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An orthogonal protection strategy for the synthesis of 2-substituted piperazines

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Abstract—Tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones are readily prepared from the bis-carbamate protected piperazine-2-carboxylic acids and serve as orthogonally protected piperazines from which a variety of 2-substituted piperazines can be prepared. Sodium benzylate and sodium phenoxides react at the C-5 carbon of the oxazolidinone to yield 2-(benzyloxymethyl)piperazines and 2-(phenoxymethyl)piperazines, respectively. The tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones also provide convenient scaffolds from which 2-benzyl- and 2-phenethylpiperazines are prepared.

1. Introduction

The piperazine ring is found in a number of biologically active compounds, including several marketed drugs,[1] and is considered to be a privileged structure in drug discovery.[2] For an exploratory medicinal chemistry program, we were interested in preparing a diverse set of trisubstituted piperazines, **4**, and required a suitably flexible synthetic route to allow for the introduction of a variety of linkers, X, and aryl groups. An orthogonal protection strategy for the two piperazine nitrogens would also be necessary to facilitate the selective introduction of the R_1 and R_2 groups.

2-Substituted piperazines are commonly prepared by ring construction and reduction of diketopiperazines[3,4] or 2-ketopiperazines,[5] via alkylation and reduction of 2-methylpyrazines,[6] or by α-lithiation and alkylation of *N*-Boc piperazines.[7] In many of these cases, the piperazine derivatives must then be selectively protected prior to further modification. Whereas most of these methods lock in the 2-substituent at an early stage in the synthesis, we were interested in introducing the substituent at a later stage in order to maximize synthetic efficiency. A second strategy involves the elaboration of 2-substituted piperazine derivatives such as piperazin-2-ylmethanol.[8] As this route offered the greatest flexibility for introducing a wide array of linkers and aryl substituents at a later stage in the synthesis, the orthogonally protected 2-(hydroxymethyl)piperazine **3** was initially chosen as a common intermediate from which compounds **4** would be prepared (Scheme 1). Compound **3** is prepared by reduction of the orthogonally protected piperazine-2-carboxylic acid **2**. This, in turn, is readily prepared from piperazine-2-carboxylic acid, which can be selectively Boc-protected at the 4-position, followed by Cbz-protection at the 1-position.[9,1b] The 4-Cbz-1-Boc-protected piperazine-2-carboxylic acid can be prepared in a similar fashion although in somewhat lower yield due to the reduced steric bulk of the Cbz protecting group and resulting formation of the bis-Cbz compound.[10,11]

In our initial attempt at preparing 2-(aryloxymethyl)piperazines via a Mitsunobu reaction between compound **3** and an aryl alcohol, the tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one **5a** was isolated as a major side product. We have since demonstrated that compounds **5** can themselves serve as orthogonally protected piperazine intermediates for the synthesis of a variety of 2-substituted piperazines. As described below, this strategy has the advantage of not requiring selective protection of the piperazine starting material since compounds **5** are prepared from the di-Boc or di-Cbz-protected piperazine-2-carboxylic acids.

2. Results and discussion

Tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones **5a** and **5b** were prepared in three steps as outlined in Scheme 2. Compounds **6**[12] and **7**[13] were readily prepared in identical 96% yields from piperazine-2-carboxylic acid using 2 equiv of di-*tert*-butyldicarbonate and benzyl chloroformate, respectively. The carboxylic acids were reduced to the

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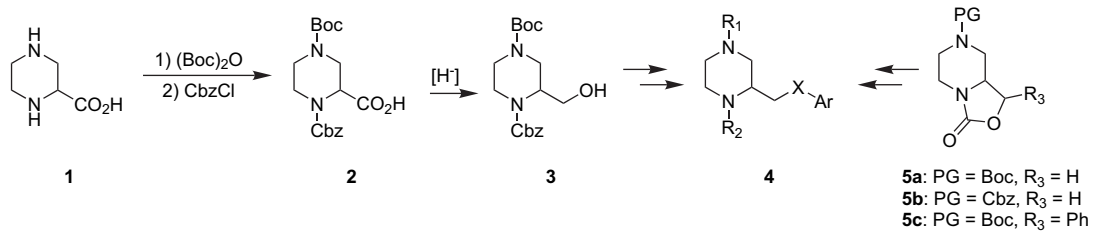
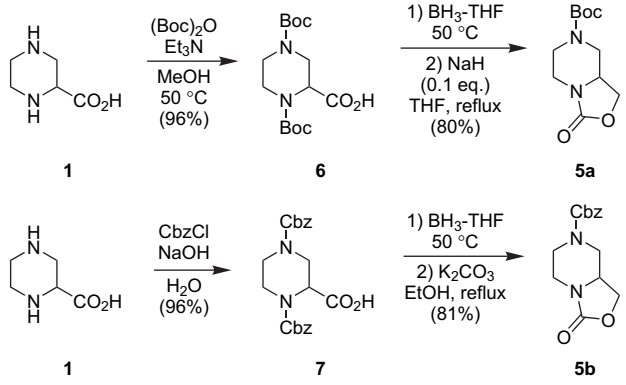


Scheme 1.

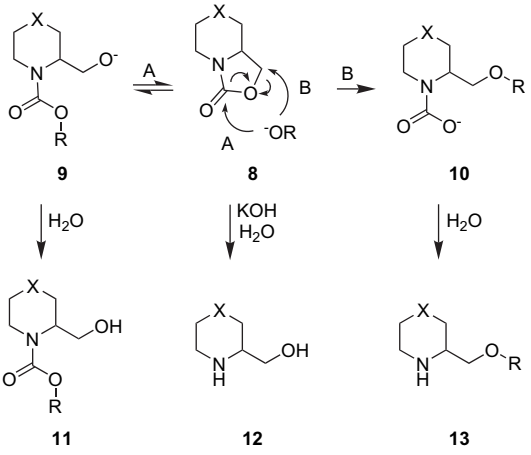
alcohols with borane–THF complex, and the compounds were cyclized to give **5a** and **5b** under basic conditions. The Cbz-protected compound cyclized more easily, requiring only potassium carbonate in refluxing ethanol.[14] The Boc-protected compound was more efficiently prepared by alkoxide formation with catalytic sodium hydride in refluxing THF. Compound **5a** was purified by recrystallization in 80% yield. While compound **5b** was also a crystalline solid, the presence of benzyl alcohol in the crude reaction mixture complicated recrystallization, and the compound was isolated in 81% yield following column chromatography. Both enantiomers of piperazine-2-carboxylic acid are commercially available, and we have applied these routes to the synthesis of both enantiomers of **5a** and **5b**.



Scheme 2.

2.1. 2-(Benzyloxymethyl)piperazines and 2-(phenoxymethyl)piperazines

Bicyclic oxazolidinones have been shown to react with alkoxides[15] at the carbonyl carbon (Scheme 3, pathway A) to provide the corresponding *N*-carbamoyl-2-(hydroxymethyl)pyrrolidines **11** (X=bond) or with aqueous hydroxide[16] to yield the corresponding 2-(hydroxymethyl)heterocycles **12** (X=bond, CH_2, NR). There have also been reports of alkoxide ring opening of monocyclic oxazolidinones on the C-5 carbon to form 2-alkoxy-1-aminoethane derivatives (pathway B).[17] While there have been no reports of this type of reaction with aryloxides,[18,19] and no examples with tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones, we were intrigued by the possibility of preparing 2-(aryloxymethyl)-piperazines from **5** by oxazolidinone ring opening via pathway B. Alkoxides were expected to react preferentially via pathway A, establishing an equilibrium between the carbamate **9** and the oxazolidinone **8**. If the alkoxide did react via pathway B, compound **10** would be formed in an irreversible process, driving the reaction toward **13** upon decarboxylation. The ratio of **11** and **13** formed would likely depend on the reaction conditions. In the case of an aryloxide, however, pathway A would not be favorable since the aryloxide is a much better leaving group than the alkoxide of compound **9**. This would leave pathway B as the only productive reaction pathway.



Scheme 3.

In order to explore the differences in reactivity between alkoxides and aryloxides, compound **5a** was reacted with benzyl alcohol or phenol under several conditions (Table 1). Haddad et al reported the reaction of lithium benzylate with a tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivative to proceed via pathway A to provide the corresponding Cbz-protected 2-(hydroxymethyl)pyrrolidine.[15b] Under these conditions, only a trace of compound **3** was observed with lithium benzylate and none of the 2-(benzyloxymethyl)-piperazine **14a** (entry 1) was observed. By increasing to 3 equiv of the alkoxide, compound **3** was isolated in 9% yield while compound **14a** was formed in 8% yield. In both examples, the remainder of the material was the unreacted **5a**. With sodium benzylate, however, only reaction products formed via pathway B were observed, with **14a** isolated in 10% yield and **15a** isolated in 27% yield, arising from reaction of excess sodium benzylate with the Boc group (entry 3). With DMF as solvent, somewhat better yields of 22% and 52% were observed for **14a** and **15a**, respectively. This counterion dependent difference in reactivity may allow for tuning of reactivity between pathways A and B. The less nucleophilic sodium phenoxide gave only an 8% yield of the 2-(phenoxymethyl)piperazine **14b** at 70 °C in THF (entry 5). As expected, neither the compound arising from pathway A nor the exchange of the