Concise Synthesis of Novel 2,6-Diazaspiro[3.3]heptan-1-ones and Their Conversion into 2,6-Diazaspiro[3.3]heptanes

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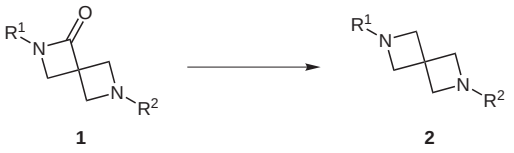
Received 21 May 2007

Abstract: A concise synthesis, amenable to library production of 2,6-diazaspiro[3.3]heptan-1-ones and their subsequent conversion into 2,6-diazaspiro[3.3]heptanes is reported.

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

The design and synthesis of novel, readily functionalised low-molecular-weight fragments is of fundamental importance in modern drug-discovery programs employing rapid parallel-synthesis techniques.[1]

The spirocyclic 2,6-diazaspiro[3.3]heptan-1-one ring system **1** is an example of such a novel[2] system and we report here a practical synthesis of this chemically interesting ring system amenable to either large-scale or plate-based library chemistries. We also report on their subsequent conversion into 2,6-diazaspiro[3.3]heptanes **2** (Scheme 1).

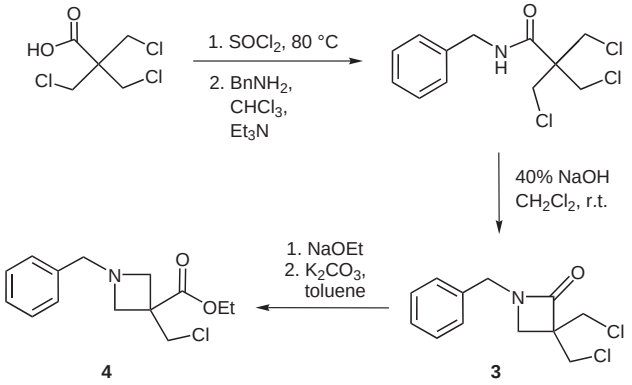


Scheme 1 2,6-Diazaspiro[3.3]heptan-1-ones and their conversion into 2,6-diazaspiro[3.3]heptanes

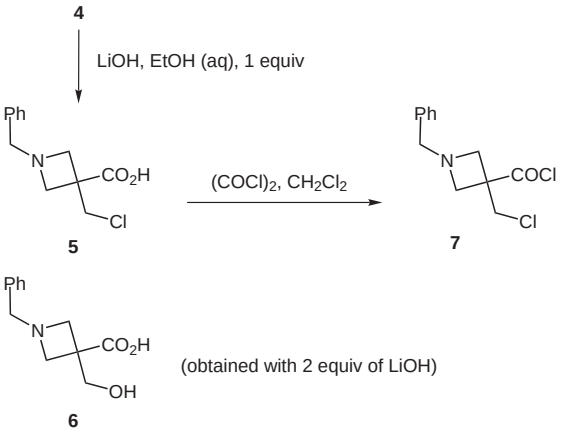
In 1991, Bartholomew and Stocks[3] reported the synthesis of 1-benzyl-3-chloromethyl-azetidine-3-carboxylic acid ethyl ester **4** from the alkoxide-induced rearrangement of a substituted azetidinone **3** (Scheme 2).

Hydrolysis of **4** occurs readily through treatment with one equivalent of lithium hydroxide in ethanol–water to afford the stable crystalline substituted carboxylic acid **5** [n.b. hydrolysis with 2 equivalents of lithium hydroxide at 60 °C affords the corresponding hydroxy-substituted carboxylic acid **6** (Scheme 3)].[4]

The acid **5** will react with a series of amines or anilines in the presence of a suitable coupling agent, such as HATU, to generate the corresponding amides **8a**–**g** in reasonable yield. However, the optimal reaction conditions for this



Scheme 2 Synthesis of 1-benzyl-3-chloromethyl-azetidine-3-carboxylic acid ethyl ester



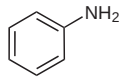
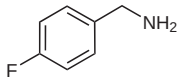
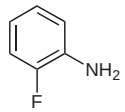
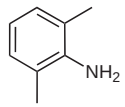
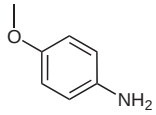
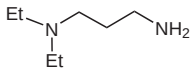
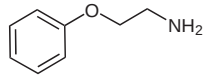
Scheme 3 Hydrolysis of ester **4** and preparation of acid chloride **7**

conversion were obtained by treating **5** with oxalyl chloride in dichloromethane to afford the acid chloride **7** isolated as the stable crystalline hydrochloride salt.[5] Premixing a suspension of **7** and the corresponding amine (R^1NH_2) in dichloromethane at 5 °C, followed by the addition of triethylamine, afforded amides **8a**–**g** in high yield (Table 1).

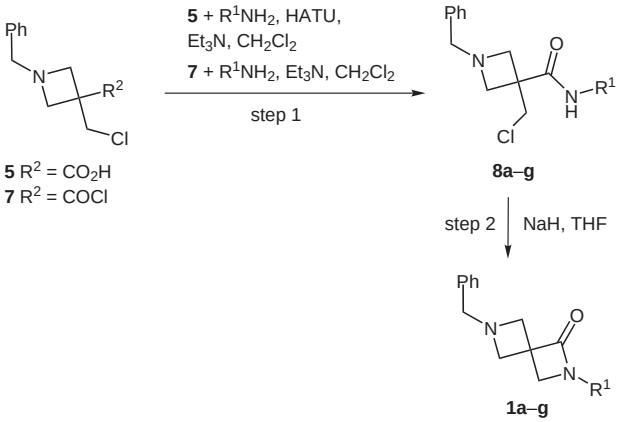
Pleasingly, the conversion of amides **8a**–**g** into their corresponding spirocyclic 2,6-diazaspiro[3.3]heptan-1-ones **1a**–**g** occurred readily, optimum conditions being sodium hydride in THF at room temperature (Scheme 4).[6]

SYNLETT 2007, No. 16, pp 2587–2589
Advanced online publication: 12.09.2007
DOI: 10.1055/s-2007-986649; Art ID: D15407ST

Table 1 Generation of Amides **8a**–**g** and 2,6-Diazaspiro[3.3]heptan-1-ones **1a**–**g**

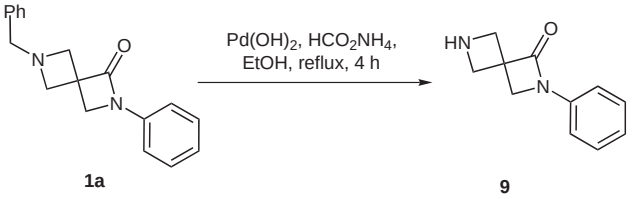
Entry	Amine R^1NH_2	Step 1 **8a**–**g** (yield, %[a])	Step 2 **1a**–**g** (yield, %[a])
1		**8a** (91)	**1a** (97)
2		[b]	**1b** (76)
3		**8c** (96)	**1c** (82)
4		**8d** (48)	**1d** (66)
5		**8e** (50)	**1e** (67)
6		**8b**	**1f** (46)[c]
7		**8g** (58)	**1g** (68)

[a] Yields refer to fully characterised and pure compounds.
[b] Combined yield, compounds **8b** and **8d** were used crude in subsequent cyclisation step.
[c] Heating required at 70 °C for 3 h to effect cyclisation.



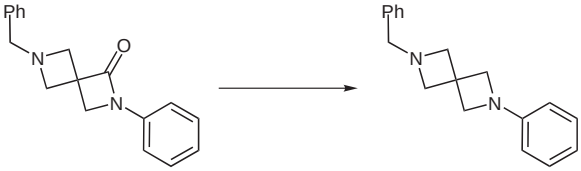
Scheme 4 Synthesis of 2,6-diazaspiro[3.3]heptan-1-ones **1a**–**g**

The following compounds **1a**–**g** have been prepared as representative examples to illustrate the applicability of the reaction sequence through reaction with primary alkyl amines as well as electron-rich, electron-poor, and sterically hindered anilines (Table 1).



Scheme 5 Hydrogenolysis of benzyl group

Table 2 Reduction of 2,6-Diazaspiro[3.3]heptan-1-one **1a**



Entry	Reagent conditions	Conversion (%)[a]	Comment
1	$LiAlH_4$, THF, 40 °C	0	1 equiv
2	BH_3·THF, 40 °C	0	Reversible complexation to borane observed
3	$LiAlH_4$, $AlCl_3$, Et_2O, 40 °C	38	1.5 equiv 55% recovered **1a**
4	$LiAlH_4$, $AlCl_3$, Et_2O, 40 °C	58	3 equiv 32% recovered **1a**
5	$LiAlH_4$, $AlCl_3$, Et_2O, 40 °C	78	5 equiv 15% recovered **1a**

[a] Yields refer to fully characterised and pure compounds.

To enable further elaboration,[7] the benzyl group can be readily removed. For example, **1a** can be converted into **9** in 74% yield using transfer hydrogenation conditions (Scheme 5).[8]

In order to convert **1a** into the corresponding 2,6-diazaspiro[3.3]heptane **2a**,[9] a series of reducing agents was tested and the results are summarised in Table 2.

Surprisingly, **1a** proved resistant to reduction with lithium aluminium hydride and only unreacted starting material was recovered after heating at 40 °C for 2 hours. Borane in THF produced a highly crystalline and insoluble borane complex[10] and no evidence of reduction was observed. The unreactive complex could be converted back into **1a** by heating in methanolic ammonia solution. Clean conversion of **1a** into **2a** was observed by the reduction with the $LiAlH_4/AlCl_3$ complex,[11] although 5 equivalents of the reagent were required for satisfactory conversion.[12,13]

In summary, a concise synthesis of the chemically novel, readily functionalised 2,6-diazaspiro[3.3]heptan-1-one ring system has been reported as well as its conversion into the substituted 2,6-diazaspiro[3.3]heptane ring system. Work is continuing within our laboratory in this area and we will report on further studies in the future.

References and Notes

(1) For some recent applications of parallel synthesis in drug design, see: (a) Habashita, H.; Kokubo, M.; Hamano, S.-I.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140. (b) Edwards, P. J. *IDrugs* **2006**, *9*, 347. (c) Lu, S.-F.; Chen, B.; Davey, D.; Dunning, L.; Jaroch, S.; May, K.; Onuffer, J.; Phillips, G.; Subramanyam, B.; Tseng, J.-L.; Wei, R. G.; Wei, M.; Ye, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1883.

(2) To the best of our knowledge the azetidine-derived spirocyclic β-lactam (2,6-diazaspiro[3.3]heptan-1-one) ring system has not previously been prepared in the chemical literature. Proline-derived spirocyclic β-lactams are represented in the chemical literature and are useful as β-turn mimetics. For examples, see: (a) Macías, A.; Morán Ramallal, A.; Alonso, E.; del Pozo, C.; González, J. *J. Org. Chem.* **2006**, *71*, 7721. (b) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97. (c) Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766. (d) Alonso, E.; Lopez-Ortiz, F.; del Pozo, C.; Peralta, E.; Macias, A.; Gonzalez, J. *J. Org. Chem.* **2001**, *66*, 6333. For recent syntheses of piperidine-derived spirocyclic β-lactams, see: (e) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325. (f) Macias, A.; Alonso, E.; del Pozo, C.; Gonzalez, J. *Tetrahedron Lett.* **2004**, *45*, 4657. (g) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.

(3) (a) Bartholomew, D.; Stocks, M. J. *Tetrahedron Lett.* **1991**, *32*, 4795. (b) Optimised experimental conditions for the synthesis of **4** from the readily available precursor **3** are given. To cold EtOH (250 mL) at 0–5 °C was added Na metal (25.5 g, 1.5 equiv). The solution was allowed to warm to r.t. and was stirred for 1 h. To the reaction mixture was added a solution of compound **3** (190 g) in EtOH (100 mL) and the reaction was stirred for 14 h at r.t. The reaction mixture was slowly poured into ice-cold H_2O and extracted with PE (3 × 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude reaction product (110 g) was dissolved in toluene (800 mL) and K_2CO_3 (110 g, 2.2 equiv) added. The reaction mixture was refluxed for 16 h, cooled, and filtered. The residue was purified over silica gel eluting with 8% EtOAc in isohexane to give 1-benzyl-3-chloromethylazetidine-3-carboxylic acid ethyl ester (60 g) as pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 5 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.05 (s, 2 H), 3.64 (s, 2 H), 3.43 (d, *J* = 8.5 Hz, 2 H), 3.31 (d, *J* = 8.5 Hz, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

(4) Hydrolysis of **4** was previously reported to afford **6**; see ref. 3 for details.

(5) Compound **7** can be stored under dry nitrogen for up to four weeks.

(6) **Preparation of 1a**
To a stirred suspension of NaH (60% in mineral oil, 0.349 g) in THF (30 mL) was added 1-benzyl-3-chloromethyl-azetidine-3-carboxylic acid phenylamide (2.5 g) in THF (15 mL) and the mixture stirred for 2 h at r.t. Then, H_2O was added and the mixture was extracted with EtOAc. The organic phase was dried with anhyd $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography eluting with EtOAc to give 6-benzyl-2-phenyl-2,6-diazaspiro[3.3]heptan-1-one (2.14 g) as a white solid after recrystallisation from Et_2O–*i*-hexane; mp 122–123 °C. MS: *m/z* = 279.2 $[M + H]^+$; 99.3% purity. Anal. Calcd. for: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.57; H, 6.55; N, 10.13. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 9 H), 7.10–7.06 (m, 1 H), 3.86 (s, 2 H), 3.66 (s, 2 H), 3.61 (d, *J* = 1.5 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 138.0, 137.4, 129.1, 128.5, 128.4, 127.2, 123.9, 116.3, 62.9, 58.2, 51.6, 50.3.

(7) The free azetidine **9** can be readily functionalised by reaction with, for example: (a) acid chlorides to generate amides; (b) aldehydes to generate N-substituted alkyl amines; (c) isocyanates to generate ureas and (d) sulfonyl chlorides to generate sulfonamides under standard reaction conditions.

(8) Analysis of 2-phenyl-2,6-diazaspiro[3.3]heptan-1-one (**9**): mp 149–150 °C. GC-MS: *m/z* = 188 $[M]^+$; 100% pure. Anal. Calcd for: C, 70.19; H, 6.43; N, 14.79. Found: C, 70.05; H, 6.51; N, 14.79. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 4 H), 7.11–7.07 (m, 1 H), 4.27 (d, *J* = 9.6 Hz, 2 H), 3.86 (s, 2 H), 3.79 (d, *J* = 9.6 Hz, 2 H), 1.83 (s, 1 H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 166.1, 138.0, 129.1, 124.0, 116.3, 54.1, 51.7, 51.5.

(9) For a recent synthesis of this interesting ring system, see: (a) Hillier, M. C.; Chen, C.-Y. *J. Org. Chem.* **2006**, *71*, 7885. (b) For an application of the use of 2,6-diaza-spiro[3.3]heptanes in drug discovery, see: Engel, W.; Eberlein, W.; Trummlitz, G.; Mihm, G.; Doods, H.; Mayer, N.; De Jonge, A. EP 417631, **1991**.

(10) For some examples of the reduction of β-lactams to azetidines, see: (a) Brayer, J. L.; Alazard, J. P.; Thal, C. *Tetrahedron* **1990**, *46*, 5187. (b) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263. (c) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339. (d) Ojima, I.; Yamato, T.; Nakahashi, K. *Tetrahedron Lett.* **1985**, *26*, 2035.

(11) (a) Van Brabandt, W.; De Kimpe, N. *Synlett* **2006**, 2039. (b) Van Elburg, P. A.; Reinhoudt, D. N. *Heterocycles* **1987**, *26*, 437.

(12) The high stoichiometry of the reduction makes this reaction incompatable with library synthesis. However, a new synthesis of 2,6-diazaspiro[3.3]heptanes, amenable to library synthesis, will be communicated separately.

(13) **Preparation of 2a**
To a stirred solution of $AlCl_3$ (0.20 g) in Et_2O (3 mL) was added $LiAlH_4$ in Et_2O (1 M, 1.49 mL) and the mixture stirred at 40 °C for 15 min before being cooled to r.t. and 6-benzyl-2-phenyl-2,6-diazaspiro[3.3]heptan-1-one (0.139 g) in THF (1 mL) was added. The reaction was warmed to 40 °C for 1 h before being cooled to r.t. Then, H_2O (0.2 mL), followed by 15% NaOH solution (0.2 mL), and finally H_2O (0.6 mL) were added. The mixture was stirred for 15 min and filtered. The solution was concentrated and the residue purified by chromatography on silica gel eluting with 2–5% 0.7 N NH_3 in MeOH in CH_2Cl_2 to afford 2-benzyl-6-phenyl-2,6-diazaspiro[3.3]heptane (0.077 g) as an oil. MS: *m/z* = 265.17 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 7 H), 6.73 (t, *J* = 7.5 Hz, 1 H), 6.44 (d, *J* = 7.0 Hz, 2 H), 3.94 (s, 4 H), 3.60 (s, 2 H), 3.40 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 137.7, 128.8, 128.4, 128.3, 127.1, 117.6, 111.5, 64.4, 63.5, 62.2, 34.7.