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Tosylation/mesylation of 4-hydroxy-3-nitro-2-pyridinones as an activation step in the construction of dihydropyrido[3,4-*b*] benzo[*f*][1,4]thiazepin-1-one based anti-HIV agents

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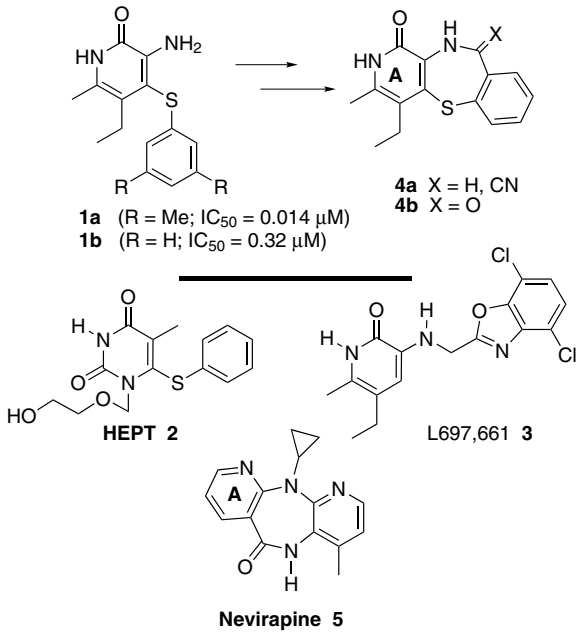
Abstract—Reaction of 4-hydroxy-3-nitropyridinone **8** with TsCl and MsCl, respectively, resulted in rapid and quantitative formation of ditosylate **13** and dimesylate **16**. Through chemoselective reaction of **16** with thiophenol **17** the key 4-thioaryl substituted intermediate **18** was obtained in 78% yield. This compound was efficiently converted to the target tricyclic products **4a** and **b**. Compound **4a**, in particular, is a potent inhibitor in vitro (IC_{50} = 2 nM) of wild type HIV-1 replication.

Arylthiopyridinones **1a** and **b** are key members of a family of potent non-nucleoside type inhibitors of HIV-1 reverse transcriptase (Scheme 1).[1] In a program to look at SAR in this series, and in particular for compounds, which maintain activity against the Tyr181/188 mutants conferring resistance to the related NNRTI's HEPT **2** and pyridinone **3**,[2,3] one objective was to construct the conformationally restrained analogues **4a** and **b**. Such dihydropyrido[3,4-*b*] benzo[*f*][1,4]thiazepin-1-ones bear a structural resemblance to nevirapine **5**.[4] However, analysis of the structures of HEPT and nevirapine complexed with RT suggests that in order for thiazepinones **4a** and **4b** to conserve a crucial hydrogen bond to the Lys101 residue in the hydrophobic pocket of rt they must adopt an orientation different to that for nevirapine.[5] It was thus of considerable interest to determine whether molecules **4** display anti-HIV activity.[6,7]

Central to our synthesis of these molecules was the need to develop effective means to activate the C-4 center in 4-hydroxy-3-nitropyridinone **8** with respect to nucleophilic (S_NAr) substitution by an appropriate *o*-substituted thiophenol. In earlier work it was found that, whereas the approach involving conversion of the less



Scheme 1.

Keywords: Mesylation; Pyridinones; Dihydropyridobenzothiazepin-1-ones; Anti-HIV; Reverse transcriptase.
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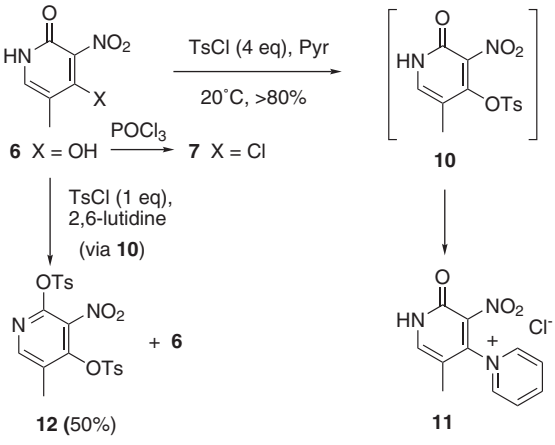
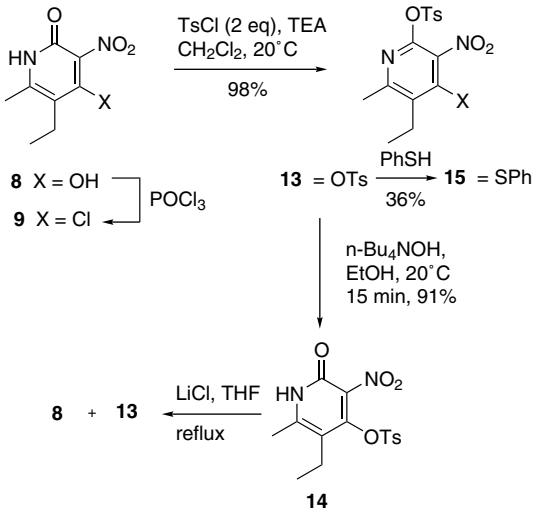
hindered 5-methyl substituted pyridinone **6** to the chloro derivative **7** using $POCl_3$ is efficient (80%), the yields for the corresponding conversion of 5,6-dialkyl substituted pyridinone **8**–**9** are low (12–34%), and in fact, poorly reproducible.[1a,8] A study was thus made of the preparation and synthetic utility of the corresponding 4-tosylates/mesylates of these two pyridinones and their subsequent conversion to the target thiazepinones.

It was found (Scheme 2) that the reaction of the 5-methyl substituted pyridinone **6** with excess TsCl (4 equiv) in pyridine at either room temperature, or at −20 °C, led to immediate formation of pyridinium salt **11** (>80% pure by NMR; remaining impurities pyridine·HCl).[9] This result indicated that selective monotosylation of the C-4 hydroxyl group had occurred, and further, that the derived tosylate **10** was highly reactive. This secondary reaction was easily suppressed using 2,6-lutidine as the amine solvent. However, when 1 equiv only of TsCl was employed in the presence of this hindered base the bistosylated compound **12**, and not the expected product **10**, was obtained in an equal mixture with the starting pyridinone **6**.[10] In the corresponding reaction of the more hindered pyridinone **8** with 2 equiv of TsCl and Et_3N in CH_2Cl_2 at room temperature the bistosylate **13** was obtained in 98% yield (Scheme 3).

A plausible explanation for this result is that rate of formation of **12** and **13** from the initially formed monotosylates is much faster than the formation of these montosylates themselves.[11] Another possibility is that the monotosylate, which is formed reacts also as a tosyl transfer reagent, in which instance the bistosylated product would accumulate as the concentration of TsCl in the medium diminishes. The later scenario was rejected following the observed formation of monotosylate **14** as a stable compound when bistosylate **13** was treated under mild hydrolysis conditions (aqueous Bu_4NOH in EtOH, RT, 15 min; 91%). Interestingly, when compound **14** was reacted with LiCl in refluxing THF a 1:1 mixture of bistosylate **13** and pyridinone **8** was obtained. In this reaction chloride ion reacts preferentially at the sulfur atom of the C-4 OTs group generating TsCl



Scheme 2.

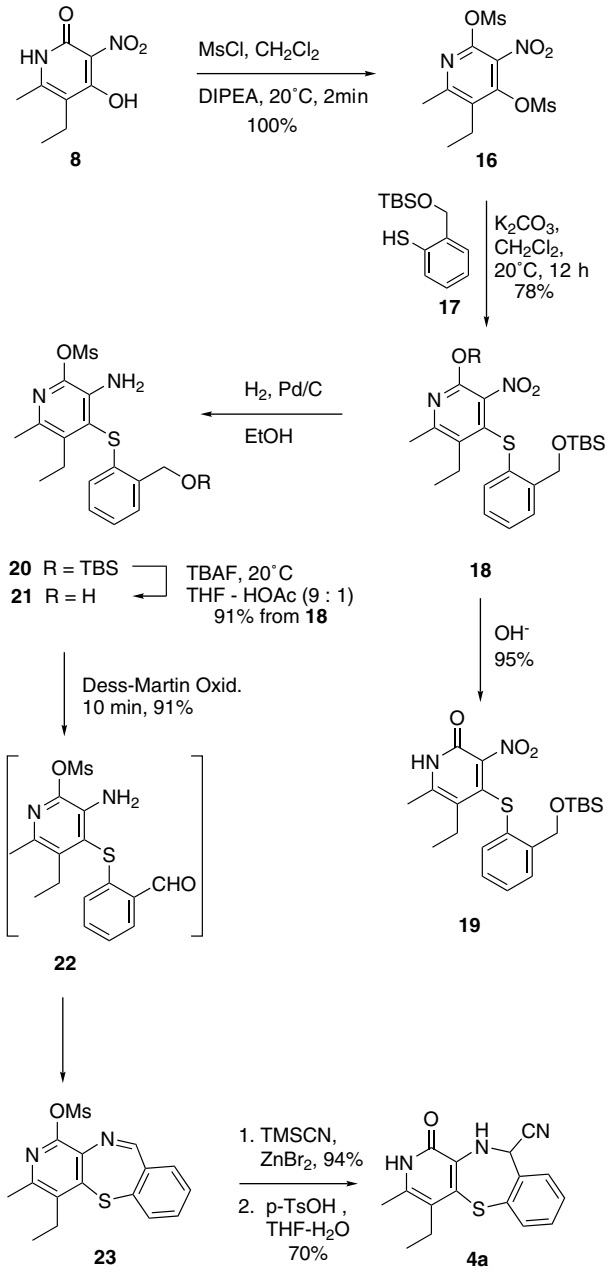


Scheme 3.

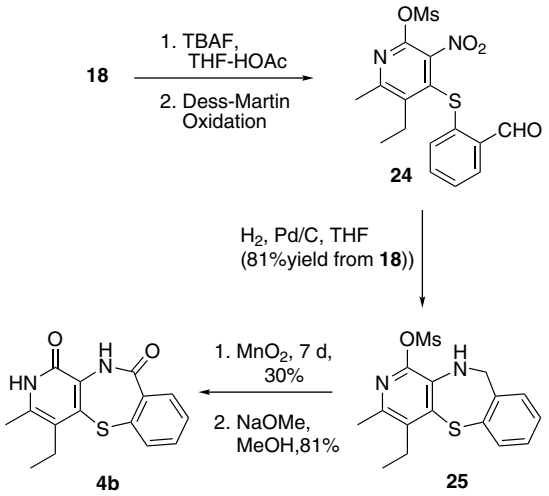
and **8**. As already shown, these molecules react with each other to give **13**. In contrast, in the reaction of bistosylate **13** with thiophenol (CH_2Cl_2, Et_3N, 20 °C, 12 h) clean displacement of the 4-OTs group occurred leading to selective formation of compound **15**, albeit in only moderate yield.

To obtain a more reactive partner in the reaction with thiophenyl derivatives, pyridinone **8** was converted to the dimesylate intermediate **16** (Scheme 4). Under optimum conditions [MsCl (3 equiv), DIPEA (3 equiv) in CH_2Cl_2 at 20 °C for 2 min] quantitative conversion to **16** [mp 134 °C (EtOH)] was achieved. The reaction of this bismesylate with thiophenol derivative **17**[12] provided the desired condensation product **18** in 78% overall yield from **8**. This sequence is thus both more rapid and more efficient than the traditional $POCl_3$ activation approach.

At this point the option was open to hydrolyze **18** to the corresponding pyridinone **19** (NaOMe/MeOH); 95%. However, as the solubility characteristics of intermediates retaining the 2-OMs facilitated isolation/purification, conditions were developed to carry this functionality through to the last steps in the synthesis of the thiazepinone ring. In this context, reduction of the nitro group in **18** to give **20** under catalytic hydrogenation conditions proved advantageous relative to the use of $SnCl_2·2H_2O$. Note that under hydrogenation conditions partial loss of OTBS group occurred. Complete transformation of **20** to **21** was achieved by treatment of the mixture with TBAF in THF–HOAc, the acid being added to neutralize any hydroxide ion present in the TBAF solution. Using the Dess–Martin reagent the primary OH group in **21** was oxidized giving aldehyde **22** (91%). This intermediate spontaneously cyclized to the water sensitive imine **23**, which was converted to its more stable aminonitrile derivative through reaction with TMSCN ($ZnBr_2$ cat, EtOAc, reflux). Treatment of this compound under aqueous base conditions led to loss of HCN and imine ring opening giving back **22**. In contrast, hydrolysis of the OMs-imidate motif with



Scheme 4.



Scheme 5.

acid [*p*-TsOH, H_2O–THF (1:1)] gave the target tricyclic pyridinone **4a**.

In an alternate series of reactions, the O-TBS group in intermediate **18** was removed, the liberated primary alcohol was oxidized, and the derived nitro aldehyde **24** was reductively cyclized under catalytic hydrogen conditions to give the amine **25** in 81% overall yield (Scheme 5). Interestingly, oxidation of amine **25** using MnO_2 proceeded beyond the formation of imine **23**, providing, after hydrolysis, direct access to amide **4b**.[13]

Tested in the LAI CEM-SS cell system assay[14] compound **4a** [$IC_{50} = 0.002\ \mu M$] proved to be essentially equipotent with the reference molecule **1a**. Most interestingly, this rigidified arylthiopyridinone analogue proved to be 100 times more active than compound **1b**, which similarly lacks the 3′,5′-dimethyl substitution on the phenyl ring. In contrast, relative to **1b** no real gain in activity was observed for the amide analog **4b** [$IC_{50} = 0.084\ \mu M$]. None of these compounds displayed any appreciable cytotoxicity ($IC_{50} > 10^{-5}$ M). From these results it can be deduced that the tricyclic structure of compounds **4** reflect the active conformation of the more flexible arylthiopyridinones **1** bound in the hydrophobic pocket of RT.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.02.128.

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