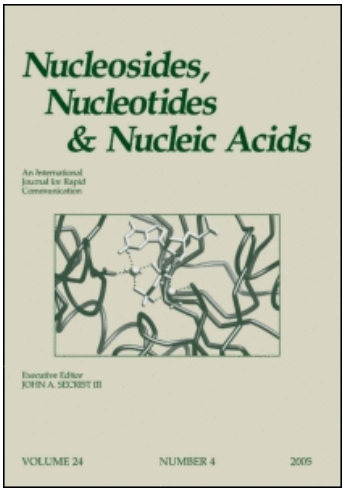

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NOVEL TSAO DERIVATIVES MODIFIED AT POSITIONS 3" AND 4" OF THE SPIRO MOIETY

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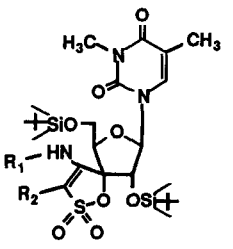
ABSTRACT: We have explored the introduction of different functional groups at positions 3" and 4" of the spiro moiety of TSAO-T. Alkylation of this spiro moiety afforded mixtures of N and/or C-alkylated derivatives, while acylation occurs, exclusively, on the amino group. Position 3" has been selectively functionalized by halogenation followed by Stille-cross coupling reaction with organostannanes under a variety of experimental conditions.

TSAO derivatives are potent and highly specific inhibitors of the human immuno-deficiency virus type 1 (HIV-1) replication. One of the most characteristic features of TSAO derivatives, whose prototype compound is TSAO-T (**1**), is the presence of the spiro ring of 4-amino-1,2-oxathiole-2,2-dioxide. Our recent data have shown that replacement of this spiro ring by closely related analogues results in 100-fold decrease of the anti-HIV-1 activity.[1,2] We have now introduced different functional groups at positions 3" and 4" of the spiro ring of TSAO-T and of its N-3-methyl derivative (TSAO-m^3T, **2**). To perform these modifications two important points have been considered: first, the chemical reactivity of this heterocyclic system has been scarcely studied. Second, the presence of the *tert*-butyldimethylsilyl groups at positions 2' and 5', sensitive to basic and acid media, respectively, but essential for antiviral efficacy, implies the selection of smooth reaction conditions compatible with such protecting groups.

When we assaied the reaction of TSAO-m^3T with alkyl halides, we noticed that the presence of strong bases (KOH or NaH) was required, in contrast to the alkylation of classical enamines where no base is needed.[3] Thus, reaction of **2** with CH_3I and KOH in dry dioxane afforded the corresponding N- and C-methylated derivatives (**3** and **4**), together with the N,C-dialkylated compound (**5**) (Figure 1). Reaction of TSAO-m^3T with ICH_2CONH_2 in the presence of NaH afforded exclusively the N,C-dialkylated derivative (**6**) together with unreacted starting material. On the other hand, reaction of **2** with allyl bromide and NaH yielded the N- and C-allylated derivatives (**7** and **8**) in a 1:1 ratio.

In contrast to the lack of selectivity of the alkylation reaction, acylation occurs exclusively on the amino group, as exemplified by the reaction of **2** with methyl oxalyl chloride to afford **9** (Figure 1). An excess of a tertiary amine (Et_3N or DIPEA) is

required to avoid deprotection of the 5'-tBuMe2Si group. The methyl ester was further transformed into the free acid (**10**) or the amide (**11**) by treatment with NaOH.1N or NH_3/MeOH, respectively.



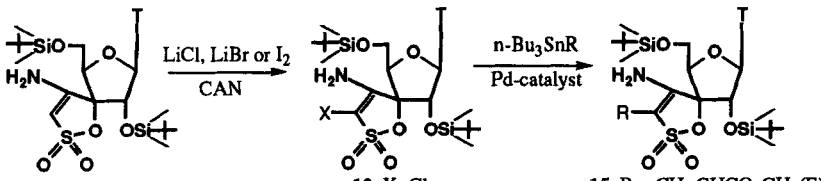
2 R_1=R_2=H (TSAO-m3T)

3 R_1=CH_3 R_2=H
4 R_1=H R_2=CH_3
5 R_1=R_2=CH_3
6 R_1=R_2=CH_2CONH_2
7 R_1=$CH_2CH{=}CH_2$ R_2=H
8 R_1=H R_2=$CH_2CH{=}CH_2$

9 R_1=$COCOOCH_3$ R_2=H
10 R_1=COCOOH R_2=H
11 R_1=$CONH_2$ R_2=H

Figure 1

To selectively functionalize the 3"-position of the spiro ring, we investigated the Stille cross-coupling reaction of vinyl halogenides with organostannanes. Very few examples are described in the literature of Stille-couplings in heterocycles containing free amines.[4] Therefore, the 3"-haloderivatives were synthesized. Reaction of TSAO-T (**1**) with methyl halides (LiCl, LiBr) or I_2 and ceric ammonium nitrate (CAN) in CH_3CN at 80°C afforded the TSAO-derivatives **12-14** (Scheme 1). Addition of Et_3N was required to avoid deprotection at 5'-position. Coupling of **14** with (E)-methyltributylstannyl acrylate was chosen as a model reaction. Traditional catalyst [$Pd(Ph_3P)_4$(5%)] or "ligandless" catalyst [$PdCl_2(CH_3CN)_2$] did not provide an efficient coupling (>80% starting material). The weakly coordinated $Pd_2(dba)_3$(2%) and the soft ligand Ph_3As(8%) afforded the coupling derivative **15** in 55% yield together with a high proportion of reduction product (TSAO-T, 40%). The ratio of reduction product was markedly disminished by subsequent addition of the organotin derivative after 1 and 2 h of reaction. Finally, addition of CuI (5%) as a cocatalyst allowed to reduce the reaction time to 2 h to obtain **15** in 72% yield. Using these optimized conditions [$Pd_2(dba)_3$(2%)/Ph_3As(8%)/CuI(4%)/nBu_3SnR(4eq)], the coupling derivatives **16** and **17** were prepared (80 and 89%, respectively). The higher the reactivity of the stannane, the higher the yield of the coupling product.



1 TSAO-T

12 X=Cl
13 X=Br
14 X=I

15 R = $CH{=}CHCO_2CH_3$(E)
16 R = $CH{=}CH_2$
17 R = $CH{=}CHCH_2OH$(E)

Scheme 1

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