Synthesis of Novel 2,6-Diazaspiro[3.3]heptanes

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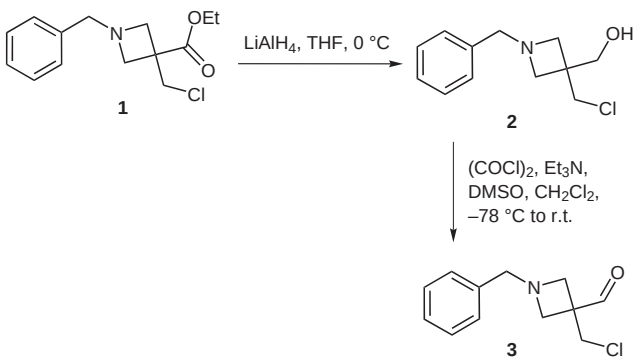
Abstract: A practical route to 2,6-diazaspiro[3.3]heptanes is described by way of reductive amination of a readily available aldehyde with primary amines or anilines. Cyclisation proceeds in high yield and the methods reported are amenable to either library or large-scale synthesis.

Key words: aminations, combinatorial chemistry, heterocycles, ring closure, spiro compounds

Novel, readily accessible templates are of paramount importance in order that custom-synthesised libraries might deliver new pharmacophores for future leads in the pharmaceutical industry. 2,6-Diazaspiro[3.3]heptanes represent exactly the kind of small molecules around which diverse libraries can be built. Although this interesting ring system was first reported over 60 years ago, it is not at all well represented in the scientific literature.[1] Herein we detail a direct synthetic route to functionalised derivatives, also applicable to multiple parallel synthesis and complimenting our previously published work on 2,6-diazaspiro[3.3]heptan-1-ones.[2]

Chloroester **1** is readily accessible via literature methods and amenable to many transformations.[3] From this key starting material a number of routes to the required 2,6-diazaspiro[3.3]heptanes can be envisaged. Aldehyde **3** provides access to one such route. Reduction of **1** with lithium aluminium hydride at reduced temperature,[4] followed by Swern oxidation afforded the corresponding aldehyde **3** in 83% isolated yield (Scheme 1).[5]



Scheme 1 Preparation of 1-benzyl-3-chloromethylazetidine-3-carbaldehyde

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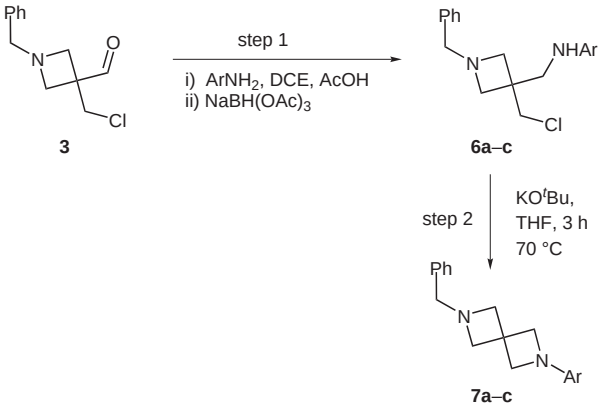
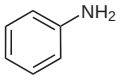
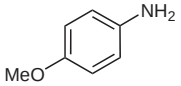
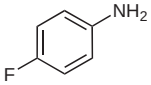
Reductive alkylation of **3** with anilines was found to proceed well by first forming the iminium ion in dichloroethane in the presence of one equivalent of acetic acid. Reduction with sodium triacetoxyborohydride afforded the required amines **6a**–**c** in good yields (Scheme 2).



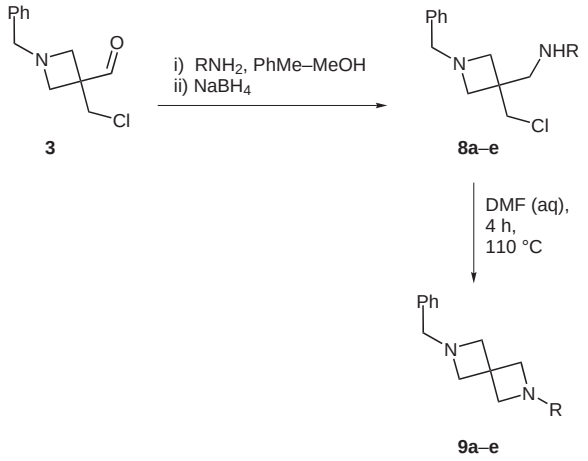
Scheme 2 Preparation of 2-benzyl-6-aryl-2,6-diazaspiro[3.3]heptanes

Cyclisation to the spirocyclic bisazetidines proceeded smoothly in THF with potassium *tert*-butoxide. Heating for three hours gave a very clean conversion into the desired products which were isolated in good yields[6] (Table 1).

Table 1 Reductive Aminations and Cyclisations with Anilines

Aniline	Step 1 yield **6a**–**c**	Step 2 yield **7a**–**c**
	**6a** (83%)	**7a** (70%)
	**6b** (86%)	**7b** (60%)
	**6c** (72%)	**7c** (65%)

In the case of an alkyl amine, the reductive amination was performed in a stepwise manner by first forming the imine in a toluene–methanol mixture. Removal of the solvents under reduced pressure accelerated imine formation. The imine was then directly reduced with sodium borohydride in methanol. This stepwise method was found to give excellent yields (Scheme 3).



Scheme 3 Preparation of 2-benzyl-6-alkyl-2,6-diazaspiro[3.3]heptanes

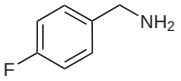
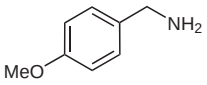
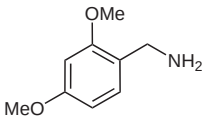
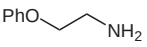
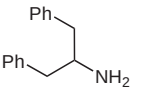
Table 2 Optimisation of Cyclisation Conditions with **8d**

Entry	Base	Temp (°C)	Solvent	Time	Conversion[a]
1	DBU	70	THF	96 h	40%
2	DBU	70	DMF	16 h	100%
3	DBU	130	DMF	3 h	100%
4	K_2CO_3	130	DMF	3 h	–[b]
5	none	130	DMF	3 h	100%
6	none	70	DMF	24	60%
7	none	110	DMF–H_2O	4 h	100%

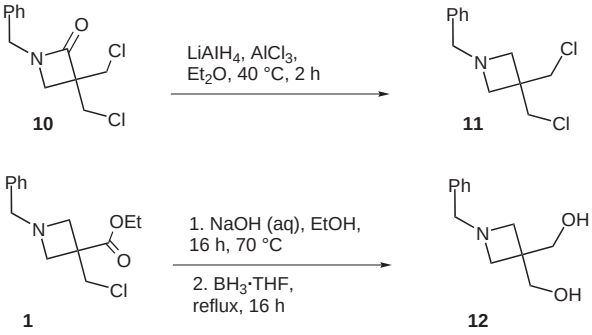
[a] Determined by LCMS.
[b] All the starting material was consumed but significant levels of unidentified impurities were generated.

Cyclisation to afford *N*-alkyl azetidines can be performed using a variety of conditions.[7] The treatment of **8d** with DBU in DMF at 70 °C gave complete conversion (Table 2, entry 2), whereas the reaction was extremely slow in THF (entry 1). Raising the temperature predictably reduced the reaction times to only a few hours (entry 3) although changing the base to potassium carbonate gave a less clean reaction profile (entry 4). Interestingly, at this temperature a base was not required (entry 5), presumably due to dissociation of the HCl salt and subsequent irreversible cyclisation. At lower temperatures (entry 6) the reaction stopped at 60% conversion, but could be made to proceed to completion by the addition of water. Indeed optimum conditions involved the use of DMF–water (8:2) mixture at 110 °C.[8] These conditions gave a rapid and clean access to the required products (Scheme 3, Table 3) obviating the need for added base.[9]

Table 3 Reductive Aminations and Cyclisations with Primary Amines

Amine	Step 1 Yield **8a–e**	Step 2 Yield **9a–e**
	**8a** (96%)	**9a** (73%)
	**8b** (90%)	**9b** (89%)
	**8c** (82%)	**9c** (93%)
	**8d** (90%)	**9d** (75%)
	**8e** (88%)	**9e** (78%)

Equation 1 Alternative routes to **9**



Scheme 4 Synthesis of alternative 2,6-diazaspiro[3.3]heptane precursors

A number of alternative methods to prepare the desired 2,6-diazaspiro[3.3]heptanes were investigated (Equation 1). Access to the dichloride **11** was achieved by hydroalane reduction[10] of the known[11] azetidinone **10** (Scheme 4).

Unfortunately, double displacement by a primary amine of dichloro analogue **11** gave no product,[12] presumably due to the hindered neopentyl centres. In related studies by Hillier and Chen,[1] ditriflates had served as effective azetidine precursors. Access to the required diol **12** was achieved by hydrolysis of the chloroester **1** with excess aqueous sodium hydroxide in ethanol, followed by borane-mediated reduction of the hydroxyacid (Scheme 4).

Activation of the diol as the ditriflate **13** was also attempted, as was activation of chloroalcohol **2** as either the mesylate **14** or the triflate **15**. However, in each case, reaction with a primary amine led to complex mixtures and resulted in either little or none of the desired product.

In conclusion, we have developed a direct method for the synthesis of functionalised 2,6-diazaspiro[3.3]heptanes. The reaction is high yielding, may be scaled up and is applicable to library synthesis. Studies are underway in our laboratory to further exploit these valuable intermediates.

References and Notes

(1) (a) Govaert, F.; Beyaert, M. *Bull. Soc. Chim. Belg.* **1946**, *55*, 106. (b) Litherland, A.; Mann, F. G. *J. Chem. Soc.* **1938**, 1588. (c) Govaert, F. J. *Proc. Acad. Sci. Amsterdam* **1934**, *37*, 156. (d) Engel, W.; Eberlein, W.; Trummlitz, G.; Mihm, G.; Doods, H.; Mayer, N.; De Jonge, A. Eur. Patent, EP 417631, **1991**. (e) Hillier, M. C.; Chen, C.-Y. *J. Org. Chem.* **2006**, *71*, 7885.

(2) Stocks, M. J.; Hamza, D.; Pairaudeau, G.; Stonehouse, J. P.; Thorne, P. *Synlett* **2007**, in press.

(3) For synthesis and reactions of **1** see ref. 2 and: Bartholomew, D.; Stocks, M. J. *Tetrahedron Lett.* **1991**, *32*, 4795.

(4) Prolonged reaction times (>30 min) resulted in significant quantities of the *des*-chloro reduction product.

(5) 1-Benzyl-3-chloromethylazetidine-3-carbaldehyde (**3**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.23–7.34 (m, 5 H), 3.95 (s, 2 H), 3.65 (s, 2 H), 3.43 (d, *J* = 8.2 Hz, 2 H), 3.27 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 137.1, 128.4 (2 × C), 127.3, 62.7, 57.3, 49.7, 44.9. GC–MS: purity = 97.8%, base peak = 91, molecular ion = 223. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}NOCl$: 224.0842; found: 224.0849.

(6) **Preparation of 2-Benzyl-6-phenyl-2,6-diazaspiro[3.3]heptane (7a)**: To a stirred solution of (1-benzyl-3-chloromethylazetidin-3-ylmethyl)phenylamine (0.209 g, 0.695 mmol, 1 equiv) in THF (1.5 mL) was added *t*-BuOK (1.53 mL, 1.53 mmol, 1.0 M solution in THF, 2.2 equiv) and the reaction was heated at 70 °C in a sealed tube. After 90 min further *t*-BuOK (0.7 mL, 0.7 mmol, 1.0 M solution in THF, 1 equiv) was added and heating was continued for a further 1 h. The reaction was then allowed to cool to ambient temperature, filtered to remove KCl and the solvents were evaporated. The residue was purified by column chromatography eluting with 20–100% EtOAc in isohexanes to afford **7a** (209 mg, 0.487 mmol, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.33 (m, 7 H), 6.73 (dt, *J* = 1.0, 14.6 Hz, 1 H), 6.41–6.45 (m, 2 H), 3.92 (s, 4 H), 3.58 (s, 2 H), 3.38 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.6, 138.0, 128.9, 128.5, 128.4, 127.1, 117.7, 111.6, 64.5, 63.7, 62.3, 34.8. HPLC–MS: purity = 98.58%, λ = 220 nm, $[M + H]^+$ = 265.2. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2$: 265.1704; found: 265.1700.

(7) (a) Huszthy, P.; Bradshaw, J. S.; Krakowiak, K. E.; Wang, T.; Dalley, N. K. *J. Heterocycl. Chem.* **1993**, *30*, 1197. (b) Latli, B.; D'Amour, K.; Casida, J. E. *J. Med. Chem.* **1999**, *42*, 2227. (c) De Kimpe, N.; De Smaele, D. *Tetrahedron Lett.* **1994**, *35*, 8023. (d) De Kimpe, N.; De Smaele, D. *Tetrahedron* **1995**, *51*, 5465.

(8) DMF was found to give cleaner reaction profiles than aq NMP, DMA or pyridine mixtures.

(9) **Preparation of 2-Benzyl-6-(4-fluorobenzyl)-2,6-diazaspiro[3.3]heptane (9a)**: (1-Benzyl-3-chloromethylazetidin-3-ylmethyl)(4-fluorobenzyl)amine (75 mg, 0.225 mmol) was dissolved in DMF–H_2O (9:1, 3.5 mL) and heated in a sealed tube at 110 °C with stirring. After 90 min, H_2O (0.4 mL) was added and the reaction was heated for a further 3 h. The reaction was allowed to cool to ambient temperature and loaded on to an SCX ion-exchange cartridge preconditioned in MeOH. After washing with MeOH the product was eluted with NH_3 (1 M in MeOH) and solvents were evaporated. The residue was purified by flash column chromatography eluting with 1–30% EtOH in CH_2Cl_2 to afford **9a** (49 mg, 0.164 mmol, 73%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.99 (m, 2 H), 7.18–7.31 (m, 7 H), 3.55 (s, 2 H), 3.50 (s, 2 H), 3.32 (s, 4 H), 3.29 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8 (d, $J_{C–F}$ = 244.9 Hz), 137.8, 133.6 (d, $J_{C–F}$ = 3.2 Hz), 129.7 (d, $J_{C–F}$ = 7.8 Hz), 128.24, 128.15, 126.9, 114.9 (d, $J_{C–F}$ = 21.2 Hz), 64.3, 64.2, 63.4, 62.6, 34.5. HPLC–MS: purity = 98.23%, λ = 220 nm, $[M + H]^+$ = 297.2. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{22}N_2F$: 297.1767; found: 297.1767.

(10) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339.

(11) Bartholomew, D.; Stocks, M. J. *Tetrahedron Lett.* **1991**, *32*, 4799.

(12) Compound **11** was heated in a sealed tube in 20% aq DMF at 130 °C for 20 h and monitored by LC–MS.