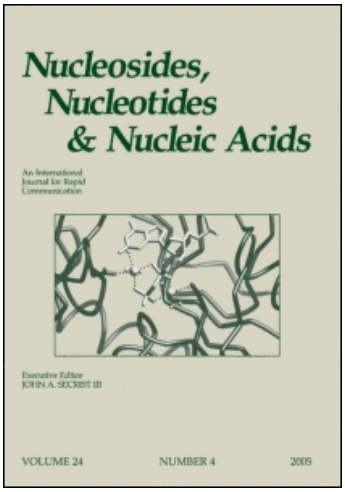

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Unexpected Results in the Reaction of 5'-Tosyl TSAO-m³T With Amines

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UNEXPECTED RESULTS IN THE REACTION OF 5'-TOSYL TSAO-m^{3}T WITH AMINES

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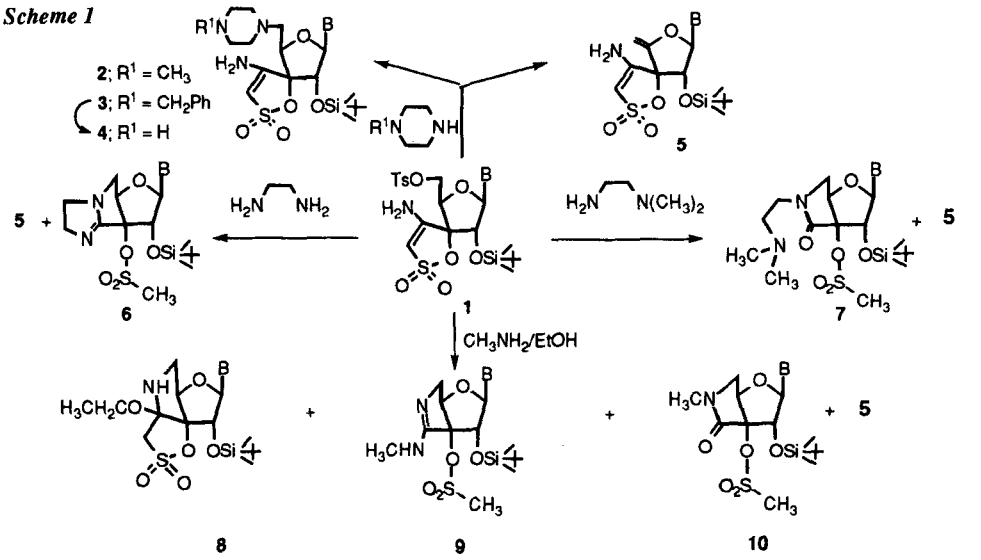
ABSTRACT: We report our strategies to prepare TSAO compounds carrying at 5'-position groups, such as amines, that may be positively charged at physiological conditions, unexpectedly, cyclic TSAO-derivatives were obtained. A possible mechanism for the formation of these unexpected compounds is advanced.

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 derivatives[3] 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.** Catalityc hydrogenation (10% Pd/C) of **3** afforded **4.** A similar treatment of **1** with ethylendiamine gave **6** as the major compound, together with the unexpected cyclic derivative **5**. Reaction of **1** with *N,N*-dimethyl ethylendiamine 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

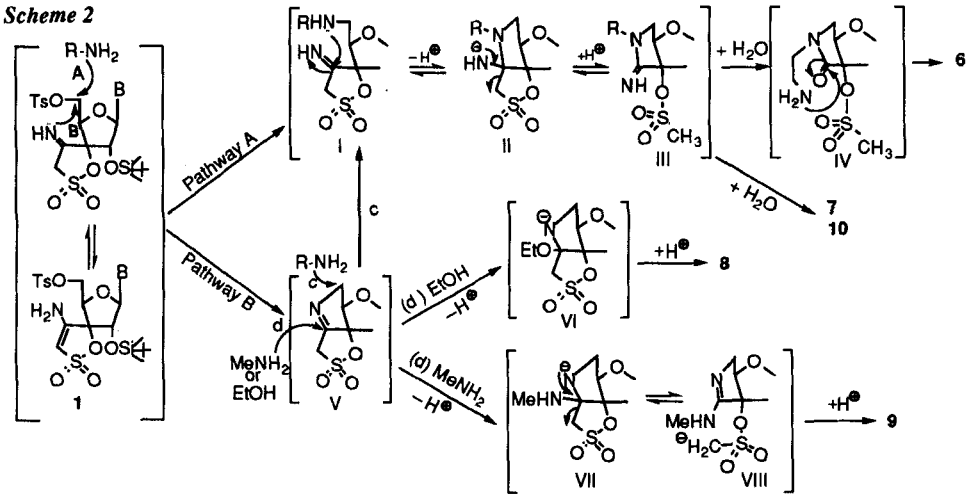
Scheme 1



product **5**. Structures of the new compounds **5-10** were determined by ^{1}H and ^{13}C 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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REFERENCES

1 Dougherty, D. A. *Science*, **1996**, *271*, 163-168.
2 Smerdon, S. J.; Jager, J.; Wang, J.; Kohlstaedt, L. A.; Chirino, A. J.; Friedman, J. M:; Rice, P. A.; Steiz, T.A. *Proc, Natl. Acad. Sci. USA*, **1994**, *91*, 3911-3915.
3 Balzarini, J.; Camarasa, M. J.; Karlsson, A. *Drugs of the Future* **1993**, *18*, 1043-1055.
4 Ingate, S.; Pérez-Pérez, M. J.; De Clercq, E.; Balzarini, J.; Camarasa, M.J. *Antiviral Res.* **1995**, *27*, 281-299.