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2,6-Diazaspiro[3.3]heptanes: Synthesis and Application in Pd-Catalyzed Aryl Amination Reactions

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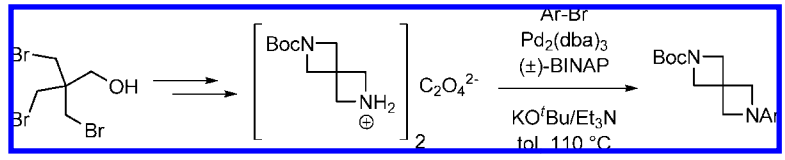
ABSTRACT



A concise and scalable synthesis of a 2,6-diazaspiro[3.3]heptane building block is reported. The usefulness of this structural surrogate of piperazine is shown in arene amination reactions yielding a variety of *N*-Boc-*N*′-aryl-2,6-diazaspiro[3.3]heptanes.

We have studied and documented the potential role of oxetanes and related spirocyclic compounds as useful building blocks for drug discovery.[1] In this context, we have become interested in further exploring the chemical space of small heterocyclic compounds for applications in medicinal chemistry. 2,6-Diazaspiro[3.3]heptane (**1**) is an intriguing ring system that may be considered at the very least as a structural surrogate for piperazines. Additionally, the spirocyclic framework confers upon it the ability to populate structural space not accessible to the parent piperazine. Its potential use as a small-molecule modulator of pharmacokinetic properties, in analogy to what we have shown with oxetanes, would require an efficient synthesis and the study of reaction chemistry that allows its ready incorporation onto molecular scaffolds. Herein, we report a convenient access route to monoprotected **1** and its participation in Pd-mediated amination reactions to furnish a variety of *N*-Boc-*N*′-aryl-2,6-diazaspiro[3.3]heptanes.

The recent advances in aryl amination processes[3] have made it common to integrate piperazines onto aromatic systems in the early stages of discovery of pharmaceutical agents.[4] In contrast, the closely related "homospiropiperazine" **1** (Figure 1[3]) is an underrepresented structural motif in drug design and discovery, even though the ring system has been known for some time.[5,6] The handful of reports on its preparation suffer from two drawbacks: lengthy syntheses or delivery of compounds that leave the two ends undifferentiated.

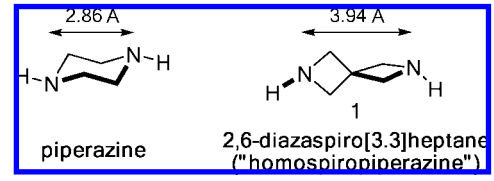


Figure 1. Comparison of piperazine and 2,6-diazaspiro[3.3]heptane, indicated as calculated N−N distances.[2]

(1) (a) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed* **2006**, *45*, 7736. (b) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512.

(2) Calculation was performed using *CambridgeSoft ChemBio3D Ultra 11.0*.

(3) For recent reviews see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.

(4) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L *Chem. Rev.* **2003**, *103*, 893, and references therein.

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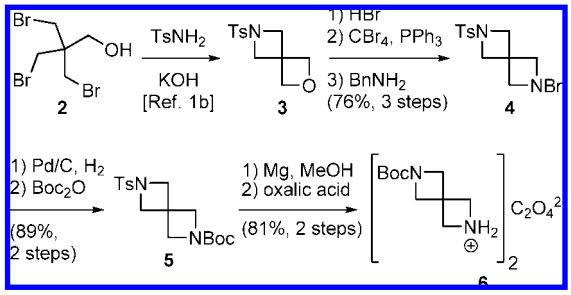
Scheme 1. Synthesis of 2,6-Diazaspiro[3.3]heptane **6**

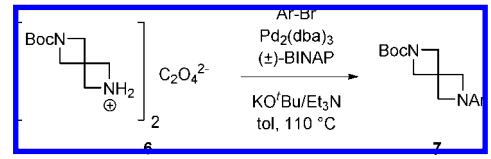


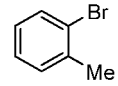
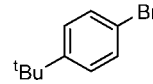
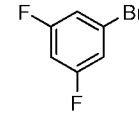
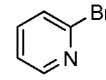
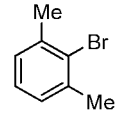
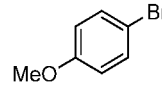
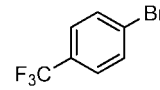
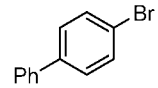
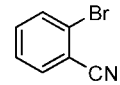
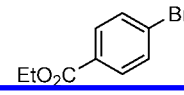
In the approach we have developed (Scheme 1), the synthesis of monoprotected **1** commenced with tribromopentaerythritol (**2**), which is commercially available because of its use as a flame retardant.[7] Following its conversion to 2-oxa-6-azaspiro[3.3]heptane **3**,[1b] oxetane opening with HBr gave a bromoalcohol,[8] which was easily transformed into **4** in two steps and 76% overall yield. Hydrogenolytic cleavage of the *N*-benzyl group and subsequent treatment with Boc_2O gave *N*-Boc protected azetidine **5**. Of various derivatives that could be prepared, we have found that oxalate salt **6** is most convenient to handle. It is accessed following cleavage of the tosyl amide with Mg/MeOH followed by treatment with oxalic acid.

To establish the synthetic potential of compound **6** in the setting commonly observed for piperazines, we have investigated its use in arene coupling reactions. Upon screening for optimum procedures, we observed that the application of standard conditions (aryl bromide, $Pd_2(dba)_3$, (±)-BINAP (1.5/Pd), *tert*-BuOK, toluene, 110 °C) resulted in unsatisfactory coupling yields. Interestingly, under otherwise identical conditions for the Buchwald−Hartwig amination, the presence of small amounts of Et_3N (~0.5 equiv) led to the corresponding aryl amines in useful yields.[9] As shown in Table 1, diazaspiroheptane **6** can be coupled to a variety of aryl bromides. The best yields were observed when these included alkyl and fluorine substituents (77−97%, products **7a**−**7c**, **7e**). Coupling to 2-bromopyridine and electron-rich as well as electron-deficient bromobenzenes furnished products in acceptable yields (56−83%, products **7d**, **7f**−**7j**).

In summary, we have developed an effective route to monoprotected 2,6-diazaspiro[3.3]heptane, which should permit its wide use in a number of applications, such as reductive alkylations and acylations. This is demonstrated in its successful use in arene amination reactions, a transformation of great interest in the pharmaceutical industry. Further studies of this fascinating ring system and its application in drug discovery are ongoing and will be reported in due course.

Table 1. Reactions with Building Block **6**[a]



product	aryl bromide	time	mol % Pd	yield
7a		21 h	2	97%
7b		17 h	2	91%
7c		22 h	2	89%
7d		13 h	5	83%
7e		13 h	2	77%
7f		22 h	4	64%
7g		21 h	5	63%
7h		21 h	2	63%
7i		12 h	2	61%
7j		46 h	4	56%[b]

[a] Typical reaction conditions: aryl bromide (0.4 mmol, 1 equiv), **6** (0.55 equiv), $Pd_2(dba)_3$ (1−2.5 mol %), (±)-BINAP (1.5/Pd), KO*t*Bu (3 equiv), Et_3N (5 drops), toluene (5 mL), 110 °C, 12−46 h. [b] Cs_2CO_3 used as base instead of KO*t*Bu.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Hamza, D.; Stocks, M. J.; Décor, A.; Pairaudeau, G.; Stonehouse, J. P. *Synlett* **2007**, 2584. (b) Stocks, M. J.; Hamza, D.; Pairaudeau, G.; Stonehouse, J. P.; Thorne, P. V. *Synlett* **2007**, 2587.

(7) See for example: Bertrand, J.-N. B. U.S. Patent 4 699 943, 1987.

(8) Hoste, J.; Govaert, F. *Bull. Soc. Chim. Belg.* **1949**, *58*, 157.

(9) The role of the Et_3N catalyst is unclear at present. It may be that it facilitates deprotonation of the ammonium oxalate **6** as a phase-transfer agent.