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Synthesis of chromanyl and dihydrobenzofuranyl piperazines

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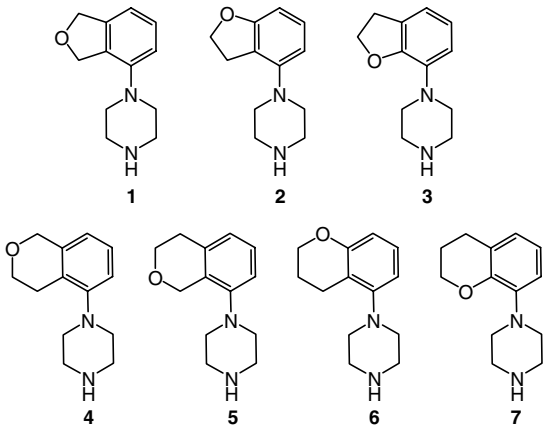
Abstract—The synthesis of a series of regioisomeric chromanyl and dihydrobenzofuranyl piperazines is described.

4-Arylpiperazines are considered 'privileged' templates in drug discovery.[1] This core structure is found in numerous biologically active compounds and drugs for a number of indications and mechanisms. Prominent among these are their activity against monoamine based GPCRs, namely, dopaminergic,[2] serotonergic,[3] and adrenergic[4] GPCRs. Subtle structural changes of the arylpiperazine moiety of a lead molecule are often desired in order to optimize the potency and selectivity against these receptors and modulate the physical and ADME (absorption, distribution, metabolism, and elimination) properties of the molecule. Often, these derivatives have similar structural characteristics (i.e., MW, *c*Log *P*, *c*Log *D*, polar surface area) but are prepared using very different starting materials. Herein we describe the synthesis of a series of regioisomeric chromanyl and dihydrobenzofuranyl piperazines, including 1-dihydroisobenzofuranyl- (**1**), 1-dihydrobenzofuranyl- (**2**), 1-isochromanyl- (**4** and **5**), and 1-chromanyl-piperazine (**6**). The synthesis of **3**[5,6] and **7**[5] have been disclosed previously.



The synthesis of previously unreported 1-(1,3-dihydro-isobenzofuran-4-yl)-piperazine (**1**) began with bromination of 1,2-dimethyl-3-nitro-benzene (**8**) as shown in Scheme 1. The resultant dibromide **9** was converted to isobenzofuran **10** by exposure to dry alumina and 1 equiv of water using a slightly modified procedure of Mirhara et al.[7] Our modification involved using toluene instead of the reported hexanes in order to be able to increase the reaction temperature to 120 °C resulting in a 90% yield of isobenzofuran **10**. Reduction of the nitro group afforded aniline **11** in quantitative yield. The piperazine was formed by reacting aniline **11** with bis-(2-chloro-ethyl)-amine in the presence of diisopropylethyl-amine in refluxing chlorobenzene to afford **1** in moderate yield.

The synthesis of 1-(2,3-dihydro-benzofuran-4-yl)-piperazine (**2**)[8] commenced with acylation of *m*-anisidine with Boc-anhydride to give **13** (Scheme 2). Directed lithiation of **13** with *tert*-butyl lithium followed by quenching with ethylene oxide at low temperature provided **14**.[9] Treatment of **14** with PPA at 125 °C resulted in cleavage of the methyl ether followed by cyclization to provide 4-amino-2,3-dihydrobenzofuran (**15**).[9] The piperazine was introduced in a similar fashion as described in Scheme 1 to give **2**.

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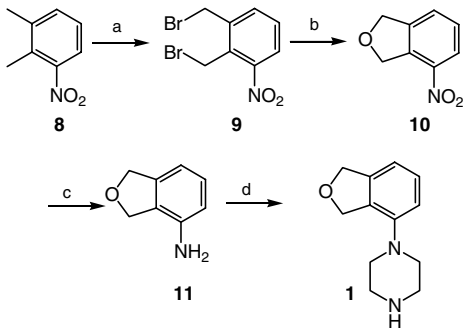
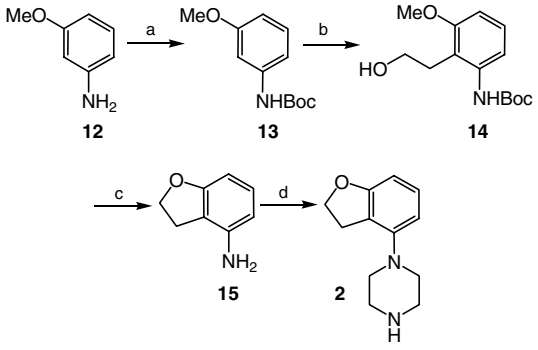
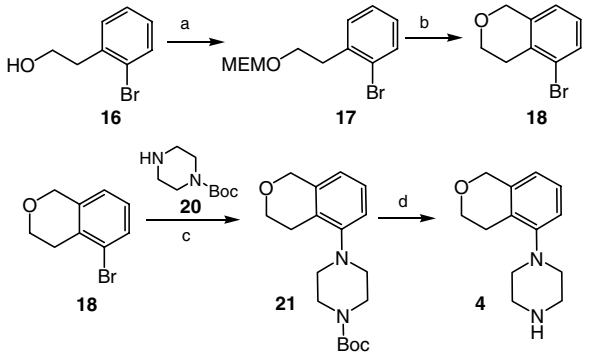


Scheme 1. Reagents and conditions: (a) NBS (2.1 equiv), benzoyl peroxide, CCl_4, 90%; (b) dry alumina, 1 equiv H_2O, toluene, 120 °C, 90%; (c) Raney Ni, H_2, THF, quant; (d) bis-(2-chloro-ethyl)amine hydrochloride, iPr$_2$EtN, PhCl, reflux, 54%.



Scheme 2. Reagents and conditions: (a) Boc_2O, dioxane, 35 °C, 3 d, 82%; (b) t-BuLi, ethylene oxide, Et_2O, −50 to 15 °C, 28%; (c) PPA, 125 °C; (d) bis-(2-chloro-ethyl)amine hydrochloride, iPr$_2$EtN, NaI, PhCl, cyclohexyl alcohol, 140 °C, 30% over two steps.

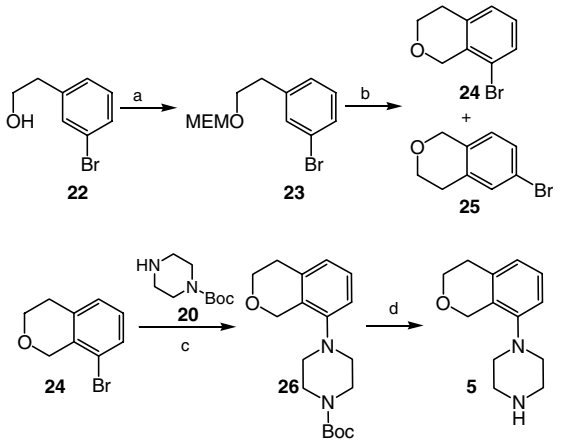
The synthesis of previously unreported 1-isochroman-5-yl-piperazine (**4**) is shown in Scheme 3. Key to the construction of **4** was the formation of the isochroman ring via an intramolecular oxonium cyclization. The precursor to the cyclization was formed by conversion of 2-(2-bromo-phenyl)-ethanol (**16**) to its corresponding (2-methoxyethoxy)methyl ether **17**. This was cyclized to form isochroman **18** by exposure to $TiCl_4$.[10] Aryl bromide **18** was coupled with *N*-Boc-piperazine (**20**) under Buchwald amination[11] conditions followed by *N*-Boc deprotection to afford 1-isochroman-5-yl-piperazine (**4**).



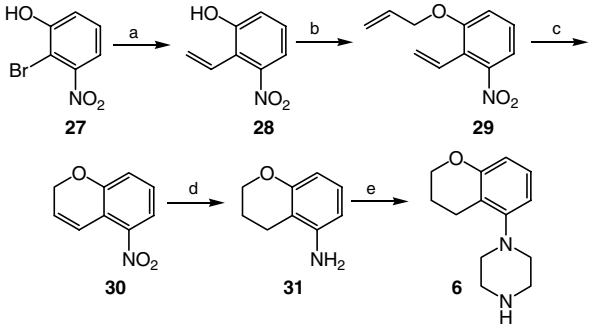
Scheme 3. Reagents and conditions: (a) MEMCl, Et_3N, CH_2Cl_2, 0 °C, 80%; (b) $TiCl_4$, CH_2Cl_2, 0 °C, 82%; (c) $Pd(OAc)_2$, NaOtBu, 2-(dicyclohexylphosphino)biphenyl, toluene, 80–90 °C, 60%; (d) TFA, CH_2Cl_2, 0 °C, quant.

In an analogous fashion to **4**, previously unreported 1-isochroman-8-yl-piperazine (**5**) was synthesized (Scheme 4). The key intermediate, 8-bromo-isochroman (**24**), was formed by the $TiCl_4$-promoted cyclization of 1-bromo-3-(2-((2-methoxyethoxy)methoxy)ethyl)benzene (**23**). Unlike in the isochroman-5-yl-piperazine (**4**) synthesis, the ring closure of the oxonium intermediate can occur to form two different regioisomers **24** and **25**. The regioselectivity of this cyclization was ~4:1 favoring the undesired bromo-isochroman **25** over the desired **24** which is presumably driven by sterics. Changes in temperature and Lewis acids had little effect on the regioselectivity. Fortunately, these isomers were separable via column chromatography. Aryl bromide **24** was converted to **5** via a two step sequence of Buchwald amination followed by removal of the *N*-Boc group.

The synthesis of 1-chroman-5-yl-piperazine (**6**)[12] involved a ring-closing metathesis strategy (Scheme 5).[13] Stille coupling of **27** with tributylvinyltin provided styrene **28**. Subsequent allylation of **28** with allyl bromide in the presence of K_2CO_3 afforded the requisite diene **29**. Ring-closing metathesis of **29** using Grubbs' second generation ruthenium catalyst proceeded smoothly to give the chromene **30**. The alkene and the nitro group



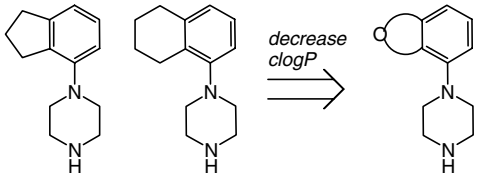
Scheme 4. Reagents and conditions: (a) MEMCl, Et_3N, CH_2Cl_2, 0 °C, 96%; (b) $TiCl_4$, CH_2Cl_2, 0 °C, 75% (1:3.4 ratio of isomers); (c) $Pd_2(dba)_3$, NaOtBu, BINAP, toluene, 110 °C, 81%; (d) TFA, CH_2Cl_2, 0 °C, 90%.



Scheme 5. Reagents and conditions: (a) $H_2C{=}CHSnBu_3$, 10 mol % $Pd(Ph_3P)_4$, toluene, reflux, 44%; (b) $H_2C{=}CHCH_2Br$, K_2CO_3, acetone, reflux, 81%; (c) 5 mol % 2nd generation Grubbs catalyst, CH_2Cl_2, 98%; (d) H_2, 10% Pd/C, MeOH, 100%; (e) bis-(2-chloro-ethyl)amine hydrochloride, iPr$_2$EtN, NaI, PhCl, cyclohexyl alcohol, 140 °C, 55%.

were both reduced via catalytic hydrogenation to give aminochroman **31**. Finally the piperazine was formed by reacting **31** with bis-(2-chloro-ethyl)-amine in the presence of diisopropylethylamine and sodium iodide in refluxing chlorobenzene with a small amount of cyclohexanol to afford **6** in moderate yield.

In summary, we have expanded the toolbox of 2,3-bicyclic arylpiperazines. In many cases, incorporation of these piperazines (**1**–**7**) into lead molecules resulted in an improved solubility and metabolic stability profile especially when compared with the corresponding indanyl- and tetrahydro-naphthalenyl-piperazines **32** and **33**. This is partially due to the reduced lipophilicity of **1**–**7** where incorporation of the oxygen atom lowers the clogP by approximately 1–2 log units.[14,15]



Acknowledgments

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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.2007.02.121.

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