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Synthesis of 2-substituted piperazines via direct α-lithiation

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Dedicated to Professor Dieter Hoppe for his contributions to this field

Abstract—A novel efficient synthetic route towards the pharmaceutically relevant 2-substituted piperazine class is described. The key step involves α-lithiation of *N*-Boc piperazines, followed by reaction with several electrophiles. To obtain high yields, in some cases transmetallation to copper after the lithiation step is required.

Piperazines are an often recurring motif in compounds displaying biological activity. Whereas most of the pharmaceutically relevant piperazines only bear nitrogen substituents, carbon-substituted piperazines have also been reported such as L-745631 (farnesyl transferase inhibitor)[1a] and FK-355 (neurokinin-1 (NK-1) antagonist)[1b] (Fig. 1).

For our own discovery program towards NK-1 antagonists a set of structurally diverse 2-substituted piperazines was required. The most common way to synthesise 2-substituted piperazines is by reduction of the corresponding 2-substituted diketopiperazines.

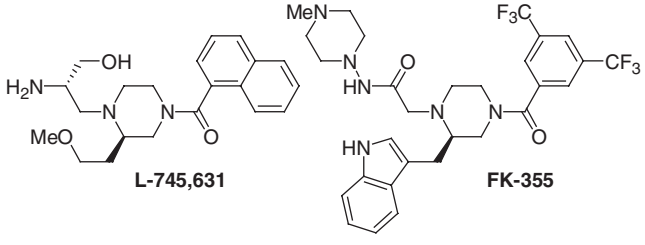
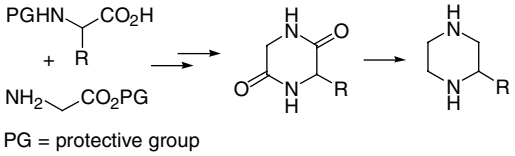


Figure 1.

Diketopiperazines in turn, can be obtained from suitable protected α-amino acids (Scheme 1).

To avoid this lengthy synthesis we looked for an alternative route, preferably one that was based on a common intermediate. In particular the work of Beak and Lee,[2] Dieter et al.[3] and others,[4] who reported the α-lithiation of acyclic and cyclic *N*-Boc functionalised amines, followed by trapping with several electrophiles, attracted our attention. Although this strategy has been thoroughly investigated starting from *N*-Boc-pyrrolidine,[5] *N*-Boc-piperidine[6] and *N*-Boc-hexahydropyrimidine,[7] to our surprise and to the best of our knowledge, no synthesis of 2-functionalised *N*-Boc-piperazines using the direct α-lithiation method has been reported so far. In this letter we disclose the successful synthesis of 2-functionalised piperazines via α-lithiation of *N*-Boc-piperazines followed by trapping with a selected set of electrophiles.[8]



Scheme 1. Multistep piperazine synthesis from α-amino acids.

Keywords: α-Lithiation; Piperazines; Transmetallation; DMG; DoM.
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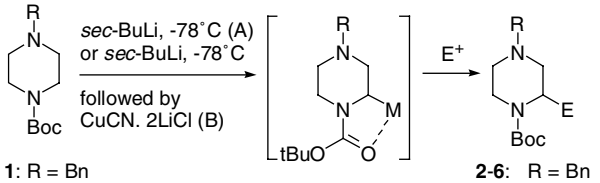
Starting from *N*-Boc-*N*′-benzylpiperazine **1**, which can be accessed easily in large quantities from commercially available mono *N*-benzyl-piperazine,[9] several parameters (solvent, lithium base plus additive and reaction temperature) were screened. For these initial experiments trimethylsilyl chloride was chosen as the electrophile (Scheme 2). The best results were obtained using *sec*-BuLi/TMEDA (2.4 equiv) as the lithiation agents and ether as solvent at −78 °C. Using these conditions, 2-trimethylsilyl *N*-Boc-*N*′-benzylpiperazine **2** was isolated in a yield of 68% (Scheme 2, entry 1A).[10]

With these optimised conditions in hand several other electrophiles were screened. Although 2-tris-*n*-butylstannyl piperazine **3** was isolated in a satisfactory 71% yield, 2-allyl piperazine **4** was only obtained in a moderate 27% yield (Scheme 2, entries 2A and 3A). The piperazines **5** and **6**, bearing benzyl and *n*-butyl groups at the 2-position, were formed in trace amounts only (entries 4A and 5A). A remarkable difference was found starting from the analogous *N*-Boc-*N*′-methylpiperazine **7**[11] with trimethylsilyl chloride as electrophile (entry 6A). Whereas the *N*′-benzyl analogue **1** gave **2** in 68% yield (entry 1A), the *N*′-methyl analogue **8** was obtained in a disappointing 5% yield for which we do not have an explanation as yet. The yields obtained for compounds **9**, **10**, **11** and **12** (entries 7A–10A) were analogous to the results obtained for the lithiation of compound **1**.

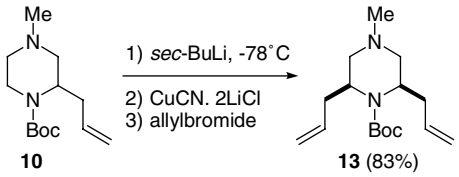
It is clear that carbon electrophiles in particular fail to give satisfactory yields (Scheme 2, entries 3A–5A and 8A–10A). During our investigation it was reported that the lithium/copper exchange strategy developed by Knochel,[12] was beneficial for the lithiation of cyclic aliphatic amines.[13] Application of this methodology, that is, transmetallation to copper by adding a CuCN·2LiCl



Entry	R	E	Product	Yield(%)	
				A[a]	**B**[b]
1	Bn	TMS	**2**	68	14
2	Bn	(*n*-Bu)$_3$Sn	**3**	71	trace
3	Bn	allyl	**4**	27	89
4	Bn	Bn	**5**	trace	54
5	Bn	*n*-Bu	**6**	trace	85
6	Me	TMS	**8**	5	22
7	Me	(*n*-Bu)$_3$Sn	**9**	82	trace
8	Me	allyl	**10**	51	95
9	Me	Bn	**11**	trace	60
10	Me	*n*-Bu	**12**	trace	72

[a]See Ref. 10.
[b]See Ref. 14.

Scheme 2. 2-Metallation of piperazines and trapping with several electrophiles.



Scheme 3.

complex before introduction of the electrophile, has a positive effect indeed and the allyl, benzyl and *n*-butyl groups could be introduced at the 2-position in *N*-Boc-*N*′-benzylpiperazine **1** in isolated yields of 89%, 54% and 85%, respectively (Scheme 2, entries 3B–5B).[14] Similar yields were obtained starting from *N*-Boc-*N*′-methylpiperazine **7** (entries 8B–10B). On the other hand, introduction of a tributylstannyl group (entries 2B and 7B), after transmetallation to the cuprate, failed. By using trimethylsilyl chloride as the electrophile in combination with transmetallation to copper *N*-Boc-*N*′-benzylpiperazine **1** gave **2** in a lower yield (14% vs 68%, entries 1A and 1B) whereas *N*-Boc-*N*′-methylpiperazine **7** provided **8** in a slightly better yield (22% vs 5%, entries 6A and B).

Finally, we wanted to extend this methodology to the 2,6-disubstituted piperazine series. To our great delight, after lithiation of 2-allyl-*N*-Boc-*N*′-methylpiperazine **10** at the 6-position followed by transmetallation to the organocuprate, *cis*-2,6-diallyl-*N*-Boc-*N*′-methylpiperazine **13** was isolated in a yield of 83% (Scheme 3).[15] The 2,6-*cis* relationship could be derived from the vicinal coupling constants of H2 with $H3_{eq}$ and $H3_{ax}$ which are 3.6 Hz and 5.9 Hz, respectively, pointing to an equatorially disposed H2. In the case of a 2,6-*trans* relationship one would expect one of the protons at C2 or C6 in the axial position leading to one larger vicinal coupling constant.[16]

In summary, a novel synthetic approach has been developed to access the pharmaceutically important 2-substituted piperazine series via direct α-lithiation of *N*-Boc piperazines in combination with a lithiation/copper transmetallation strategy. These 2-substituted piperazines may be elaborated further to give *cis*-2,6-disubstituted piperazines via a subsequent lithiation/transmetallation/electrophile introduction. Currently, work is in progress to further expand the scope of this method.

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References and notes

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10. Procedure A for the lithiation of the Boc-piperazines **1** and **7**, illustrated for the synthesis of compound **2**: A flame dried 50 ml three-necked reaction vessel was charged with **1** (138 mg, 0.5 mmol), TMEDA (140 mg, 1.2 mmol) and dry diethyl ether (15 ml) under a nitrogen atmosphere. After cooling to −78 °C, *sec*-BuLi (0.92 ml of a 1.3 M solution in hexane, 1.2 mmol) was added slowly using a syringe. The reaction mixture was allowed to warm to −10 °C at which temperature the reaction mixture was stirred for 1 h. After cooling down again to −78 °C, trimethylsilyl chloride (130 mg, 1.2 mmol) was added and the reaction mixture was stirred at −60 °C for 1 h after which the temperature was allowed to reach room temperature. After stirring for 14 h, the reaction mixture was poured into a saturated NH_4Cl solution from which the product was isolated by extraction with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by flash column chromatography (hexanes–EtOAc = 1:4) to give **2** in 68% yield as a slightly yellow oil. $R_f = 0.10$ (hexanes–EtOAc = 1:4); ^1H NMR ppm (500 MHz, DMSO, 125 °C): $\delta = 7.18–7.39$ (m, 5H), 3.70–3.94 (d, 1H), 3.31–3.57 (m, 3H), 2.96 (br s, 2H), 2.80 (d, 1H, $J = 11.2$ Hz), 2.68 (d, 1H, $J = 10.0$ Hz), 2.30 (br s, 1H), 1.44 (s, 9H), 0.07 (s, 9H); ^{13}C (125 MHz, DMSO, 125 °C): $\delta = 153.39, 128.43, 127.40, 126.35, 77.96, 61.91, 53.21, 52.26, 44.68, 41.97, 40.02, 27.58, -1.53$. HRMS (EI): calcd for $C_{19}H_{33}N_2O_2Si$: 349.2311. Found: 349.2297.
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14. Procedure B for the lithiation and *trans*-metallation to copper of the Boc-piperazines **1** and **8**, illustrated for the synthesis of compound **4**: a flame dried 50 ml three-necked reaction vessel was charged with **1** (138 mg, 0.5 mmol), TMEDA (140 mg, 1.2 mmol) and dry diethyl ether (15 ml) under a nitrogen atmosphere. After cooling to −78 °C, *sec*-BuLi (0.92 ml of a 1.3 M solution in hexane, 1.2 mmol) was slowly added. The reaction mixture was allowed to warm to −10 °C and stirred for 1 h. After cooling again to −78 °C, a freshly prepared solution of the CuCN·2LiCl complex (CuCN (107 mg, 1.2 mmol) and LiCl (100 mg, 2.4 mmol) in the minimum amount of THF), was added and the reaction mixture was stirred for 30 min at −50 °C. The temperature was again lowered to −78 °C after which allylbromide (145 mg, 1.2 mmol) was added, followed by stirring at −60 °C for 1 h. After stirring overnight at room temperature the mixture was poured into a saturated NH_4Cl solution from which the product was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified by flash column chromatography using dichloromethane–MeOH = 98:2 as the eluent to give **4** in a yield of 89%. $R_f = 0.1$ (dichloromethane–MeOH = 98:2); ^1H NMR ppm (500 MHz, $CDCl_3$): $\delta = 7.22–7.31$ (m, 5H), 5.68–5.69 (m, 1H), 4.93–5.03 (m, 2H), 4.10 (br s, 1H), 3.86 (br s, 1H), 3.54 (d, 1H, $J = 13.3$ Hz), 3.39 (d, 1H, $J = 13.3$ Hz), 3.08 (t, 1H, $J = 12.2$ Hz), 2.78 (d, 1H, $J = 10.8$ Hz), 2.71 (d, 1H, $J = 11.5$ Hz), 2.50 (m, 2H), 2.06 (m, 2H), 1.39 (s, 9H); ^{13}C (100 MHz, $CDCl_3$): $\delta = 154.0, 138.16, 135.27, 128.63, 128.14, 126.84, 116.75, 79.24, 62.63, 59.50, 54.30, 52.97, 28.21$. HRMS (EI): calcd for $C_{19}H_{28}N_2O_2$: 316.2151. Found: 316.2161.
15. Compound **13** was prepared starting from **10** using the same procedure as described for **4** in Ref. 14 in 83% yield (0.47 g scale). $R_f = 0.35$ (EtOAc); ^1H NMR ppm (500 MHz, $CDCl_3$): $\delta = 5.81–5.73$ (m, 2H), 5.10–5.03 (m, 4H), 3.80–3.75 (m, 2H), 2.61–2.50 (m, 4H), 2.44 (dd, 2H, $J = 11.6$ Hz and $J = 3.6$ Hz), 2.33 (dd, 2H, $J = 11.5$ Hz and $J = 5.9$ Hz), 2.24 (s, 3H), 1.46 (s, 9H); ^{13}C (125 MHz, $CDCl_3$): $\delta = 155.78, 135.41, 116.78, 79.48, 57.28, 52.69, 46.10, 36.33, 28.24$; HRMS (FAB): calcd for $C_{16}H_{29}N_2O_2$: 281.2229. Found: 281.2231. To obtain further proof of the relative stereochemistry the Boc group was removed to liberate the secondary amine, now amenable for asymmetric functionalisation. Attempts to acylate the resulting amine with Mosher's acid chloride group failed and gave several side products. Most probably, due to steric hindrance caused by the 2,6-allyl groups, side reactions at the 4-amine occurred. (See: Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 2056–2064). Addition of Pirkle's amine (up to 1.5 equiv) only gave a shift of the peaks. The observation that no doubling of the peaks occurred points at an achiral compound thus supporting the previous coupling constant based 2,6-*cis* stereochemistry assignment.
16. For calculation of the coupling constants the refined Karplus equation was used as published in: Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.