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Complete Regioselective Addition of Grignard Reagents to Pyrazine *N*-Oxides, Toward an Efficient Enantioselective Synthesis of Substituted Piperazines

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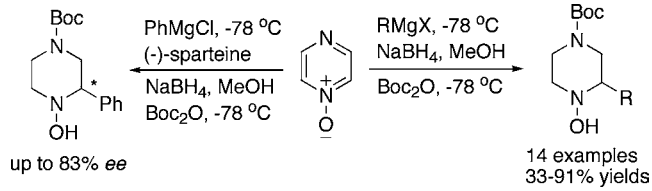
ABSTRACT



A conceptually new one-pot strategy for the synthesis of protected substituted piperazines via the addition of Grignard reagents to pyrazine *N*-oxides is presented. This strategy is high yielding (33−91% over three steps), step-efficient, and fast. The synthesized *N*,*N*-diprotected piperazines are convenient to handle and allow for orthogonal deprotection at either nitrogen for selective transformations. In addition, this is a synthetic route to enantiomerically enriched piperazines by using a combination of phenyl magnesium chloride and (−)-sparteine, which resulted in enantiomeric excesses up to 83%.

Organometallic additions to activated pyrazines have received little or no attention, whereas the analogous reactions for pyridines are expedient methods for the synthesis of substituted pyridines[1] and piperidines.[2] For the synthesis of substituted piperazines, this is especially surprising, as organometallic additions to activated pyrazines potentially constitute an efficient route to this class of privileged structures.[3] In a recent survey it was shown that piperazines are among the most frequently occurring structural motifs in drugs; in fact, more than 60 of the analyzed orally administrated drugs contained a piperazine fragment.[4] Typically, piperazines are currently obtained by hydrogenation of substituted pyrazines[5] or via various cyclocondensation

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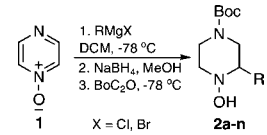
reactions.[6] However, although hydrogenation is an efficient strategy, it has limitations in terms of starting materials because it requires the corresponding substituted pyrazines to be available. The catalyst required can also be costly, and the potential presence of catalyst traces in the product may complicate its use in late stages of pharmaceutical synthesis. Furthermore, asymmetric hydrogenation has only been reported for pyrazine carboxylic acid derivates, with an ee up to 78%.[7] The synthesis of piperazines via cyclocondensation reactions often requires multistep synthesis, and the structural diversity is limited depending on the access of commercially available starting materials. In 2009, Guercio et al. reported on an excellent scalable route to a chirally pure arylpiperazine based on a dynamic kinetic resolution. This key fragment, used in the synthesis of the NK1 antagonist GW597599, was synthesized after significant optimization in an overall yield of 60% over nine steps.[8]

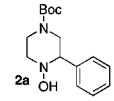
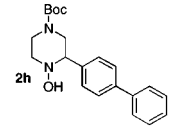
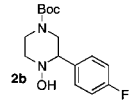
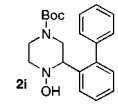
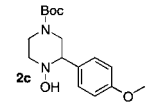
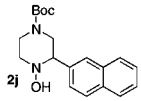
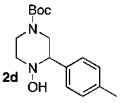
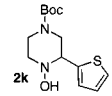
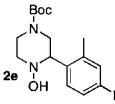
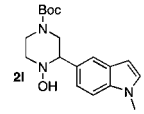
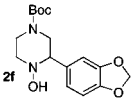
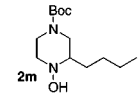
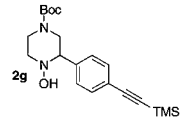
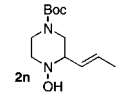
Herein, we report a conceptually new synthesis of substituted piperazines via the reaction between Grignard reagents and activated pyrazines (i.e., pyrazine *N*-oxides (**1**)) followed by a reduction. After *N*-Boc protection, the corresponding *N*,*N*-diprotected substituted piperazines formed are easy to handle and can be orthogonally deprotected giving the opportunity of synthetic modifications on either nitrogen. This synthetic sequence is performed in one pot with only a purification of the final product. Finally we show that in the presence of (−)-sparteine this reaction offers an enantioselective synthesis to substituted piperazines.

The reaction was explored in studies using pyrazine *N*-oxide (**1**) and phenylmagnesium chloride, which indicated that addition of pyrazine *N*-oxide to Grignard reagents at −78 °C in dichloromethane followed by reduction with $NaBH_4$ and protection with di-*tert*-butyl dicarbonate anhydride gave the best results. The *N*-Boc protected *N*-hydroxyl piperazine **2a** was isolated in an excellent 91% yield, considering that it is a three-step, one-pot synthesis. Several Grignard reagents were reacted with pyrazine *N*-oxide (**1**) to give substituted piperazines (**2**) in good to high yields (Table 1).

The addition of 4-biphenylmagnesium chloride gave **2h** in 67% yield, whereas the sterically more demanding 2-biphenylmagnesium chloride yielded the corresponding piperazine **2i** in 33% yield (entries 8 and 9, Table 1). Notably, the steric exerted by an *ortho*-methyl is well tolerated, and **2e** was isolated in 72% yield (entry 5, Table 1). A TMS substituent was also compatible with the method, and the 4-((TMS)ethynyl)phenyl Grignard reagent yielded piperazine **2g** in 53% yield (entry 7, Table 1). The heteroaromatic thienyl and indole Grignard reagents resulted in 52% and 55% isolated yields, respectively (entries 11 and 12). Last

Table 1. One-Pot Synthesis of Substituted Piperazines[c]



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1		91[b]	8		67
2		83	9		33
3		81	10		76
4		74	11		55
5		72	12		52
6		87	13		40
7		53	14		54

[a] Yields of isolated products. [b] Also performed in gram-scale resulting in piperazine **2a** in a isolated yield of 76%. [c] Reaction conditions: *N*-oxide (1 equiv) in CH_2Cl_2, Grignard reagent (2.5 equiv), $NaBH_4$ (1.1 equiv) in 2 mL of MeOH, Boc_2O (3.0 equiv).

year (2008), we reported the *ortho*-metalation of pyridine *N*-oxides using alkylmagnesium halides.[9] However, when analogously reacting pyrazine *N*-oxide with *n*-butylmagnesium chloride we did not observe the expected formation of an *ortho*-metalated derivative after trapping experiments. Instead, the corresponding *n*-butyl-substituted piperazine **2m** was isolated after reduction and *N*-Boc protection in 40% yield (Table 1, entry 13). Finally, the reactivity of the propenyl Grignard reagent was studied, yielding piperazine **2n** in 54% isolated yield over three steps (entry 14, Table 1).

The incorporation of piperazine fragments in pharmaceuticals often requires selective synthetic modifications at either nitrogen; therefore an orthogonal deprotection of the *N*-Boc *N*-hydroxyl piperazine **2a** was developed. Zinc dust in MeOH and acetic acid selectively removed the *N*-hydroxyl group,

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(6) (a) Nordstrom, L. U.; Madsen, R. *Chem. Commun.* **2007**, 5034–5036. (b) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Chem.Commun.* **2003**, 2286–2287.

(7) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

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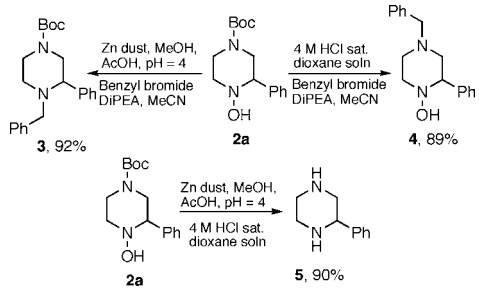
and a subsequent alkylation yielded piperazine **3** in 92% yield (Scheme 1). Furthermore, a selective *N*-Boc deprotection was

Scheme 1. Deprotection of Piperazine **2a**



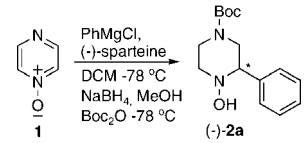
accomplished by using a 4 M HCl saturated dioxane solution, and piperazine **4** was isolated in 89% yield after the reaction with benzyl bromide. Deprotection of both nitrogens gave piperazine **5** in 90% yield (Scheme 1).

Inspired by Fu and co-worker's use of Grignard reagents in combination with (−)-sparteine,[10] pyrazine *N*-oxide was added to phenylmagnesium chloride in the presence of (−)-sparteine, which gave a promising ee of 62%. However, the isolated yield was not satisfactory, mainly due to unconsumed starting material. Increasing the equivalents of Grignard reagents and (−)-sparteine resulted in a decrease in % ee (entry 3, Table 2). Fortunately, decreasing the equivalents of PhMgCl and (−)-sparteine to 1.2 equiv with 1 equiv of pyrazine *N*-oxide substantially increased enantioselectivity, and (−)-**2a** was obtained in a high 83% ee (entries 3−5, Table 2). Prolongation of the reaction time, up to 22 h, gave no improvement in yield, and the % ee remained more or less unchanged. Whereas the use of toluene as solvent gave similar results compared with CH_2Cl_2, THF or 2-Me THF gave racemic mixtures.

In summary, we have described a conceptually new one-pot strategy for the synthesis of protected substituted piperazines. This strategy is high yielding, step-efficient, and

(10) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057–1059.

Table 2. Enantioselective Synthesis of Substituted Piperazine[a]



entry	Grignard/sparteiene	solvent	time (h)	ee	yield (%)[b]
1	3/3	DCM	2.5	62	26
2	4/4	DCM	2.5	41	18
3	1.5/1.5	DCM	16.0	78	28
4	1.2/1.2	DCM	2.5	82	21
5	1.2/1.2	DCM	22.0	83	18
6	1.5/1.5	toluene	2.5	75	24

[a] See Supporting Information (SI) for details, including reaction and HPLC conditions. [b] Yields of isolated products.

fast. We included an *N*-Boc protection step solely to allow convenient handling of the products, but it also provides options for further transformations on either nitrogen. In addition, we have shown that this is a synthetic route to enantiomerically enriched piperazines. Although the yields are not yet optimal, this methodology holds potential, especially since few methods are currently available for the synthesis of enantiomerically pure piperazines.

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Note Added after ASAP Publication. The toc/abstract graphic was incorrect in the version published ASAP December 11, 2009; the correct version published ASAP December 15, 2009.

Supporting Information Available: Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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