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Stereoselective synthesis of enantiopure N-protected-3-arylpiperazines from keto-esters

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ABSTRACT

An efficient method for a stereoselective synthesis of optically pure *N*-Boc-3-arylpiperazines has been developed. After optimization of the protecting group strategy and experimental conditions, compounds were obtained via a highly stereoselective synthesis in up to 45% overall yield. This is a practical route to optically pure piperazines for medicinal chemistry.

The piperazine ring is present in many bioactive molecules and acts as a linker,[1] a pharmacophore,[2] or a modulator of pharmacokinetics.[3] Consequently, 2- or 3-substituted piperazines are interesting target compounds. In these structures, the residue on the carbon adjacent to one nitrogen atom alters the piperazine pK_a[4] and lipophilicity.[5] It can also protect the ring from N-dealkylation thanks to steric hindrance and from hydroxylation, which are both key metabolic pathways of N-substituted piperazines.[6]

In that context, a convenient and rapid synthesis of N-protected-substituted piperazine building-blocks is of high interest for medicinal chemists. Classical synthetic strategies to access racemic 2- or 3-substituted-piperazines include reduction of keto- or diketo-piperazines, alkylation and reduction of substituted pyrazines, lithiation, and alkylation of N-Boc piperazines, and multicomponent reactions.[7] We have recently published an efficient synthesis of N-benzyl-2-substituted piperazines via Ugi's reaction.[8] This methodology allowed the preparation of an array of racemic piperazines which expanded the availability of the protected piperazines found currently in commercial databases.

As 2- or 3-monosubstituted piperazines are chiral, their highly stereoselective synthesis is greatly desirable for medicinal chemists.

Recent examples of chiral 2- or 3-aryl substituted piperazine-based bioactive compounds were reported (Fig. 1).[9] Enantiopure 2- or 3-substituted piperazines may be prepared following non-stereoselective syntheses including an enantiomeric resolution requiring most of the time functionalization of both nitrogen atoms.[10] In addition, the resolution step is carried out quite often late in the synthesis. A dynamic kinetic resolution would increase the overall yield significantly.[11]

Other methods include first the synthesis of chiral 2-oxopiperazines.[12] As such, the preparation of enantio-enriched piperazines using an asymmetric hydrogenation of tetrahydropyrazines has been reported (up to 97% ee).[13]

Procedures via stereoselective opening of an optically pure epoxide (synthesized using a chiral auxiliary) or aminolysis of enantiomeric aziridines were also described.[14] An interesting method based on a stereoselective Grignard addition in the presence of (−)-sparteine constitutes one example of enantio-enriched piperazine preparation through a one-pot procedure starting from pyrazine *N*-oxide (20% yield, 83% ee).[15] At last, a recent method uses a three-step to access alkyl substituted piperazines proline as a catalyst (21–50% yield, 55–96% ee).[16]

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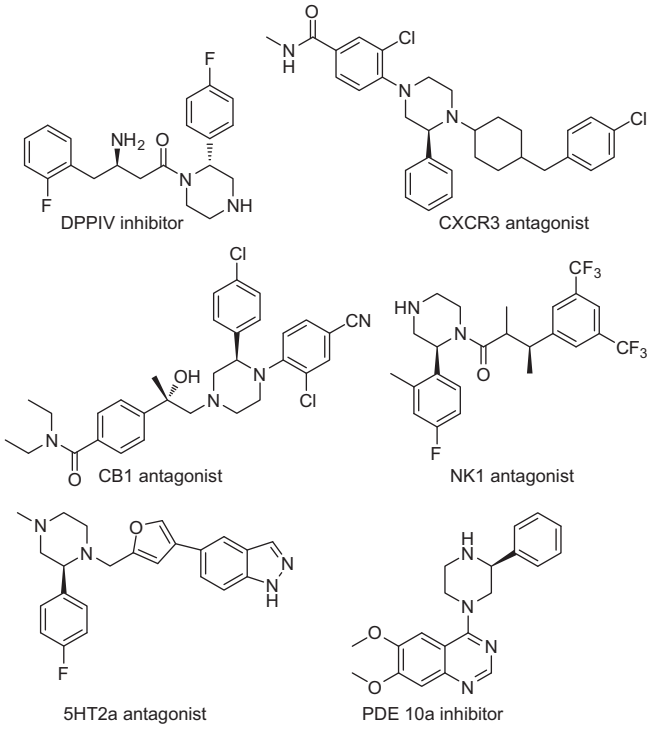
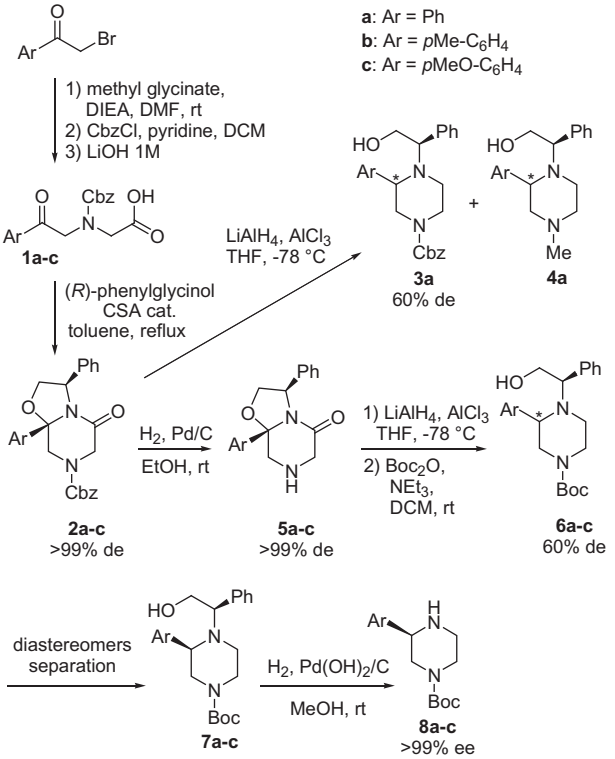


Figure 1. Examples of chiral bioactive compounds bearing 2- or 3-substituted piperazines.



Scheme 1. Route A: Synthesis of piperazines from carbobenzyloxy-protected keto-acids.

Following our ongoing interest in the use of chiral bicyclic lactams,[17] we sought to extend their use in the stereoselective synthesis of aryl-substituted piperazines.[18]

In this paper, we report a facile and rapid method to access ready-to-use *N*-protected substituted piperazines in good overall yields, high purity, and ee, starting from easily accessible keto-acid derivatives and the chiral auxiliary (*R*)-phenylglycinol (Fig. 2).

N-Cbz-3-aza-5-keto acids **1a–c** were obtained by alkylation of methyl glycinate with bromoacetophenones followed by protection using CbzCl and finally hydrolysis of the methyl esters.[19] Inspired by previous reports on the synthesis of chiral piperidines like anabasine,[20] we then prepared first the enantiopure bicyclic lactams **2a–c** by reaction of **1a–c** with (*R*)-phenylglycinol in toluene in the presence of camphorsulfonic acid (Scheme 1).[21] Under these conditions, the absolute configuration of the ring-junction carbons is well established.[22]

We next attempted a concomitant opening of the oxazoline ring and reduction of lactam **2a** with $LiAlH_4$ in the presence of $AlCl_3$.[17] Simultaneous reduction of lactams and reductive opening of oxazoline by $LiAlH_4$ is known to be highly stereoselective in the case of pyrrolidines.[22] In the case of piperazines however, we show here that the procedure leads to the desired compound **3a** in 50% yield but as a diastereomeric mixture (80/20) due to some partial inversion of configuration. In addition, a reduction of the carbamate was inevitable and provided compound **4a** in 50% yield.

To avoid the undesired reduction of the carbamate, we removed first the Cbz group from **2a–c** via hydrogenolysis in the presence of Pd/C, to obtain compounds **5a–c** in 70–92% yields. Then, treatment with $LiAlH_4/AlCl_3$ gave the desired 2-phenyl-(piperazin-1-yl)-ethanol) intermediates as a mixture of diastereomers in 80/20 ratio.

These intermediates were reacted with Boc_2O providing derivatives **6a–c** with preservation of the diastereomeric ratio. After separation of diastereomers by column chromatography, (**7a–c**) and subsequent hydrogenolysis of using Pearlman's catalyst ($Pd(OH)_2/C$), the desired piperazines **8a–c** were obtained (Scheme 1). The *p*Me- and *p*MeO- substituted phenyl derivatives were obtained in similar yields (24–32% from the corresponding bromoacetophenones). Thus, piperazines **8** were obtained in five steps from Cbz-protected keto-esters following route A.

Though the desired compounds were obtained, we thought that several aspects of the process should be changed to increase the value of this methodology. First, diastereoisomeric excess should be improved. Second, the number of steps could be reduced. Third, manipulation of the protecting groups should be simplified.

The lactamization can be carried out with keto-esters as well as with acids. As esters are intermediates in the synthesis of **1a–c**, we decided to spare the ester hydrolysis step. The protecting groups on keto-aminoacid precursors are required for the lactamization step avoiding thus by-products formation implying the secondary amine. As described above, in the case of use of Cbz, a deprotection step is required to prevent the reduction of the carbamate in the presence of $LiAlH_4$ into an undesirable *N*-methyl piperazine derivative. To avoid manipulation of protecting groups, carbamates were

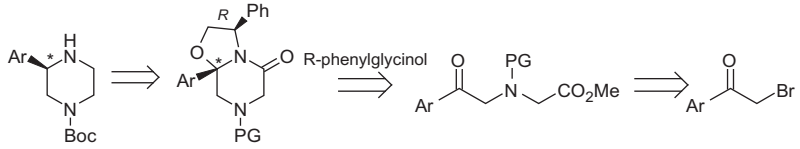


Figure 2. Retrosynthetic analysis.