Synthesis of a Highly Functionalised Azepine via a New TBSOTf-Mediated Cyclisation of a Terminal Formamide

Stefan Heuser*

Lilly Forschung GmbH, a Division of Eli Lilly Research Laboratories, Essener Bogen 7, 22419 Hamburg, Germany
Fax +49(40)52724601; E-mail: heuser_stefan@lilly.com

Received 21 December 2006

Abstract: The synthesis of a highly functionalised azepine which can be further derivatised by common chemical transformations is described herein. The present synthesis comprises high-yielding reaction steps and features a new method for the synthesis of azepines via TBSOTf-mediated cyclisation of terminal formamides.

Key words: azepines, enamines, cyclisation, condensation, heterocycles

Azepines are widely found in natural products that often show interesting biological profiles. Representative examples are brasilibactin A,[1] nocardimicins,[2] A-503083[3] and bengamide,[4] which show cytotoxic, M_3 receptor binding inhibitory, bacterial translocase I inhibitory or methionine aminopeptidase inhibitory activities, respectively. Furthermore, the azepine moiety is an important pharmacophore in a number of drug candidates being investigated in pharmaceutical industry (Figure 1). Equally noteworthy is its application as a β-turn mimetic in peptidomimetic drug development approaches.[5]

Despite its importance, there is only a limited number of syntheses that conveniently form the azepine ring.[6] Among the most frequently used methodologies is the Beckmann rearrangement of oxime derivatives,[7] and

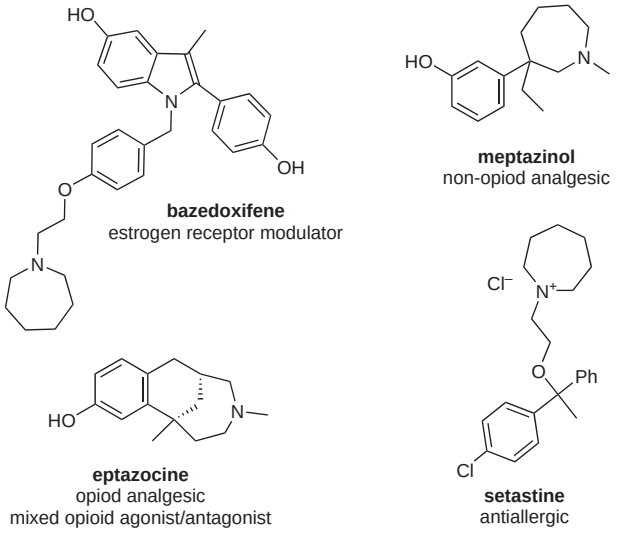
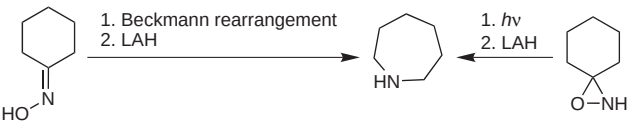


Figure 1 Azepine-containing pharmaceutical compounds

SYNLETT 2007, No. 3, pp 0497–0499
Advanced online publication: 07.02.2007
DOI: 10.1055/s-2007-967942; Art ID: G33406ST

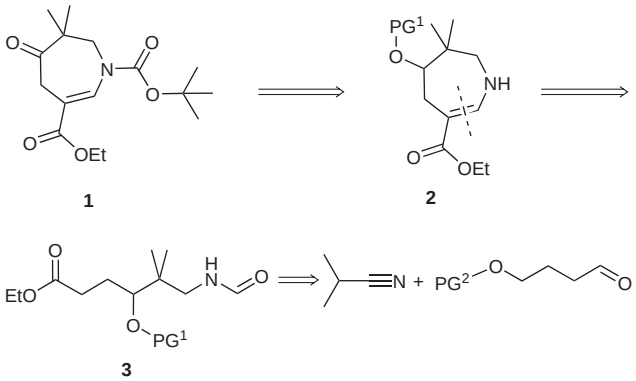
Aubé et al. developed a photochemical rearrangement employing oxaziridine derivatives[8] (Scheme 1). The lactams, which are obtained in both cases, are then reduced with, for example, lithium aluminium hydride.



Scheme 1 Classic azepine syntheses

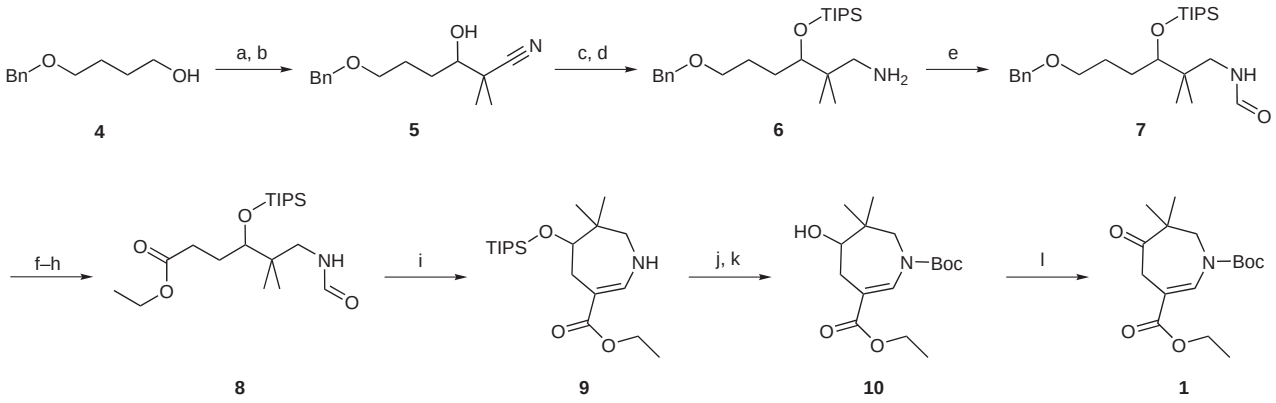
Very recently, Houpis et al.[9] and Diederich et al.[10] independently developed elegant methodologies based on ring-closing metathesis.

In the course of our ongoing efforts to explore new chemical space, we became interested in the syntheses of 6,6-dimethyl-5-oxo-4,5,6,7-tetrahydroazepine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester (**1**, Scheme 2). To the best of our knowledge, such highly substituted azepine ring systems are little described in the literature. If the methods mentioned above would furnish the desired compound at all, tedious, multistep syntheses would be required. We therefore planned to accomplish the synthesis via an intramolecular enamine formation as the key step by cyclisation of formamide **3**.



Scheme 2 Retrosynthetic analysis

We started our synthesis by oxidising commercially available benzyl-protected 1,4-butanediol **4** with Dess–Martin periodinane.[11] The desired aldehyde was obtained in quantitative yield and was directly used for the following nucleophilic addition of isobutyronitrile[12] to give **5** in 67% yield (Scheme 3). Protection of the secondary



Scheme 3 *Reagents and conditions*: (a) 1.1 equiv Dess–Martin periodinane, r.t., 90 min, CH_2Cl_2, quant.; (b) 1 equiv isobutyronitrile, 1 equiv LDA, –78 °C to r.t., 2 h, THF, 67%; (c) 1.1 equiv NaH, 0 °C, 30 min, then 1.3 equiv TIPSCl, 50 °C, 16 h, THF, quant.; (d) 3 equiv DIBAL-H, –30 °C to –20 °C, 30 min, then 6 equiv $NaBH_4$, toluene, quant.; (e) ethylformate, reflux, 16 h, quant.; (f) H_2 (1 bar), 10% Pd/C, r.t., 1 h, EtOAc, 90%; (g) 0.02 equiv $RuCl_3 \cdot H_2O$, 3 equiv $NaIO_4$, r.t., 2 h, CCl_4, MeCN, H_2O, 88%; (h) 1.1 equiv EtI, 1.5 equiv K_2CO_3, r.t., 2.5 d, acetone, quant.; (i) 7 equiv TBSOTf, 15 equiv Et_3N, r.t., 5 d, CH_2Cl_2, 51%; (j) 5 equiv $(Boc)_2O$, 1.2 equiv Et_3N, 1.2 equiv DMAP, r.t., 16 h, THF, not isolated; (k) 2 equiv TBAF, r.t., 20 h, THF, 45% (2 steps); (l) 1.2 equiv Dess–Martin periodinane, r.t., 2 h, CH_2Cl_2, 92%.

alcohol succeeded in quantitative yield using triisopropylsilyl chloride (TIPSCl) at 50 °C. The reduction of the nitrile to a primary amine was first attempted using LAH, but unfortunately under these reaction conditions the TIPS group was cleaved off. Here a combination of DIBAL-H and $NaBH_4$ was much milder and the desired amine **6** was obtained quantitatively without any deprotection of the alcohol.[13] Formylation of the amino group and hydrogenolytic cleavage of the benzyl ether afforded the free primary alcohol in 90% yield. Its oxidation to the corresponding carboxylic acid was achieved using $RuCl_3 \cdot H_2O$ and $NaIO_4$[14] which was followed by immediate esterification with ethyl iodide and potassium carbonate. For the cyclisation of **8** we tried several procedures with limited literature precedence. Thus, in our first attempts we used phosphorylchloride to form the enamine functionality via an intramolecular condensation,[15] but under varying conditions only decomposition occurred. The same was found using sodium ethanolate or potassium *tert*-butanolate.[16] We then envisioned a two-step approach, first preparing an intermediate silyl-protected aminal using *tert*-butyldimethylsilyl triflate (TBSOTf)[17] and then to eliminate silanol to finally obtain enamine **9**. Surprisingly, after five days reaction time compound **9** was obtained in only one step using an excess of TBSOTf in dichloromethane.[18] This reaction, to our knowledge, is undescribed in literature and should in general be applicable to the synthesis of cylic enamines containing five, six or more ring atoms, and which have an electron-withdrawing group in the 3-position. Alcohol **10** was then obtained by protection of the amino group and reaction with tetrabutylammonium fluoride. Another Dess–Martin oxidation finally afforded 6,6-dimethyl-5-oxo-4,5,6,7-tetrahydroazepine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-ethyl ester (**1**) in 92% yield.[19]

In conclusion, we have synthesised the desired azepine **1** in 11 steps and in 11% overall yield, starting from readily available starting materials. The key step in the synthesis was the cyclisation of formamide **8** using TBSOTf in dichloromethane. This protocol promises to be superior to traditional condensation methods with regard to yield, reaction conditions and functional group tolerance. Thereby it offers a new methodology for the synthesis of azepines having an electron-withdrawing group in the 3-position, which previously were not easily accessible via known methods. This protocol should in general be applicable to the synthesis of cyclic enamines with other ring sizes, which is going to be the subject of further investigations.

References and Notes

(1) Tsuda, M.; Yamakawa, M.; Oka, S.; Tanaka, Y.; Hoshino, Y.; Mikami, Y.; Sato, A.; Fujiwara, H.; Ohizumi, Y.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 462.
(2) Ikeda, Y.; Furumai, T.; Igarashi, Y. *J. Antibiot.* **2005**, *58*, 566.
(3) Muramatsu, Y.; Ohnuki, T.; Ishii, M. M.; Kizuka, M.; Enokita, R.; Miyakoshi, S.; Takatsu, T.; Inukai, M. *J. Antibiot.* **2004**, *57*, 639.
(4) Towbin, H.; Bair, K. W.; DeCaprio, J. A.; Eck, M. J.; Kim, S.; Kinder, F. R.; Morollo, A.; Mueller, D. R.; Schindler, P.; Song, H. K.; van Oostrum, J.; Versace, R. W.; Voshol, H.; Wood, J.; Zabludoff, S.; Phillips, P. E. *J. Biol. Chem.* **2003**, *278*, 52964.
(5) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039.
(6) For a review on azepines and their syntheses, see: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.
(7) (a) Sainsbury, M.; Mahon, M. F.; Williams, C. S.; Naylor, A.; Scopes, D. I. C. *Tetrahedron* **1991**, *47*, 4195.
(b) Sainsbury, M.; Williams, C. S.; Naylor, A.; Scopes, D. I. C. *Tetrahedron Lett.* **1990**, *31*, 2763.
(8) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Velde, D. V. *J. Am. Chem. Soc.* **1990**, *112*, 4879.
(9) Delhaye, L.; Merschaert, A.; Diker, K.; Houpis, I. N. *Synthesis* **2006**, 1437.
(10) Brass, S.; Gerber, H.-D.; Dörr, S.; Diederich, W. E. *Tetrahedron* **2006**, *62*, 1777.
(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(12) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.
(13) Gallagher, T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347.
(14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(15) (a) Kato, T.; Chiba, T.; Okada, T. *Chem. Pharm. Bull.* **1979**, *27*, 1186. (b) Deady, L. W.; Rogers, M. L.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2005**, *13*, 1341.
(16) Verboom, W.; Orlemans, E. O. M.; Berga, H. J.; Scheltinga, M. W.; Reinhoudt, D. N. *Tetrahedron* **1986**, *42*, 5053.
(17) Very recently Hoye et al. published their remarkable results on silylative Dieckmann-like cyclisations of ester-amides which yield silylated aminals using the same reagent combination. They also discuss the mechanism of this reaction in more detail: Hoye, T. R.; Dvornikovs, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191.
(18) **Procedure for the Preparation of 9.**
To a solution of formamide **8** (353 mg, 912 μmol) in 10 mL anhyd CH_2Cl_2 were added Et_3N (1.39 g, 1 mL, 13.7 mmol) and TBSOTf (1.73 g, 1.5 mL, 6.53 mmol). After stiring at r.t. for 5 d 20 mL CH_2Cl_2 were added and the solution was washed successively with sat. $NaHCO_3$ solution and sat. NH_4Cl solution. The organic phase was then filtered through a hydrophobic filter and concentrated. Purification of the residue via flash chromatography on silica eluting with 1:3 EtOAc in hexane afforded 170 mg (51%) of **9** as a pale yellow oil.
^{1}H NMR: (300 MHz, DMSO-d_6): δ = 0.82 (s, 3 H), 1.01 (br s, 24 H), 1.12 (t, ^3J = 7.1 Hz, 3 H), 2.49 (m, 1 H), 2.61 (m, 2 H), 3.13 (dd, ^2J = 11.9 Hz, ^3J = 3.1 Hz, 1 H), 3.76 (dd, ^2J = 11.9 Hz, ^3J = 2.2 Hz, 1 H), 3.96 (m, 2 H), 6.54 (br s, 1 H), 7.32 (d, ^3J = 6.5 Hz, 1 H). MS (ESI): *m/z* = 370 [M + H$^+$].
(19) **Analytical Data for 1.**
^{1}H NMR: (300 MHz, DMSO-d_6): δ = 0.80 (s, 3 H), 0.95 (s, 3 H), 1.19 (t, ^3J = 7.1 Hz, 3 H), 1.44 (s, 9 H), 3.09 (d, ^2J = 14.2 Hz, 1 H), 3.31 (m, 1 H), 3.67 (d, ^2J = 14.2 Hz, 1 H), 4.09 (q, ^3J = 7.1 Hz, 2 H), 4.80 (m, 1 H), 7.82 (s, 1 H). MS (ESI): *m/z* = 336 [M + Na$^+$].