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Assembling of 3,6-diazabicyclo[3.1.0]hexane framework in oxidative triflamidation of substituted buta-1,3-dienes

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ABSTRACT

Reaction of trifluoromethanesulfonamide (triflamide) $CF_3SO_2NH_2$ with 2,3-dimethylbuta-1,3-diene (**2**) and 2,5-dimethylhexa-2,4-diene (**3**) in the oxidative system (*t*-BuOCl+NaI) results in the formation of 2,4-dimethyl- or 2,2,4,4-tetramethyl-3,6-bis(triflyl)diazabicyclo[3.1.0]hexane through two successive heterocyclizations. Reaction of diene (**3**) with arenesulfonamides $ArSO_2NH_2$ (Ar=Ph, Tol), stops at the formation of the product of oxidative 1,4-addition, *N,N′*-(2,3-dimethylbut-2-ene-1,4-diyl)diarenesulfonamides, providing evidence of the essential difference between the reactivity of triflamide and arenesulfonamides.

1. Introduction

Aziridines are important structural units of many biologically active molecules and, due to versatility of the aziridine motif, useful intermediates for the synthesis of numerous nitrogen-containing compounds.[1] Compounds having an aziridine ring in their structure are found in many natural products and possess antitumor, antibiotic, and other kinds of biological activity.[2] *N,N′N″*-Triethylenephosphoramide and *N,N′N″*-triethylenethiophosphoramide containing three aziridine units in the molecule are known as alkylating agents and exhibit therapeutic activity against various malignant tumors.[3]

In a series of works[4–11] we have studied the reactions of trifluoromethanesulfonamide (triflamide) with alkenes and dienes aiming at the synthesis of N-triflyl aziridines, but none of them led to the target compounds. Up to now, the only approach succeeded in preparation of N-triflyl aziridines was that of *Ochiai* et al.,[12,13] who suggested to use imino-λ^3-bromane $CF_3SO_2N{=}BrC_6H_4CF_3$ as an efficient aziridinating reagent. Also, the protocol including dehydration of a β-aminoalcohol with triflic anhydride was reported.[14]

In the present paper we have studied the reaction of triflamide with two substituted buta-1,3-dienes, 2,3-dimethylbuta-1,3-diene, and 2,5-dimethylhexa-2,4-diene, in oxidative conditions, as well as the reaction of the former with arenesulfonamides. Based on our previous experience and the results of examination of other sulfonamides,[15–19] the reaction may follow different reaction paths: oxidative 1,2-addition to one or two double bonds, heterocyclization into 3-pyrroline (2,5-dihydro-1*H*-pyrrole) ring, or aziridination to one or two double bonds. However, as will be shown below, the reaction selectively produces the products of successive cyclizations having the structure of 3,6-diazabicyclo[3.1.0]hexanes and containing fused aziridine and pyrrolidine rings.

3,6-Diazabicyclo[3.1.0]hexane motif presents in the structure of many antitumor agents and antibiotics, derivatives of mitomycin.[20–23] The synthesis of bicyclic aziridine-containing compounds, in particular, those with fused aziridine and pyrrole rings, like in mitomycin C, is a challenging multi-step task,[24] which requires the use of not easily accessible substrates and severe reaction conditions. One of the first syntheses of these structures was the reaction of *N*-arylmaleimides with arylazides leading to the corresponding 2,4-dioxo-3,6-diazabicyclo[3.1.0]hexanes.[25]

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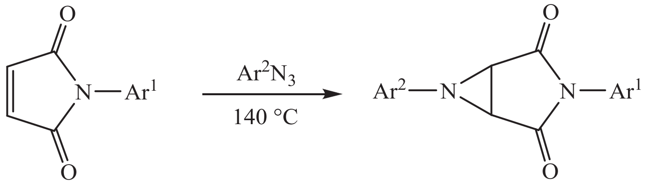
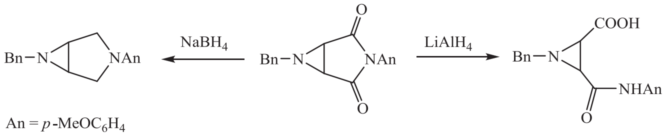
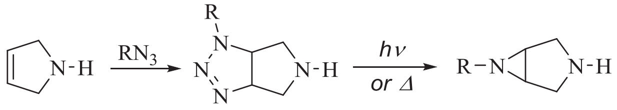


However, an attempt to reduce the carbonyl groups to the corresponding methylene groups by the action of $LiAlH_4$ led mainly to hydrolysis products and only to trace amounts of the target products, while treatment with $NaBH_4$ gave the desired bicyclic products.[26]



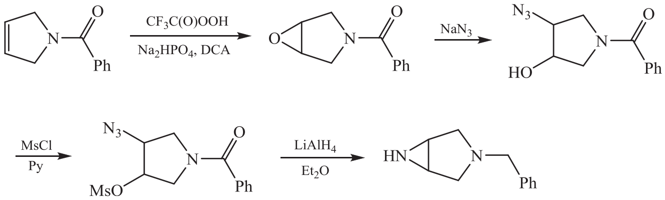
An = p-MeOC$_6$H$_4$

The reaction of arylazides with 3-pyrroline, after elimination of nitrogen, directly affords 6-aryl-3,6-diazabicyclo[3.1.0]hexanes in good to quantitative yields.[27]

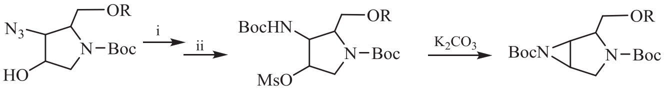


R=p-BrC$_6$H$_4$, C$_6$H$_5$, p-CH$_3$OC$_6$H$_4$

The second approach is based on the use of 3-pyrrolines, which are not easily accessible. For example, N-benzoyl-3-pyrroline is epoxidized by trifluoroperacetic acid to N-benzoyl-3,4-epoxypyrrolidine, which enters successively the reaction with sodium azide and MsCl to form the corresponding ester of methanesulfonic acid. After reduction with $LiAlH_4$ on Co(II) catalyst 3-benzyl-3,6-diazabicyclo[3.1.0]hexane is formed in 60% total yield whereas with $NaBH_4$/Co(II) 3-benzoyl-3,6-diazabicyclo[3.1.0]hexane is formed in 68% yield.[28,29] The substituents at the nitrogen atom in the 3-pyrroline ring do not alter the course of the reaction.[30]



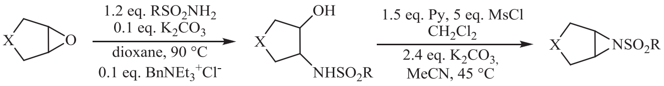
Then the products are usually treated with acyl halogenides to give 6-acyl derivatives.[29–31] A similar technique for the synthesis of 3,6-diazabicyclo[3.1.0]hexanes from 3-pyrrolines was used in more recent works. Thus, formation of the aziridine moiety in the molecule can be achieved by transformation of the azide group to the amide followed by further treatment with MsCl in pyridine, elimination of MsOH by the action of a base and, finally, formation of 3,6-diazabicyclo[3.1.0]hexane framework.[32]



i : = Pd/C/H$_2$, Boc$_2$O, MeOH
ii : MsCl, Et$_3$N, CH$_2$Cl$_2$
R = SiPh$_2$Bu-t

If the azide group is transformed into the N-alkylamino or carbamate group, mesylate formation is unnecessary and dehydration of the N-methylamino derivative can be performed directly using the $Ph_3P/CCl_4/Et_3N$ system in a yield of 76%.[33] Dehydration of the benzylcarbamate derivative is performed by Ph_3P in THF in the presence of DIAD.[34]

The epoxide ring can be opened directly by the use of arenesulfonamides as the source of nitrogen in the presence of a base. In this case, in the second step the corresponding mesylate is to be prepared, which under the action of K_2CO_3 in MeCN gives finally the target product having the N-arylsulfonylaziridine motif in the molecule.[35,36]



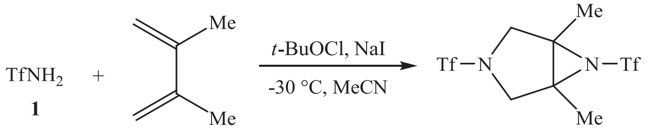
X=CH$_2$, O, TsN, BocN, 2,4,6-^{i}Pr$_3$C$_6$H$_2$SO$_2$N
R=4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4,6-Me$_3$C$_6$H$_4$, 2,4,6-^{i}Pr$_3$C$_6$H$_2$

With organolithium reagents, 3,6-bis(arenesulfonyl)-3,6-diazabicyclo[3.1.0]hexanes (X=ArSO$_2$N) suffer both the aziridine and pyrrolidine ring opening reaction leading to acyclic bis(arenesulfonamides).[37]

Therefore, it can be concluded that preparation of 3,6-diazabicyclo[3.1.0]hexanes is a 3–5-step synthesis based on successive functionalization of 3-pyrroline derivatives.

2. Results and discussion

Here, we present a simple one-pot synthesis of 3,6-diazabicyclo[3.1.0]hexanes based on the reaction of triflamide (**1**) to 2,3-dimethylbuta-1,3-diene (**2**) and 2,5-dimethylhexa-2,4-diene (**3**). The reaction of triflamide with 2,3-dimethylbuta-1,3-diene proceeds under mild conditions and results in the formation of the single product, 2,4-dimethyl-3,6-bis(trifluoromethylsulfonyl)-3,6-diazabicyclo[3.1.0]hexane (**4**) in a yield of 80% (Scheme 1). When the reaction is carried out at room temperature or even with cooling to 0 °C strong resinification of the reaction mixture is observed.



1 **2** **4**

Tf = CF$_3$SO$_2$

Scheme 1. Bicyclization in oxidative triflamidation of 2,3-dimethyl-buta-1,3-diene.

The structure of **4** is confirmed by ^1H, ^{13}C, ^{19}F NMR spectroscopy, which showed a singlet of 1,5-methyl groups at 1.7 ppm and two doublets of diastereotopic methylene protons at 3.5 and 4.2 ppm in the proton spectrum, the corresponding signals of CH_3 (12.8 ppm), CH_2 (54.3 ppm) and quaternary carbons (61.7 ppm), as well as two CF_3 signals at 119.5 and 120.9 ppm in the ^{13}C NMR spectrum. The presence of two different triflyl groups is also proved by the