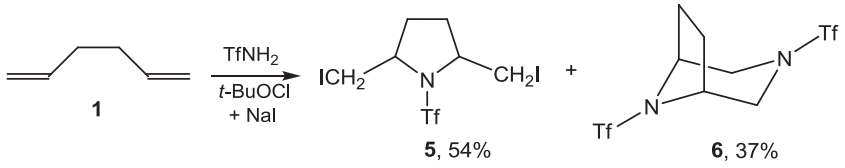
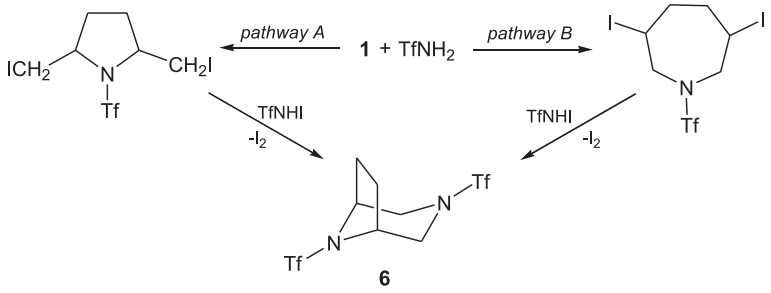


Fig. 2. X-ray structure of *trans*-2,5-bis(iodomethyl)-1-(trifluoromethylsulfonyl)pyrrolidine **5**. Beside the drawn 2*R*/5*R* enantiomer the 2*S*/5*S* enantiomer exists in the crystal.

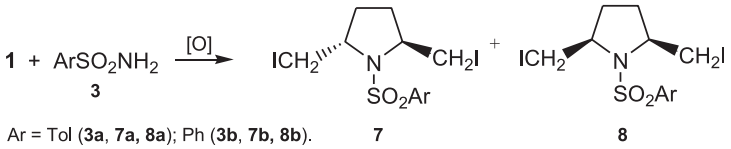
This explains why compound **5** does not react with triflamide to afford **6**, but leaves open the question whether the final product **6** is formed by pathway B or by pathway A via the transient cis isomer of **5**. Additional light was shed by the experiments with arenesulfonamides and methanesulfonamide. The reaction of **1** with arenesulfonamides **3a**,**b** proceeds in a different way than with triflamide. In both cases, two products were formed in approximately equal amounts (1:1.1 for **3a** and 1:1.2 for **3b**) and were identified as the trans and cis isomers of 2,5-bis(iodomethyl)-1-(arenesulfonyl) pyrrolidines **7** and **8** (Scheme 3).



Scheme 1. Mono and bicyclization in oxidative triflamidation of 1,5-hexadiene.



Scheme 2. Two possible routes to the product of bicyclization **6**.



Scheme 3. Formation of isomeric products of arenesulfonamidation of 1,5-hexadiene.

In pathway A, the formation of **6** is possible only for the cis arrangement of the two iodomethyl groups in 2,5-bis(iodomethyl)-1-(triflyl)pyrrolidine. Therefore, the structure of the isolated compound **5** (Scheme 1) was of particular interest. A special experiment showed that compound **5** does not react with triflamide under the conditions in Scheme 1. X-ray analysis showed

The mixture of diastereomers **7a** and **8a** was separated by column chromatography and the structure of **8a** was determined by X-ray analysis (Fig. 3). Note, that because of non-planarity of the pyrrolidine ring, the compound is not *meso* but exists in the crystal as a mixture of enantiomers (in solution, the ring is vibrationally averaged to planarity).

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