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Practical and scalable synthesis of orthogonally protected-2-substituted chiral piperazines†

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A synthetic route to orthogonally protected, enantiomerically pure 2-substituted piperazines is described. Starting from α-amino acids, within four steps chiral 2-substituted piperazines are obtained. The key transformation involves an aza-Michael addition between an orthogonally bis-protected chiral 1,2-diamine and the *in situ* generated vinyl diphenyl sulfonium salt derived from 2-bromoethyl-diphenylsulfonium triflate. Further validation using different protecting groups as well as synthesis on multigram scale was performed. The method was also applied to the construction of chiral 1,4-diazepanes and 1,4-diazocanes. Additionally, the method was utilized in a formal synthesis of chiral mirtazapine.

Despite their popularity, piperazine compounds are mostly confined to substitutions on both nitrogen atoms, indicating there is an abundance of unexplored chemical space related to this heterocycle.[1–7] For example, 2-substituted piperazine compounds, which would display more 3-dimensional complexity, are much less pursued. However, 2-substituted analogs are contained in a limited number of marketed drugs and various biological probes suggesting their relavance.[8–12] Only a few methods are known for the synthesis of chiral 2-substituted piperazines. Most commonly, chiral 2-substituted piperazines are prepared from mono or di-keto piperazines since they can readily be prepared from α-amino acids.[8,10,11,13–16] These methods suffer from the inability to differentially protect the nitrogen atoms which precludes the ability to substitute them with regiocontrol. The synthesis of 2-substituted piperazines has also been achieved from *N*-Boc protected piperazines through lithiation followed by electrophilic trapping; however, controlling the absolute stereochemical configuration is complicated.[15,17,18] Several other reports are known from aziridine intermediates,[19] multicomponent Ugi reactions[20,21] and some late stage S_N2 ring closure reactions.[22,23] Recently SnAP (stannyl amine protocol) and SLAP (silicon amine protocol) reagents have been used to construct piperazines and other heterocycles.[24,25] Most of these reports for the synthesis of 2-substituted piperazines involve multi-step processes and again suffer from the lack of regiochemical control of nitrogen substitution.

Given the prominence of the piperazine motif in biologically active compounds, our laboratories have aimed at expanding their stereochemical diversity.[26–30] We reasoned that building libraries of novel chiral piperazine compounds could lead to a variety of previously unknown drug-like small molecules. Here we focus on developing orthogonally protected, enantiomerically pure 2-substituted piperazines that can be synthesized efficiently, affordably and on multigram scale to serve as building blocks for library development.

We initiated our efforts to find a synthetic route to enantiopure 2-substituted piperazines with several considerations in mind. Ideally, the route would be short, practical, scalable, low cost and use readily available starting materials. We were intrigued by a method developed by Aggarwal and coworkers, an annulation reaction between appropriately substituted diamines and bromoethyldiphenylsulfonium triflate.[31–37] However, the protecting group strategies employed in these previous studies would not readily suit our goal for their facile removal and functionalization in a regioselective manner.

We previously reported the synthesis of orthogonally protected chiral 1,2-diamines on multigram scale (~50 g) in two steps from commercially available amino acids.[26] Using the Aggarwal conditions, we thought that such precursors would be ideal for producing the orthogonally substituted chiral piperazines that we desired. We used the reported conditions

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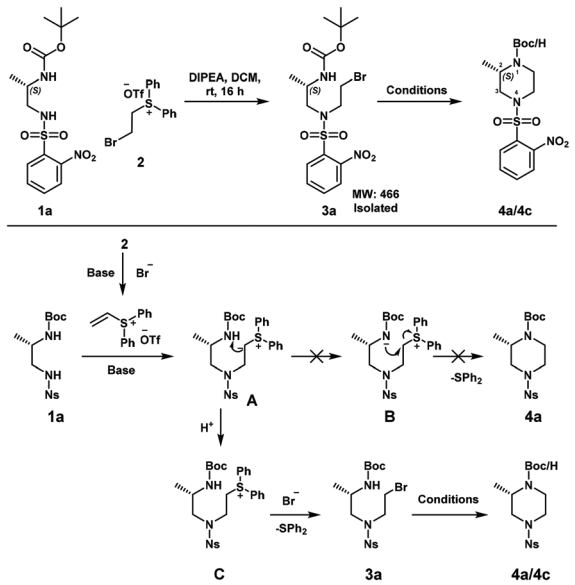
for generating the desired product from such protected 1,2-diamines. Unfortunately, to our surprise the expected products were not generated. Varying the solvent (DCM, MeCN, DMF, THF), base (DIPEA, NaH, DBU, Cs_2CO_3) and temperature (rt to 60 °C) were unproductive. We also substituted bromoethyldiphenylsulfonium triflate with the commercially available vinyl diphenyl sulfonium salt (preformed Michael acceptor). In our hands, this did not result in the desired product (for details see ESI†); however, in most cases, we did observe the consumption of the starting material and the formation of the initial Michael adduct (Scheme 1, intermediate **A**) by LCMS. Over time, this intermediate was either converted into a complex mixture or into a product that was +81 higher mass units (467 *m*/*z*) than the expected product. To confirm the identity of this compound we acquired the proton and carbon 1D and 2D NMR spectra. Interestingly, an additional proton in the ^{1}H NMR spectrum was found compared to the expected product. HSQC NMR indicated that the additional proton was bound to a heteroatom (by HSQC). This suggested the presence of a carbamate –NH proton, which was confirmed based on coupling with the chiral center proton (confirmed by COSY and HSQC). We therefore concluded that under the reaction conditions attempted, the cyclization step was not occurring. Furthermore, the HRMS data showed masses of 466.0645 and 468.0623 in a 1 : 1 isotopic abundance demonstrating that the compound contained a bromine atom. Taken altogether, we assigned the structure of the isolated product as the uncyclized bromide **3a** (Scheme 1).

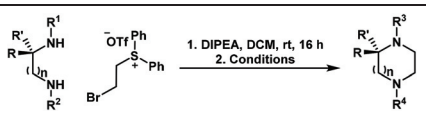
Mechanistically (Scheme 1), we surmise that after the Michael reaction, the carbamate proton is not abstracted by the carbanion intramolecularly leading to intermediate **B** possibly due to steric hinderance. Instead, the anion is simply quenched intermolecularly by a protic source (DIPEA-H) in the reaction medium to yield **C**. The bromide counter ion produced in the elimination of the bromoethyldiphenylsulfonium triflate displaces the diphenylsulfonium ion to provide **3a**. Based on this realization, the isolated bromide product was then treated with TFA to remove the *N*-Boc protecting group and, on basic workup, cyclization ensued to deliver the desired 2-substituted piperazine which was confirmed by detailed NMR studies and HRMS. Alternatively, on treatment with NaH the bromide compound cyclized to give the piperazine with the *N*-Boc group intact providing evidence that the initial anion is quenched before cyclization.

After structural confirmation of the isolated product, we tested this two-step reaction sequence on various substrates containing different protecting group combinations, including –Boc, –Cbz, 2-Ns and 4-Ns (Table 2). Additionally, we tested 1,3- and 1,4-diamines to construct higher membered rings (1,4-diazepanes and 1,4-diazocanes). The use of DIPEA as a base led to the best results compared to other bases. We started with 1,2-diamine substrates containing a –Boc protecting group on N1 and sulfonamide (2-Ns or 4-Ns) on N4 (Table 2, entries 1–9).[26] In all cases we isolated the bromide intermediates (**3a–h**) in good yields, including a substrate with disubstitution at the 2-position indicating that quaternary centers are tolerated in the reaction (**3h**). Cyclization of these bromide intermediates to the desired piperazines was effected



Scheme 1 Synthesis of 2-substituted piperazines.

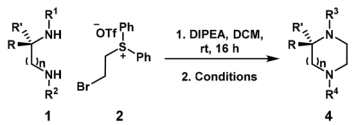
Table 1 Synthesis of 2-substituted piperazines, 1,4-diazepanes (*n* = 2) and 1,4-diazocanes (*n* = 3)



Method	*n*	R^1 and R^2	R^3 and R^4	Conditions	Yield[a] (%)
A	1	–Boc, –Ns	–Boc, –Ns	NaH, THF	75–79
B	1	–Boc, –Ns	–H, –Ns	TFA, DCM, basic workup	65–82
B	1	–Ns, –Boc	–Ns, –H	TFA, DCM, basic workup	60–79
C	1	–Cbz, –Ns	–H, –Ns	TMSOTf, TBAI, DCM, basic workup	74
D	2 or 3	–Boc, –Ns	–H, –Ns	1. TFA, DCM; 2. K_2CO_3, THF	36–47

Ns = 2-nitrobenzenesulfonyl or 4-nitrobenzenesulfonyl. [a] Overall yield.

Table 2 Synthesized 2-substituted piperazines, 1,4-diazepanes and 1,4-diazocanes from appropriately protected diamines



1 2 4

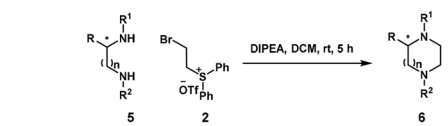
S. no	R and R′	*n*	R^1 and R^2	Conditions (method)	R^3 and R^4	**3a–u**; **4a–u** Yield (%)
1	–H, $–CH_3$ (**1a**)	1	–Boc, 2-Ns	A	–Boc, 2-Ns	**3a**, 91; **4a**, 87
2	$–CH_3$, –H (**1b**)	1	–Boc, 4-Ns	A	–Boc, 4-Ns	**3b**, 87; **4b**, 87
3	–H, $–CH_3$ (**1a**)	1	–Boc, 2-Ns	B	–H, 2-Ns	**3a**, 91; **4c**, 89
4	$–CH_3$, –H (**1d**)	1	–Boc, 2-Ns	B	–H, 2-Ns	**3d**, 90; **4d**, 80
5	–H, $–CH_3$ (**1e**)[a]	1	–Boc, 2-Ns	B	–H, 2-Ns	**3e**, 85; **4e**, 77
6	$–^iBu$, –H (**1f**)	1	–Boc, 2-Ns	B	–H, 2-Ns	**3f**, 86; **4f**, 85
7	$–CH_2OBn$, –H (**1g**)	1	–Boc, 2-Ns	B	–H, 2-Ns	**3g**, 89; **4g**, 93
8	$–CH_3$, $–CH_3$ (**1h**)	1	–Boc, 2-Ns	A	–Boc, 2-Ns	**3h**, 91; **4h**, 89
9	$–CH_3$, $–CH_3$ (**1h**)	1	–Boc, 2-Ns	B	–H, 2-Ns	**3h**, 91; **4j**, 91
10	–H, –Bn (**1k**)	1	–Cbz, 4-Ns	C	–H, 4-Ns	**3k**, 78; **4k**, 95
11	–H, $–CH_3$ (**1m**)	1	2-Ns, –Boc	B	2-Ns, –H	**3m**, 80; **4m**, 97
12	–H, $–^iBu$ (**1n**)	1	2-Ns, –Boc	B	2-Ns, –H	**3n**, 85; **4n**, 93
13	$–^iBu$, –H (**1o**)	1	2-Ns, –Boc	B	2-Ns, –H	**3o**, 70; **4o**, 86
14	–Bn, –H (**1p**)	1	2-Ns, –Boc	B	2-Ns, –H	**3p**, 83; **4p**, 78
15	–H, $–CH_2OBn$ (**1q**)	1	2-Ns, –Boc	B	2-Ns, –H	**3q**,78; **4q**, 93
16	–Ph, –H (**1r**)	1	2-Ns, –Boc	B	2-Ns, –H	**3r**, 80; **4r**, 82
17	–H, $–CH_3$, (1s)	2	–Boc, 2-Ns	D	–H, 2-Ns	**3s**, 69; **4s**, 61
18	$–CH_3$, –H (**1t**)	2	–Boc, 2-Ns	D	–H, 2-Ns	**3t**, 72; **4t**, 51
19	–H, –H (**1u**)	3	–Boc, 2-Ns	D	–H, 2-Ns	**3u**, 91; **4u**[b], 52

Ns = nitrobenzenesulfonyl. [a] Racemic. [b] Reaction at 55 °C, 10 days.

on treatment with sodium hydride (method A, Table 1) which retained the *N*-Boc group or by –Boc removal using trifluoroacetic acid (TFA) followed by a basic workup (method B, Table 1). In one case, we chose the –Cbz protecting group on N1 and a 4-nosyl on N4 (Table 2, entry 10). Gratifyingly, this protecting group combination also yielded the expected bromide intermediate. Removal of N-Cbz group with TMSOTf/TBAI followed by basic workup (method C, Table 1), once again gave the piperazine product in good yield without affecting the nosyl group. The enantiopurity of the generated scaffolds (Table 2, entries 3 and 4, chiral HPLC) was determined and as expected, the chiral integrity was maintained during this synthetic process. To further display the protecting group generality of this reaction sequence, we reversed the protecting groups on the 1,2-diamines[28] to generate substrates having the 2-nosyl protecting group on N1 and –Boc protecting group on N4. These substrates also provided bromide intermediates (**3m–r**) and upon treatment with TFA followed by basic workup (method B) afforded the desired chiral piperazines in good yields (Table 2, entries 11–16).

We further extended the methodology to constructing larger rings (1,4-diazepane and 1,4-diazocanes, Table 2, **4s–u**). Differentially protected 1,3 and 1,4-diamine substrates (**1s–u**) were prepared from commercially available diamines and subjected to our optimized reaction conditions. In all cases the bromide intermediates (**3s–u**) were produced in good yields. However, upon *N*-Boc removal followed by basic workup no cyclized product was observed as was the case for the 6-membered rings. We then treated the substrates with base for extended periods (method D, Table 2). Over 16 h the bromide was consumed to afford the diazepane product (Table 2, **4s** and **4t**). In the case of the 8-membered ring product, only a trace amount was detected even after 16 h (**4u**). Elevating the temperature (THF, 55 °C) allowed the reaction to progress; however, it took 10 days to complete the reaction.

Rather than a 2-step process proceeding through a bromide intermediate, we surmised that increasing the acidity of the NH-carbamate while additionally reducing the steric hindrance of the NH protecting group might under appropriate conditions promote direct cyclization to the piperazine products. Accordingly, we chose the trifluoroacetyl group as a protecting group for N4 (Scheme 2).[28] Upon subjection to the reaction conditions we were pleased to find that the desired annulated product was generated as the bis-protected piperazine in one step. Subjection of various trifluoroacetyl protected 1,2-diamine substrates including a diamine containing an ester functionality in the side chain (**5g**), underwent the annulation reaction as expected in good yield. We further tested a trifluor-



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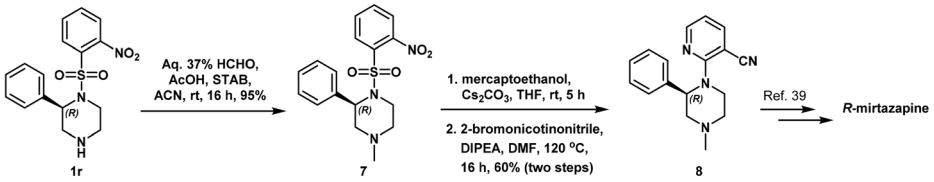
5a n= 1; R = (*S*) -Me; R^1 = 2-Ns; R^2 = $-COCF_3$
5b n= 1; R = (*R*) -Me; R^1 = 2-Ns; R^2 = $-COCF_3$
5c n= 1; R = (*S*) -Bn; R^1 = 2-Ns; R^2 = $-COCF_3$
5d n= 1; R = (*R*) -Bn; R^1 = 2-Ns; R^2 = $-COCF_3$
5e n= 1; R = (*R*) -/Bu; R^1 = 2-Ns; R^2 = $-COCF_3$
5f n= 1; R = (*S*) -Ph; R^1 = 2-Ns; R^2 = $-COCF_3$
5g n= 1; R = (*S*) $-CH_2CO_2Et$; R^1 = $-COCF_3$; R^2 = 2-Ns
5h n= 2; R = (*S*) -Me; R^1 = $-COCF_3$; R^2 = 2-Ns

6a n= 1; R = (*S*) -Me; R^1 = 2-Ns; R^2 = $-COCF_3$; 77%
6b n= 1; R = (*R*) -Me; R^1 = 2-Ns; R^2 = $-COCF_3$; 88%
6c n= 1; R = (*S*) -Bn; R^1 = 2-Ns; R^2 = $-COCF_3$; 83%
6d n= 1; R = (*R*) -Bn; R^1 = 2-Ns; R^2= $-COCF_3$; 84%
6e n= 1; R = (*R*) -/Bu; R^1 = 2-Ns; R^2 = $-COCF_3$; 79%
6f n= 1; R = (*S*) -Ph; R^1 = 2-Ns; R^2 = $-COCF_3$; 85%
6g n= 1; R = (*S*) $-CH_2CO_2Et$; R^1 = $-COCF_3$; R^2 = 2-Ns; 80%
6h n= 2; R = (*S*) -Me; R^1 = $-COCF_3$; R^2 = 2-Ns; not formed

Scheme 2 Annulation reaction to synthesize 2-substituted piperazines.



Scheme 3 Formal synthesis of *R*-mirtazapine.

oacetyl protected 1,3-diamine (**5h**) in this annulation reaction to produce the 1,4-diazepane in one step; however, only the bromide intermediate (**S$_7$**, details in ESI†) was isolated even at the higher temperature and extended reaction time (80 °C, 48 h).

We next applied our short four step sequence to produce a chiral 2-substituted piperazine (–Boc, –Ns) on multigram scale (6 g) using the methyl substituted 1,2-diamine as an example. The *N*-Boc protected alanine (6 g) afforded 4.5 g of the chiral diamine **1a** over two steps.[26] Subjection of this material to the optimized sequence (method B) yielded 3.1 g of the 2-methyl substituted piperazine (**4c**) in 34% yield over four steps.

Finally, we demonstrated our methodology in the context of a targeted formal synthesis of the chiral antidepressant drug mirtazapine (Scheme 3). Although mirtazapine is marketed as a racemic mixture, *R*-mirtazapine but not its enantiomer was reported to have antinociceptive effects in rats suggesting its use as an analgesic.[38] The nosyl protected enantiopure phenylpiperazine (**4r**) was methylated on N4 to produce the key piperazine intermediate **7**. Subjection of **7** to deprotection followed by SnAr reaction with 2-bromonicotinonitrile generated the key intermediate **8**, which can be further converted to *R*-mirtazapine as previously reported.[39]

Conclusions

In conclusion, we have successfully demonstrated the synthesis of enantiomerically pure orthogonally protected mono -2-substituted piperazines within four steps from commercially available amino acids. The reaction of bromoethyldiphenylsulfonium triflate with carbamates results in formation of a bromide intermediate that can be induced to cyclize under several conditions. Appling the reaction specifically to trifluoroacetamide substrates resulted in direct cyclization to produce differentially bis-protected piperazines. We demonstrated the method on multigram scale and produced more than 3 g quantities of enantiomerically pure 2-piperazine products. Further, the reaction conditions were extended to the construction of 1,4-diazepane and 1,4-diazocanes rings. The compounds produced in this study can be readily used as substrates in the synthesis of small molecule libraries since they can be substituted on either nitrogen under a variety of conditions. Finally, we synthesized a key enantiopure intermediate of the drug *R*-mirtazapine demonstrating the utility of the methodology for producing known biologically active chiral 2-substituted piperazines.

Author contributions

S.C. is the lead contributor to this work. M.M.S. is primary contributor and D.C.H.Y. is supporting contributor.

Conflicts of interest

The authors declare no competing financial interest.

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