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Unexpected Results in the Reaction of 5'-Tosyl TSAO-m³T With Amines

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UNEXPECTED RESULTS IN THE REACTION OF 5'-TOSYL TSAO-m³T WITH AMINES

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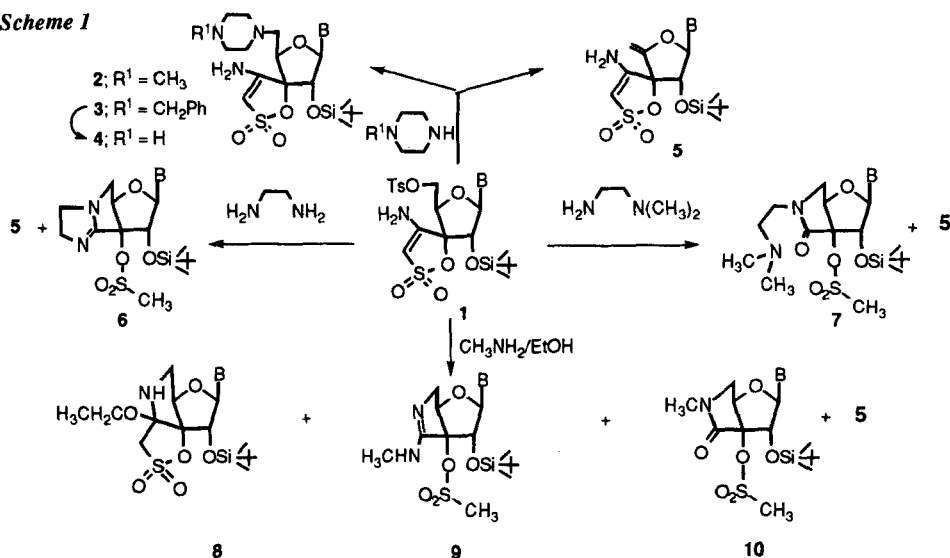
ABSTRACT: We report our strategies to prepare TSAO compounds carrying at 5'-position groups, such as amines, that may be positively charged at physiological conditions, unexpectedly, cyclic TSAO-derivatives were obtained. A possible mechanism for the formation of these unexpected compounds is advanced.

Cations, including complex organic structures, are strongly attracted to the π face of benzene and aromatic aminoacids.¹ Several features distinguish this interaction from other noncovalent binding forces and make it well suited to novel types of biological binding.

A common feature of non-nucleoside reverse transcriptase inhibitors (NNRTIs) is that they all bind in a highly hydrophobic pocket only present in HIV-1 RT.² Within this pocket there is a cluster of three aromatic residues namely Tyr 181, Tyr 188 and Trp 229, involved in the binding of most of the NNRTIs. TSAO derivatives³ represent a particular family of NNRTIs whose prototype is TSAO-T [1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)- β -D-ribofuranosyl]thymine]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide). Our currently working model of interaction of TSAO-T with HIV-1 RT suggests that the 5'-TBDMSi group may be interacting in the above mentioned cavity defined by the three aromatic residues.

Based on the hypothesis of cation- π interaction, we were interested in preparing TSAO compounds carrying at 5'-position groups, such as amines, that may be positively charged at physiological conditions. Our strategy to synthesize such 5'-amino TSAO derivatives is outlined in *Scheme 1*. Thus, treatment of the 5'-tosyl derivative **1**⁴ with excess of methyl or benzylpiperazine gave **2** and **3**, respectively, together with the β -elimination product **5**. Catalytic hydrogenation (10% Pd/C) of **3** afforded **4**. A similar treatment of **1** with ethylenediamine gave **6** as the major compound, together with the unexpected cyclic derivative **5**. Reaction of **1** with *N,N*-dimethyl ethylenediamine afforded the β -elimination product **5** as the major compound and the cyclic compound **7**. Finally, reaction of **2** with ethanolic methylamine, gave the cyclic derivatives **8-10** together with the β -elimination

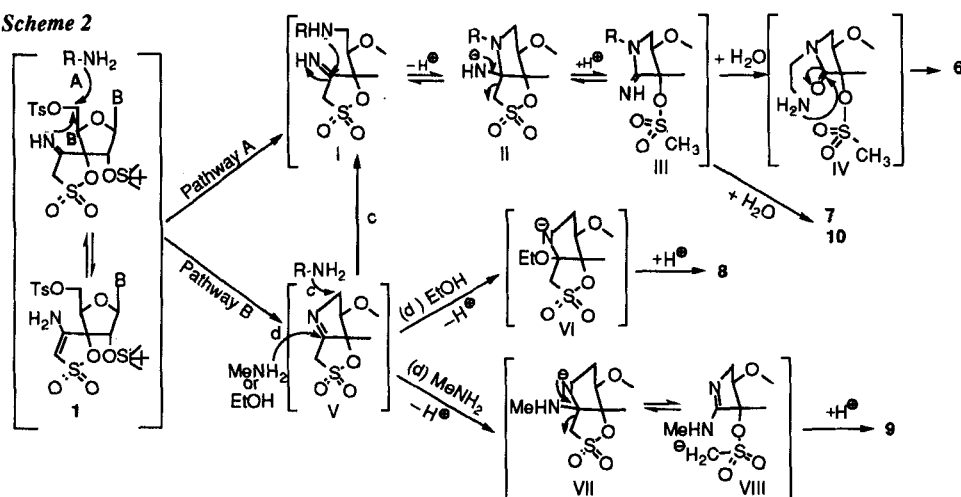
Scheme 1



product 5. Structures of the new compounds 5-10 were determined by ¹H and ¹³C NMR spectroscopy and Mass spectrometry. Full assignment of proton and carbon resonances were achieved using mono and bidimensional techniques (HMQC and HMBC).

A possible rational for the formation of the cyclic derivatives 6-10 is outlined below in Scheme 2.

Scheme 2



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