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Expedite Protocol for Construction of Chiral Regioselectively N-Protected Monosubstituted Piperazine, 1,4-Diazepane, and 1,4-Diazocane Building Blocks

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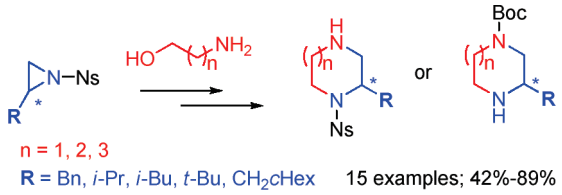

This paper describes the first study of solution-phase synthesis of chiral monosubstituted piperazine building blocks from nosylamide-activated aziridines. The protocol, involving aminolysis of the starting aziridines with ω-amino alcohols and subsequent Fukuyama−Mitsunobu cyclization, offers the advantage of mild conditions as well as short reaction times, and it leads to optically pure *N*-Boc- or *N*-Ns-protected piperazines. This four-step sequence, requiring only a single final chromatographic purification, was extended to include novel diazepane and diazocane derivatives.

Piperazines, diazepanes, and diazocanes are structural motifs of important pharmacophores found in a large number of drugs; e.g., *N*-arylpiperazines are considered "privileged structures" in medicinal chemistry. Thus, the piperazine moiety is present in antimicrobial agents such as pefloxacin and related quinolones,[1] in antipsychotics such as trifluoperazine,[2] in dopaminergic D3 agents,[3] in HIV-protease inhibitors,[4] and in the antidepressant agent clozapine.[5] While the 1,4-diazepane scaffold is present in several marketed drugs,[6] pharmacologically active compounds containing a diazocane nucleus, such as novel interleukine-1B converting inhibitors[7] and high-affinity ligands for the $\alpha4\beta2$ nicotinic receptor,[8] have been reported only recently.

A major constraint when incorporating such saturated heterocyclic scaffolds into biologically active compounds is that introduction of structural diversity via substituents on their carbon backbones often is quite tedious. Due to the limited commercial large-scale availability of this type of monosubstituted chiral building blocks, their potential for applications in novel therapeutics appears to be poorly explored. Thus, there is an apparent lack of general stereoselective routes to chiral monosubstituted piperazines and their homologues, whereas the development of synthetic methods for preparation of the corresponding oxo-derivatives has progressed considerably during the past decade.[9] A synthesis of *N*-Boc-protected (2-hydroxymethyl)-piperazine from optically pure, commercial piperazine-2-carboxylic acid in four steps with good overall yield has recently been published by Gao and co-workers, but this route is strongly restricted in terms of possibilities for side chain variation.[10] Commonly, chiral piperazine building blocks are prepared by reduction of substituted mono- and diketopiperazines, which may be obtained by using either chiral building blocks or via asymmetric synthesis employing a chiral auxiliary.[11] However, this methodology generally involves the use of high temperatures, extended reaction times, and harsh reducing agents, and elaborate changes of the N-protection scheme are usually required to produce synthetically useful compounds. Finally, Berkheij and co-workers have recently described the synthesis of 2-substituted, but racemic, piperazines by a direct

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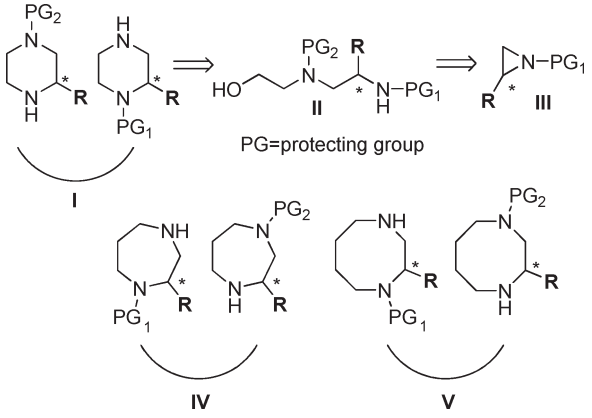
α-lithiation and subsequent electrophilic trapping of *N*-Boc piperazines.[12]

While a survey of the literature did not reveal many studies concerning synthesis of chiral diazocanes,[13] a few papers describe routes to chiral 1,4-diazepanes,[14] which may be commonly prepared either by reduction of the corresponding diketo-1,4-diazepanes obtained via intermolecular condensation of α- and *β*-amino acid derivatives[15] or by condensation of a ditriflate with a resin-bound diamine in a solid-phase synthesis (SPS).[16] Therefore, a short and versatile sequence allowing preparation of such selectively N-protected chiral heteroalicyclic building blocks for combinatorial applications is of particular interest.

As part of our ongoing investigations within aziridine chemistry[17] we were intrigued by the apparent lack of systematic solution-phase studies concerning influence of ring size and bulkiness of substituents,[18] and we decided to devise a general method for the construction of chiral monoprotected piperazines **I**. In addition, we intended to explore the possibilities for obtaining larger heterocyclic rings as well as establish the potential of the method for gram-scale preparations. Thus, in the present work we report on intramolecular Fukuyama−Mitsunobu cyclization of protected *β*-aminosulfonamides **II** obtained by nucleophilic ring-opening of activated aziridines **III** with *ω*-amino alcohols. The protocol was found also to provide access to novel 1,4-diazepane and 1,4-diazocane derivatives **IV** and **V** (Scheme 1), albeit with less efficiency.

Our initial focus was on optimizing the synthesis of piperazine **3** by a four-step sequence only requiring chromatographic purification after the final step. Nucleophilic opening of (*S*)-*N*-(*p*-nitrobenzenesulfonyl)-2-benzylaziridine **2a**[19] with 2-aminoethanol (*n* = 1)[20] in 1,2-dichloroethane (DCE) was monitored by TLC and HPLC-DAD (254 nm), and complete conversion of the starting aziridine was observed after 30 min at room temperature. Subsequent removal of excess 2-aminoethanol by a simple extraction was

SCHEME 1. Modular Synthesis of Piperazine, 1,4-Diazepane, and 1,4-Diazocane Building Blocks



followed directly by N-Boc-protection of the crude product, using Boc_2O and triethylamine. Subsequent Fukuyama−Mitsunobu cyclization[21] was accomplished with diisopropyl azodicarboxylate (DIAD)[22] and triphenylphosphine (Ph_3P) during 3 h at room temperature.[23] A simple Boc-deprotection in TFA−CH_2Cl_2 provided N-nosylated piperazine **3** in good yield (Table 1, entry 1).

To obtain piperazines **4**−**6**, the conditions for ring-opening of the requisite aziridines were modified. Thus, aziridines bearing *i*-Bu (**2b**), CH_2cHex (**2c**), and *i*-Pr (**2d**) as substituents required heating with 2-aminoethanol at 40 °C for 1 h to reach full conversion. Sequential N-protection and cyclization similarly afforded the corresponding piperazines in good overall yields (Table 1, entries 2−4). Having obtained these promising results, the scope of the protocol was further explored to include preparation of homologous ring systems. Thus, sequences involving initial aminolysis of the enantiomeric aziridines **2a** and **2f** with 3-aminopropan-1-ol (*n* = 2) or 4-aminobutan-1-ol (*n* = 3) provided monoprotected chiral α-substituted enantiomeric 1,4-diazepanes **7** and **9** and 1,4-diazocanes **8** and **10**, respectively, in good overall yields (Table 1, entries 5−8). Measurement of the optical rotation of enantiomers **7** and **9** gave the same value but with opposite sign. Likewise, the enantiomers **8** and **10** exhibited identical numerical $[\alpha]_D$ values confirming the validity of this protocol.[24] In addition, the reactivity and selectivity of an amino diol was examined.[25] Hence, after ring-opening of **2a** with (2*R*)-3-aminopropan-1,2-diol and subsequent protection, the resulting Boc-protected *β*-aminosulfonamide

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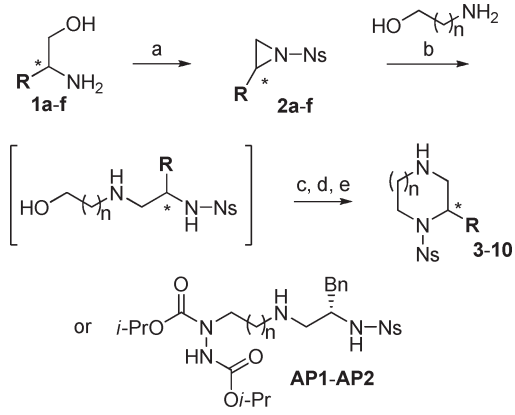
TABLE 1. Synthesis of Monosubstituted Nosylated Piperazine, 1,4-Diazepane, and 1,4-Diazocane Building Blocks from Activated Aziridines 2[a]



entry	aziridine (conf)[b]	*n*	R	method[c]	product (%)
1	**2a** (*S*)	1	Bn	A	**3** (78)
2	**2b** (*S*)	1	*i*-Bu	B	**4** (73)
3	**2c** (*S*)	1	CH_2cHex	B	**5** (89)
4	**2d** (*S*)	1	*i*-Pr	B	**6** (63)
5	**2a** (*S*)	2	Bn	A	**7** (72)
6	**2a** (*S*)	3	Bn	A	**8** (72)
7	**2f** (*R*)	2	Bn	A	**9** (72)
8	**2f** (*R*)	3	Bn	A	**10** (71)
9	**2a** (*S*)	4	Bn	A	**AP1** (30)
10	**2a** (*S*)	5	Bn	A[d]	**AP2** (28)

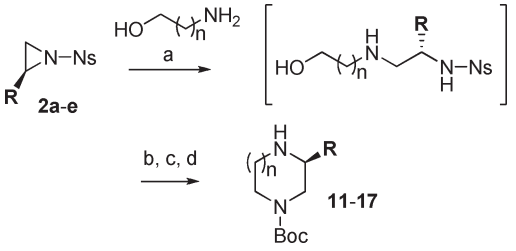
[a] Reagents and conditions: (a) NsCl (3 equiv), CH_2Cl_2–pyridine (2:1), 4 h, then KOH (2 M); (b) amino alcohol (15 equiv), DCE, method A or B; (c) $(Boc)_2O$ (1.1 equiv), Et_3N (2 equiv), MeCN, rt, 2–3 h; (d) Ph_3P (1.5 equiv), DIAD (1.5 equiv), rt, 3–4 h; (e) TFA–CH_2Cl_2 (1:1), rt, 3–4 h. [b] Conf = absolute configuration. [c] Method A: rt, 30 min. Method B: 40 °C, 60 min. [d] DCE–THF (1:1) was used as solvent.

was engaged in the Fukuyama–Mitsunobu reaction with the reagent pair DIAD/PPh_3. However, only starting material was recovered in this case.

Finally, construction of larger azacycles[26] was undertaken to establish at which ring size the reaction mode might shift from intramolecular cyclization to intermolecular oligomerization.[27] Examining the use of higher homologous amino alcohols ($n = 4$ and 5) showed that preparation of α-substituted diazonane and diazecane rings, respectively, was not feasible under the dilution conditions employed. Instead, aliphatic products **AP1** and **AP2**, arising from the alternative substitution with the hydrazine derived from DIAD, were obtained (Table 1, entries 9 and 10).

To obtain chiral heterocyclic building blocks with a Boc protecting group, the last step in the synthetic sequence was modified. Thus, after Fukuyama–Mitsunobu cyclization, removal of the nosyl group[28,29] was initially performed under

TABLE 2. Synthesis of Monosubstituted Boc-Protected Piperazine, 1,4-Diazepane, and 1,4-Diazocane Building Blocks[a]



entry	aziridine (**R**)	*n*	method[b]	product (%)
1	**2a** (Bn)	1	A	**11** (70)
2	**2b** (*i*-Bu)	1	B	**12** (86)
3	**2d** (*i*-Pr)	1	B	**13** (61)
4	**2e** (*t*-Bu)	1	C	**14** (62)
5	**2a** (Bn)	2	A	**15** (69)
6	**2c** (CH_2cHex)	2	B	**16** (69)
7	**2a** (Bn)	3	A	**17** (42)

[a] Reagents and conditions: (a) amino alcohol (15 equiv), DCE, method A, B, or C; (b) $(Boc)_2O$ (1.1 equiv), Et_3N (2 equiv), MeCN, rt, 2–3 h; (c) Ph_3P (1.5 equiv), DIAD (1.5 equiv), rt, 3–4 h; (d) DBU (2 equiv), 1-octanethiol (2 equiv), rt, 15 min. [b] Method A: rt, 30 min. Method B: 40 °C, 60 min. Method C: 50 °C, 60 min.

standard conditions, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2 equiv) and 2-mercaptoethanol (3 equiv) in MeCN at 50 °C. Although complete deprotection was observed after 30 min, the obtained products were contaminated by small amounts of bis(2-hydroxyethyl)disulfide, difficult to remove by column chromatography. To avoid this polar impurity, 1-octanethiol was used instead, which proved beneficial as it led to a shorter reaction time at room temperature, providing pure heterocycles **11**–**17** in good to high overall yields (Table 2).[30]

In conclusion, the present solution-phase procedure for ring-opening of activated aziridines with ω-amino alcohols followed by Fukuyama–Mitsunobu cyclization appears to be an efficient means for the preparation of a diverse array of optically pure monosubstituted piperazines, 1,4-diazepanes, and 1,4-diazocanes. The protocol involves mild conditions and short reaction times, as well as just one final purification step. However, its main advantage is that regioselectively protected versatile building blocks displaying either a Boc or a nosyl protecting group may be obtained directly. In contrast to our previous work concerning the utility of aziridines in solid-phase synthesis,[17] we did not observe any limitations due to steric bulk of the introduced side chain, as compound **14**, displaying a *tert*-butyl group, was isolated in an equally satisfactory overall yield as the less congested products (Table 2). Moreover, the solution-phase methodology was shown to be compatible with gram-scale synthesis exemplified by the preparation of piperazine **11**.[31] Hence, for the purpose of synthesizing chiral building blocks in useful amounts, a solid-phase procedure seems less attractive due to both cost and scalability issues. Thus, the present method that involves reactions carried out at room temperature or with slight traditional heating constitutes a more versatile

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(30) For compounds **15**, **16**, and **17** almost all ^{13}C NMR signals were doubled indicating the presence of two rotamers involving the carbamate group. For further details, see the Supporting Information.

(31) For further details, see the Experimental Section.

and readily scalable protocol as compared to aziridine ring-opening and Boc-protection on solid-phase, which required microwave heating to be convenient and high-yielding conversions.[17a,17c]

Experimental Section

Representative Procedure for the Synthesis of Monosubstituted Nosylated Piperazines: (2*S*)-2-Cyclohexylmethyl-1-(4-nitrobenzenesulfonyl)piperazine (5). Aziridine **2c** (102 mg, 0.3 mmol, 1 equiv) was added in one portion to a solution of 2-aminoethanol (288 mg, 4.7 mmol, 15 equiv) in dry DCE (1 mL) at 40 °C. The mixture was stirred for 60 min, and was then concentrated in vacuo. The residue was taken up in EtOAc (30 mL), and the solution was washed with water (4 × 40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellow oil was dissolved in MeCN (6 mL) and treated with Et_3N (86 μL, 0.6 mmol, 2 equiv) and $(Boc)_2O$ (74 mg, 0.34 mmol, 1.1 equiv) for 3 h at room temperature. Then the solvent was removed in vacuo, the crude material was taken up in EtOAc (30 mL), and the solution was washed successively with water (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellow oil was dissolved in dry THF (5 mL), and then Ph_3P (122 mg, 0.5 mmol, 1.5 equiv) was added at room temperature under N_2. The mixture was stirred for 5 min prior to addition of DIAD (91 μL, 0.5 mmol, 1.5 equiv). Subsequently the mixture was stirred for 3.5 h. After removal of the solvent in vacuo, the crude material was treated with TFA−CH_2Cl_2 (1:1, 6 mL) for 3.5 h, and then concentrated in vacuo. The residue was purified by preparative HPLC (see the Supporting Information for details) to provide **5** as a yellow solid (135 mg, 89%). $[\alpha]_D$ +23.4 (*c* 0.85, MeOH). $HPLC_{254\ nm}$ 99% (t_R = 18.1 min). ^{1}H NMR (300 MHz, CD_3OD) δ 8.43 (d, *J* = 9.3 Hz, 2H), 8.14 (d, *J* = 9.3 Hz, 2H), 4.33−4.40 (m, 1H), 4.05 (dd, *J* = 15.3 and 3.3 Hz, 1H), 3.48 (ddd, *J* = 15.3 Hz, 12.9 and 2.7 Hz, 1H), 3.22−3.30 (m, 2H), 3.02 (dd, *J* = 13.5 and 4.5 Hz, 1H), 2.81 (ddd, *J* = 12.9 and 3.9 Hz, 1H), 1.41−1.98 (m, 7H), 0.74−1.28 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 150.7, 146.2, 128.7 (2C), 125.0 (2C), 48.9, 45.8, 42.7, 37.5, 36.3, 34.1, 33.4, 32.8, 26.5, 26.4, 26.2. HRMS (*m*/*z*) $[M+H]^+$ calcd for $[C_{17}H_{26}N_3O_4S]^+$ 368.16385, found 368.16385; Δ*M*, 0.0 ppm.

Representative Procedure for Gram-Scale Synthesis of Monosubstituted Boc-Protected Piperazines: (3*S*)-3-Benzylpiperazine-1-carboxylic Acid *tert*-Butyl Ester (11). Aziridine **2a** (1.50 g, 4.7 mmol, 1 equiv) was added in one portion to a solution of 2-aminoethanol (4.32 g, 70.7 mmol, 15 equiv) in dry DCE (15 mL) at room temperature. The mixture was stirred for 30 min, and was then concentrated in vacuo. The residue was taken up in EtOAc (180 mL), and the solution was washed with water (4 × 240 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellow oil was dissolved in MeCN (90 mL) and treated with Et_3N (1.30 mL, 9.4 mmol, 2 equiv) and $(Boc)_2O$ (1.13 g, 5.2 mmol, 1.1 equiv) for 3 h at room temperature. Then the solvent was removed in vacuo, the crude material was taken up in EtOAc (180 mL), and the solution was washed successively with water (240 mL) and brine (240 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting yellow oil was dissolved in dry THF (75 mL) and Ph_3P (1.85 g, 7.1 mmol, 1.5 equiv) was added at room temperature under N_2. The mixture was stirred for 5 min prior to addition of DIAD (1.37 mL, 7.1 mmol, 1.5 equiv). Subsequently, the mixture was stirred for 3.5 h. After removal of the solvent in vacuo, the crude material was dissolved in MeCN (75 mL), and then DBU (1.41 mL, 9.4 mmol, 2 equiv) and 1-octanethiol (1.64 mL, 9.4 mmol, 2 equiv) were added. After 15 min of stirring at room temperature the solvent was removed in vacuo and the crude material was taken up in EtOAc (180 mL), then the solution was washed successively with aqueous 10% Na_2CO_3 (180 mL) and brine (180 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column size: chromatography on silica gel (column 60 × 200 mm), using a gradient elution with CH_2Cl_2−MeOH (400:10 to 200:10) followed by CH_2Cl_2−MeOH−NH_3 (200:10:1 to 150:10:1) to give **11** as a yellow oil (0.91 g, 70%). $[\alpha]_D$ −1.1 (*c* 0.90, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.42 (m, 5H), 3.90−4.16 (br, 2H), 2.78−3.02 (m, 4H), 2.55−2.74 (m, 3H), 2.00 (br, 1H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 138.1, 129.5 (2C), 128.9 (2C), 126.9, 79.9, 49.3−50.4 (br), 46.1, 44.0−45.1 (br), 40.6, 28.9 (3C). HRMS (*m*/*z*) $[M+H]^+$ calcd for $[C_{16}H_{25}N_2O_2]^+$ 277.19105, found 277.19105; Δ*M*, 0.1 ppm.

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Supporting Information Available: Materials, full experimental procedures, compound characterization data including ^{13}C NMR spectra for all compounds, and HPLC chromatograms for all *N*-nosylated building blocks. This material is available free of charge via the Internet at http://pubs.acs.org.