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Generation and Reactions of Aza-*ortho*-xylylenes in the Injector of GC/MS System

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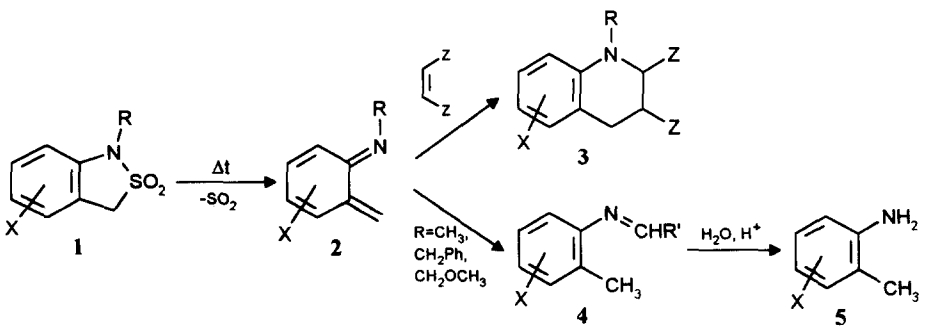
Abstract: Nitro derivatives of 2,1-benzisothiazoline 2,2-dioxide (benzosultams) undergo thermal elimination of sulfur dioxide yielding very reactive, non-isolable aza-*ortho*-xylylenes. It was found that this reaction can be performed in the injector of the gas chromatograph at 300 - 350°C and the formed aza-*ortho*-xylylenes can be trapped by appropriate reagents added to the injected solution. In the preliminary experiments aza-*ortho*-xylylenes were reacted with dienophiles (methyl acrylate, dimethyl maleate, vinyl acetate, *N*-phenylmaleimide etc.) resulting in the formation of the [4+2] cycloaddition reaction products, and also with nucleophilic reagents (alcohols, amines) to give appropriate adducts. In the absence of the trapping reagent dimers of aza-*ortho*-xylylenes were formed.

Nitro derivatives of 2,1-benzisothiazoline 2,2-dioxide (benzosultams, **1**) are easily synthesized from appropriate *m*-nitroanilines.[1] Recently, the synthetic utility of some reactions of these compounds have been reported.[2-4] It was found that they undergo thermal elimination of sulfur dioxide yielding very reactive, non-isolable aza-*ortho*-xylylenes **2**. This was confirmed by the isolation of the products of Diels-Alder reaction **3** when reactive dienophile was present in the reaction mixture. The yields of these reactions were very high. In the absence of dienophile the reaction products depend on the substituent at the *N*-1 atom. Compounds with methyl, benzyl or methoxymethyl group in this position give aldimines **4**, most likely formed *via* a [1,5]hydrogen shift in the intermediate aza-*ortho*-xylylene,[3] while unsubstituted ones give a complex mixture of several products. In the case of the methyl group, the aldimines **4** are too labile to be isolated, so only the corresponding nitroanilines **5** are obtained. There was found also, that the benzosultams with a hydrogen on *N*-1, when heated with the dienophile give a mixture of unidentified products.

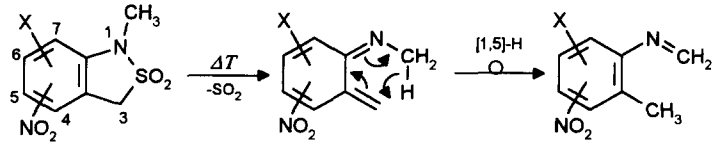


Searching for the fast and efficient way to investigate the formation and reactions of aza-*ortho*-xylylenes we decided to use the GC/MS instrument.[5] We expected that by varying the GC injector temperature, decomposition of the benzosultam **1** will be easy to control, and gas-phase reactions of preliminary formed aza-*ortho*-xylylene **2** will be possible to perform during injection of mixtures of benzosultams with appropriate reagents.

Mixture of the products will be separated on GC column and its components will be characterized by their mass spectra. This approach is in some aspects similar to so-called "reaction gas chromatography/mass spectrometry".[6] The latter, however, had not been used for performing the reactions with reactive species generated *in situ* in the injector of the GC/MS system.

Taking standard gas chromatograms of benzosultams **6** it was found, that two GC peaks were present. Peak with the longer retention time corresponded to the unchanged benzosultam **6**, while the second one was identified as aldimine **7**. This result shows that the rearrangement of aza-*ortho*-xylylene to aldimine, proceeding *via* a [1,5]hydrogen shift, is a very fast process in the gas phase.

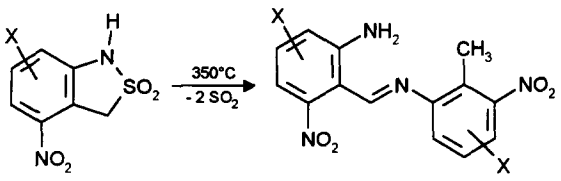
Ratio of the unreacted benzosultam to aldimine depends on the temperature of the GC injector. By changing this temperature it is possible to estimate the activation energy of the SO_2 extrusion from benzosultams. For example the activation energy for **6a** was found to be equal to 42.9 ± 0.8 kcal/mol.



6a - e **7a - e**

a: 4-NO_2, X = H; **b:** 5-NO_2, X = H; **c:** 4-NO_2, X = 5-Cl; **d:** 4-NO_2, X = 7-F; **e:** 4-NO_2, X = 7-OCH_3

Benzosultams without a substituent on the 1-*N* atom **8a-d** behave differently in comparison with derivatives with 1-*N*-CH_3 group. When compound **8a** was injected into GC at 350°C (column temperature 200°C), two peaks were observed (Fig. 1). The first one was assigned to unreacted substrate and the second - to compound with MW = 300, which corresponds to the dimer **9a** of the aza-*ortho*-xylylene formed *via* SO_2 extrusion from **8a**. Similar results have been obtained for compounds **8b-d**.



8a-d **9a-d**

a: X = H; **b:** X = 5-Cl; **c:** X = 7-Cl; **d:** X = 7-CH_3

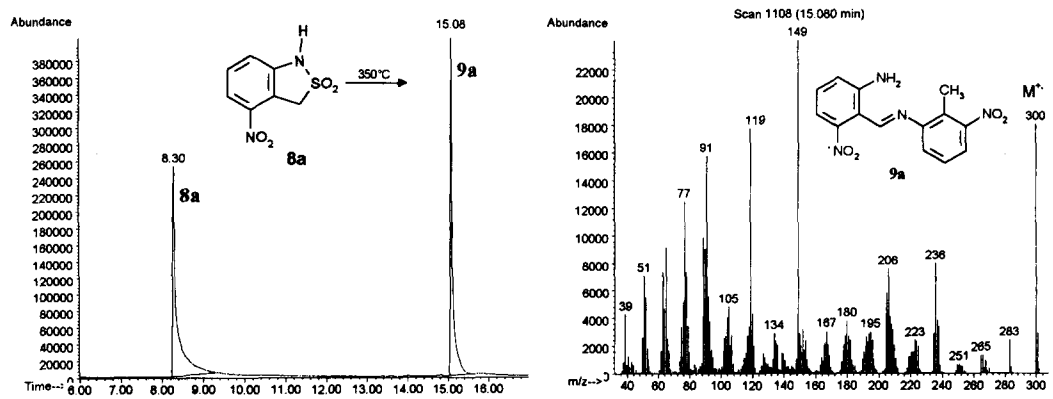
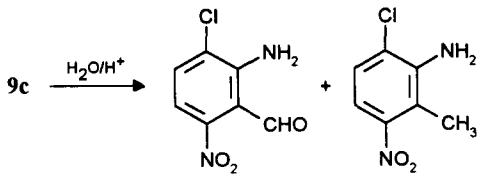


Figure 1. Injection of **8a** at 350°C. Gas chromatogram (left) and mass spectrum of the dimer **9a** (right).

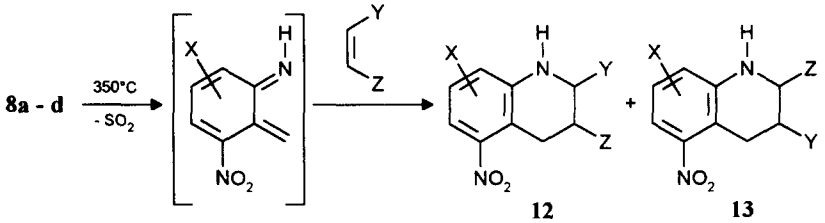
The structure of dimers **9** were proposed on the basis of their mass spectra and confirmed by the synthesis of **9c**. Sultam **8c** while heating in boiling 1,2,4-trichlorobenzene (215°C) produces **9c** in low yield. Crude **9c** was hydrolysed to give two products, which were identified as compounds **10** and **11**.



10 **11**

In the case of compounds **8c** and **8d** additional products other than **9** were observed, one of them in significant amount. Mass spectra of these products indicate, that their molecular weight is 2 units lower than for **9**. The structure of these products is not clear. However, the main fragmentation of the product formed from **8c** is a loss of HCl which can suggest that at least one benzene ring has lost its aromaticity during the reaction.

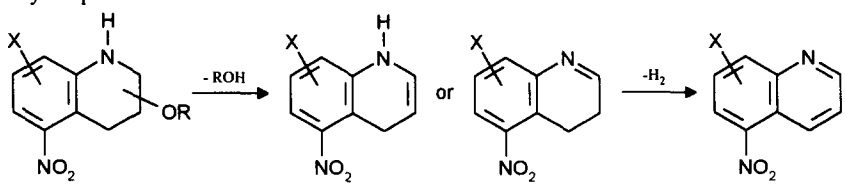
When the mixture of **8** with a suitably substituted alkene was injected on GC at 350°C, peaks corresponding to [4+2] cycloaddition products **12** and **13** were observed in the chromatogram.



12 **13**

Y = H, Z = COOMe; Y = H, Z = CN; Y = H, Z = $OCOCH_3$; Y = H, Z = OEt;
Y = Z = CN (*E*-); Y = Z = COOMe (*Z*-); Y = Z = COOMe (*E*-); Y,Z = -CO-NPh-CO-.

In the case of the reactions with ethyl vinyl ether and vinyl acetate, the major peak on the chromatogram can be assigned to the appropriate dihydroquinoline derivative **14** or **15**, which can be formed by the elimination of ethyl alcohol or acetic acid from the preliminary formed cycloadduct **12** or **13**. In some instances the major product was identified as nitroquinoline derivative **16**. The formation of **16** was a result of dehydrogenation of the dihydroquinoline **14** or **15**.



12 or **13** (R = $COCH_3$, OEt) **14** **15** **16**

When the mixture of **8** with the nucleophilic reagent (alcohol or amine) was injected on GC at 350°C, peaks corresponding to the products **17** or **18**, formed by addition of the nucleophile to aza-*ortho*-xylylene, appear in the chromatogram.

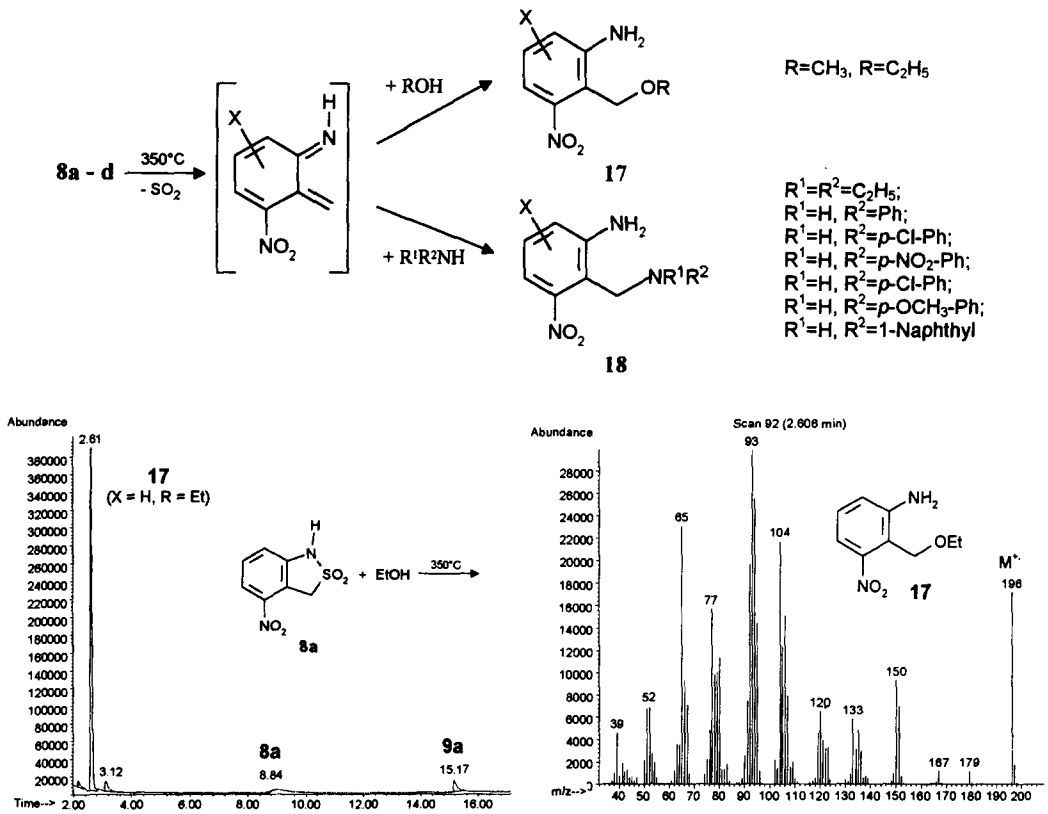


Figure 2. Injection of the solution of **8a** in ethanol at 350°C. Gas chromatogram (left) and mass spectrum (right) of the adduct **17** (X = H, R = Et).

Reactions with short-chain alcohols and aliphatic amines proceed with very high yields (Fig. 2). Reactions with aromatic amines give much more complex reaction mixtures, however in these cases also the amine addition product dominates.

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2. Wojciechowski, K., *Synlett*, **1991**, 571-572.
3. Wojciechowski, K., *Tetrahedron*, **1993**, *49*, 7277-7286.
4. Wojciechowski, K., *Tetrahedron*, **1993**, *49*, 10017-10026.
5. All experiments were performed using Hewlett-Packard GC/MS system containing HP 5890 Series II gas chromatograph coupled directly to MSD 5972A mass-sensitive detector. HP-5 capillary column (30 m length, 0.25 mm ID) was used. Injector temperature was usually set to 350°C and the column temperature was programmed according to the experiment requirements. The injector glass liner was filled with a deactivated quartz wool on the length of 10 mm to achieve better mixing of the reagents. Samples were injected in ethyl acetate solutions or, in some instances, in the solution in an appriopriate reagent.
   Synthesis of the starting materials has been published elsewhere.[1]
6. Mikaya, A.I., Zaikin, V.G. *Mass Spectrom. Rev.*, **1990**, *9*, 115-132.

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