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Synthesis of 2,6-disubstituted-7,8-dihydro-6*H*-pyrano[2,3-6]pyrazines

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ABSTRACT

A straightforward synthesis of a 2,6-disubstituted-7,8-dihydro-6*H*-pyrano[2,3-6]pyrazine is described. The synthesis relies on a versatile dichloropyrazine–aldehyde intermediate and an olefination partner.

In our pursuit of superior agonists of the G-protein coupled receptor 119 (GPR119) we were interested in constrained analogs of compound **1** (Fig. 1).[1,2] To achieve this conformational goal while incorporating superior physicochemical properties (lower *C*log*P*), we envisioned the use of a dihydro-6*H*-pyrano[2,3-6]pyrazine ring system as exemplified by compound **2**.

While this ring system has precedent in the literature,[3,4] it is only sparsely described and no substitution is reported on the pyran ring. Herein we describe a more versatile synthesis wherein the ring system is rapidly assembled from dichloropyrazine using a formylation–Wittig-etherification sequence, allowing substitution at both ends of the molecule.

Key to our synthesis is the novel and versatile pyrazine-aldehyde **4** shown in Scheme 1. Formylation of 2,5-dichloropyrazine **3** was accomplished in a 21% yield in a fashion similar to the published work on 2-chloropyrazine[5] using commercially available 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex and 4-formylmorpholine.[6]

The Wittig partner for aldehyde **4** was prepared as shown in Scheme 2. Starting with the known acetyl piperidine **5**,[7] selective silylenol ether formation and reaction with bromine provided **6** in a good yield. The more straight-forward reaction of **5** with bromine in methanol provided only a 20% yield of the desired bromo acetate **6**. Generation of the Wittig reagent **7** was achieved by phosphonium salt formation followed by treatment with hydroxide. In principle, a β-ketophosphonate analogous to **7** could have been prepared from a *N*-Boc-piperidine-4-carboxylate as reported

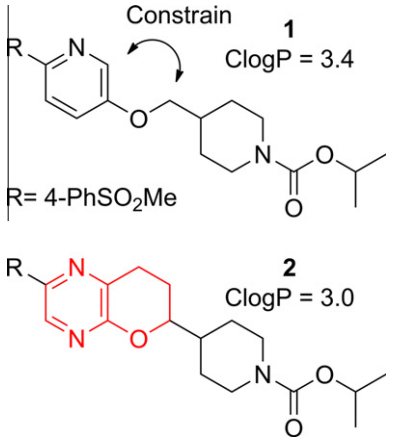
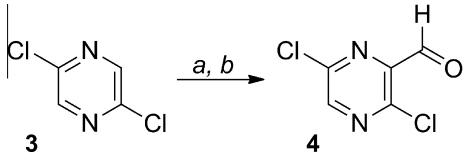


Figure 1. Pyridyl-ether versus dihydro-6*H*-pyrano[2,3-6]pyrazine.



Scheme 1. Synthesis of 3,6-dichloropyrazine-2-carbaldehyde. Reagents and conditions: (a) 2,2,6,6-tetramethylpiperidinylmagnesium chloride,·LiCl, THF/toluene, −78 °C, 1 h; (b) 4-formylmorpholine, −78 °C, 2 h (one pot, 21%).

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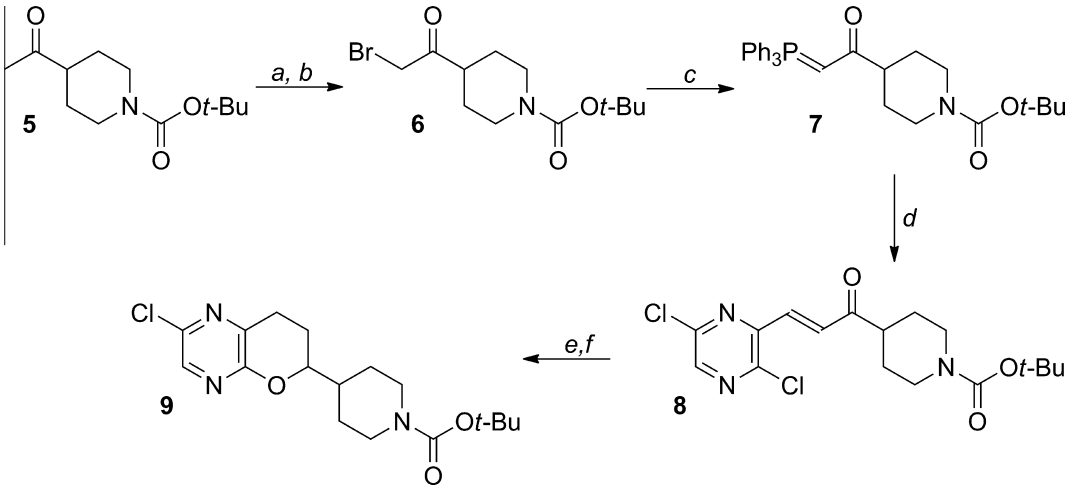
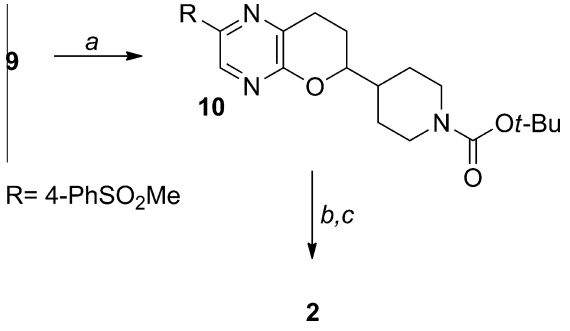


Scheme 2. Assembly of the dihydro-6*H*-pyrano[2,3-6]pyrazine ring system. Reagents and conditions: (a) $LiN(TMS)_2$, TMSCl, THF, −78 °C to 0 °C; (b) Br_2, −78 °C to 22 °C, 1 h (one pot, 88%); (c) Ph_3P, toluene, 22 °C, 16 h, then NaOH (77%); (d) **4**, CH_2Cl_2, 22 °C, 16 h (78%); (e) $NaBH_4$, EtOH, 22 °C, 3 h (96%); (f) NaH, THF, reflux, 4 h (30%).



Scheme 3. Synthesis of dihydro-6*H*-pyrano[2,3-6]pyrazine GPR119 analog. Reagents and conditions: (a) 4-(methanesulfonyl)phenylboronic acid, dioxane, water, $Pd(PPh_3)_4$, K_2CO_3, 100 °C, 3 h (90%); (b) (1:1) TFA/CH_2Cl_2, 22 °C, 1 h (100%); (c) isopropyl chloroformate, Et_3N, CH_2Cl_2, toluene, 22 °C, 2 h (46%).

by Maloney.[8] This alternative was not tried. Nevertheless, reaction of ylide **7** with aldehyde **4** smoothly provides the α,β-unsaturated derivative **8**. Reduction of **8** with three equivalents of sodium borohydride followed by ring closure provided **9** with the target core structure. It is worth noting that the borohydride reduction appears highly 1,4-selective as none of the olefin containing 1,2-reduction product was observed in the crude proton spectrum. The formation of the pyran ring in **9** proved more challenging. Deprotonation of the reduction product of **8** with sodium hydride and heating of the resulting alkoxide at reflux was required to induce the ring cyclization to give **9**.

From **9** the desired target was constructed as shown in Scheme 3. Suzuki coupling with commercial 4-(methanesulfonyl)phenylboronic acid and **9** in a sealed tube under an argon atmosphere provided **10** in a high yield. Trifluoroacetic acid removal of the Boc group and acylation with isopropyl chloroformate gave the desired comparator compound **11**. Unfortunately, **11** has only modest human GPR119 agonist pharmacology (63% response at 10 μM; $N = 3$) in our previously described recombinant cAMP functional assay.[9]

In summary, we have developed a straightforward approach to 2,6-disubstituted-7,8-dihydro-6*H*-pyrano[2,3-6]pyrazines. The synthesis relies on the versatile aldehyde intermediate **4** and an olefination partner, enabling variation at both ends of the ring system.

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