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Studies toward the synthesis of cinachyramine. An efficient route to 1,5-diazabicyclo[4.4.0]dec-5-enes

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Dedicated to the memory of Professor Harry H. Wasserman

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ABSTRACT

Hydrogenation (3 atm) of readily available pyrido[1,2-*a*]pyrimidines **10**, **14**, and **17** over 5% Rh/Al_2O_3 forms 1,5-diazabicyclo[4.4.0]dec-5-enes **9**, **15**, and **18** in >95% yield, providing a general route to this little-studied class of compounds. All attempts to form the tetrahydro-1,2,4-triazine moiety of cinachyramine (**1**) by rearrangement of amidinium dimethylhydrazone **8** using the procedures developed by Kamatori to convert hydrazone **3a** to tetrahydro-1,2,4-triazine **4a** were unsuccessful.

Introduction

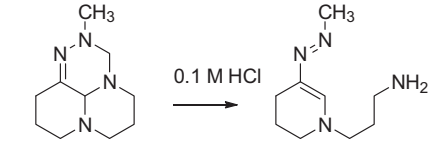
Cinachyramine (**1**), a novel alkaloid possessing a hydrazone and two aminals, was isolated in 2006 from the Okinawan sponge *Cinachyrella* sp. (see Scheme 1).[1] The structure was assigned by spectroscopic analysis and degradation under acidic conditions to afford azoalkene **2**. Cinachyramine trifluoroacetate showed weak cytotoxic activity against HeLa S_3 cells with an IC_{50} of 6.8 μg/mL. The structural novelty of cinachyramine and our continuing interest in amidine- and guanidine-containing natural products prompted us to attempt its synthesis.

Kamatori and co-workers reported an extensive series of studies on the rearrangements of the dimethylhydrazones of 1,1,1-trifluoro-2,3-diones such as **3a** (see Scheme 2).[2] Heating **3a** absorbed on silica gel with ammonium acetate (50 equiv) at 60 °C for 2 days afforded **4a** (36%) with the same tetrahydro-1,2,4-triazine ring as cinachyramine.[2c] The mechanism probably involves imine formation and protonation to give **5a**, which can also be drawn as the resonance structure **6a**. A 1,5-sigmatropic hydrogen shift will give iminium salt **7a**, which will cyclize to give **4a** after deprotonation.

We hoped that amidinium dimethylhydrazone **8** would undergo a similar 1,5-sigmatropic hydrogen shift followed by cyclization to give cinachyramine (**1**) (see Scheme 3). This route was particularly appealing because the conditions are mild enough for a similar sequence to occur in the biosynthesis of **1**. We expected that oxidation of the hydroxy group of **9** to a ketone and hydrazone formation would lead to **8**. We thought that hydroxy amidinium salt **9** should be available by partial hydrogenation of the readily available pyrido[1,2-*a*]pyrimidinium salt **10**.[3,4]

Results and discussion

Reaction of 2-amino-3-hydroxypyridine (**11**) with 1,1,3,3-tetraethoxypropane in 60% perchloric acid and ethanol at 80 °C by the literature procedure led to the formation of **10** which precipitated from solution and was isolated in pure form in 85% yield by filtration (see Scheme 4).[4] We were delighted to find that hydrogenation[5] of **10** under 3 atm of H_2 over 5% Rh/Al_2O_3 provided **9** as the



cinachyramine (**1**) **2**

Scheme 1. Structure and decomposition product of cinachyramine (**1**).

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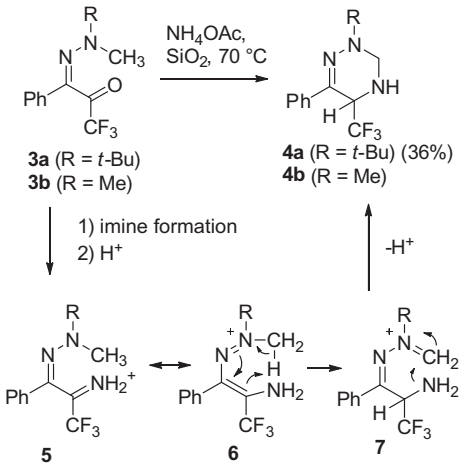
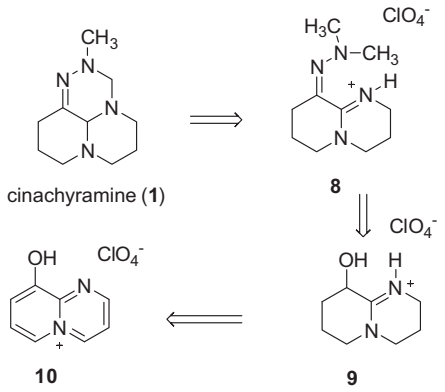
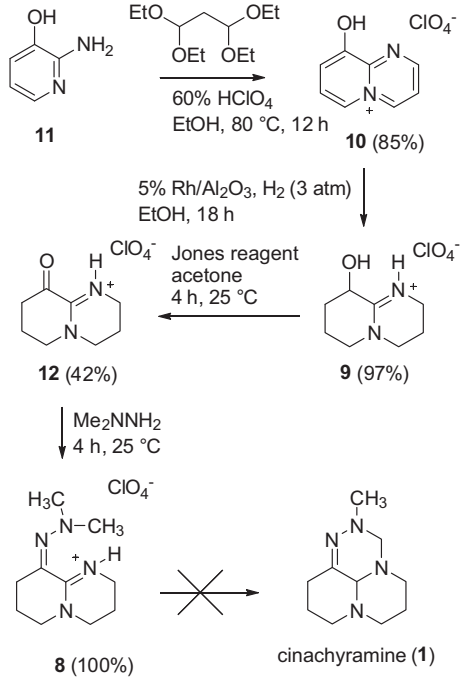


Scheme 2. Conversion of hydrazone **3** to tetrahydro-1,2,4-triazine **4**.



Scheme 3. Retrosynthesis of cinachyramine (**1**).



Scheme 4. Synthesis of amidinium hydrazone **8**.

perchlorate salt in 97% yield. Oxidation of the hydroxy group in **9** with Jones reagent gave oxo amidinium perchlorate salt **12** in 42% yield. Although the amidinium salt is quite stable, deprotonation with K_2CO_3 or NaOH led to partial hydrolysis of the unprotonated amidine. Consistent with this observation, the Swern oxidation and other neutral or basic oxidation procedures were unsuccessful. Therefore, Jones oxidation was the method of choice despite the moderate yield.

The structure of **12** was confirmed by X-ray crystal structure analysis (see Fig. 1), which also established that the perchlorate ion was tightly bound and did not exchange with the sulfate ion from the sulfuric acid in the Jones oxidation.[6] It should also be noted that oxo amidinium cation **12** appeared to slowly equilibrate with the hemiketal during prolonged storage in CD_3OD solution.[7]

Oxo amidinium perchlorate **12** was stirred in excess 1, 1-dimethylhydrazine for 4 h to afford hydrazone salt **8** in quantitative yield. With the key intermediate **8** in hand we began to investigate the 1,5-sigmatropic hydrogen shift and cyclization needed to complete the synthesis of cinachyramine (**1**). Unfortunately, no reaction occurred on heating **8** in the presence of silica gel with or without NH_4OAc in an oil bath or in a MW oven at 70–100 °C. No reaction occurred in TFA at 25 °C or on microwave heating with silica gel prior to decomposition at 250 °C.

To verify that we were carrying out the reaction properly, trifluoroacetyl hydrazone **3b** was prepared by the literature procedure.[2a,b] Heating **3b** with NH_4OAc in the presence of silica in the MW oven for 1 h cleanly afforded a 1.7:1 mixture of

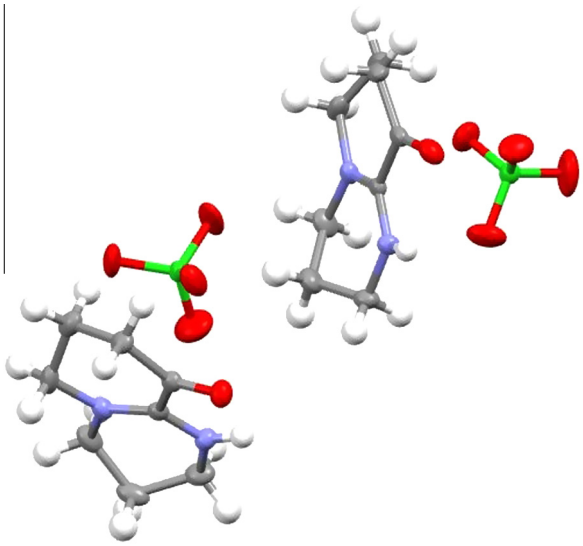


Figure 1. Crystal structure of oxo amidinium perchlorate **12**.

tetrahydro-1,2,4-triazine **4b** and the analogous tetrahydro oxadiazine resulting from a 1,5-sigmatropic hydrogen shift prior to imine formation. Therefore the facile 1,5-sigmatropic hydrogen shift that occurs with the trifluoromethyliminium dimethylhydrazone cation **5** does not occur under the same conditions with amidinium dimethylhydrazone **8**. Presumably the trifluoromethyliminium cation of **5** is much more acidic and therefore more reactive than the amidinium cation of **8**.

We briefly investigated other procedures for the conversion of **8** to cinachyramine (**1**). No reaction occurred on irradiation with 300 or 350 nm UV light in CD_3OD or D_2O. Treating **8** with a wide range of bases either gave recovered **8** or extensive decomposition without any evidence for the formation of cinachyramine (**1**).

Although this approach to cinachyramine was not successful, the hydrogenation of **10** provides a very simple and practical route