Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 4847–4850
Tetrahedron Letters

Synthesis of a novel series of 4,4-disubstituted 2,3,4,7-tetrahydroazepines

Mario Barberis, Pablo García-Losada, Sehila Pleite, Juan Ramón Rodríguez, José Francisco Soriano and Javier Mendiola*

Lilly S.A., Avda de la Industria 30, Alcobendas-Madrid 28108, Spain

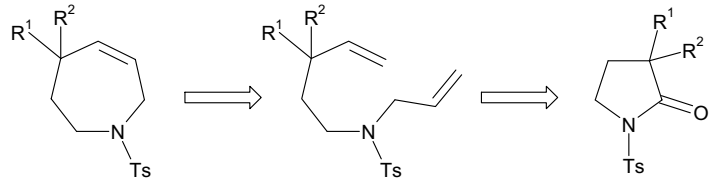
Received 13 April 2005; revised 12 May 2005; accepted 17 May 2005
Available online 4 June 2005

Abstract—A general, simple and straightforward strategy for the synthesis of a novel series of 4,4-disubstituted 2,3,4,7-tetrahydroazepines is described. This route involves a one-pot Wittig olefination/N-allylation process on a five-membered hemi-aminal followed by a final ring closing metathesis reaction.

Alkaloids represent a significant subset of all biologically active compounds,[1] and so the development of new general methods for their construction remains an important goal in organic synthesis. Such is the case of azepines, which in the past few years have been the subject of an increasing number of published synthetic methods due to their biological activities. These N-containing seven-membered rings have been readily obtained in the past by condensation reactions or by rearrangement of three-, five- and six-membered rings following Beckmann and Schmidt's conditions.[2] There is ample precedent for the selective ring expansion of mixtures of *syn* and *anti* oximes, under both harsh[3] and weak[4] acidic conditions. An alternative to these routes is the very popular approach of ring closing metathesis (RCM)[5] that uses the ruthenium alkylidene catalysts that have been developed by Grubbs and co-workers.[6] The application of this novel methodology has continually increased over the last decade due to the ease of synthesis by metathesis of carbo- or heterocyclic seven-membered rings.[7] Below, we present a novel approach to this powerful tool in organic synthesis, which widens its application to other acyclic di-olefins.

The work we describe here details our studies on the synthesis of a novel series of 4,4-disubstituted 2,3,4,7-tetrahydroazepines **1**, involving, as key steps, a one-pot Wittig reaction/N-allylation process followed by final ring closing metathesis reaction (Fig. 1).

Alkylation reactions on analogous pyroglutamate rings have been previously reported by our research group.[8] Applying this methodology we envisaged a simple and straightforward strategy starting from



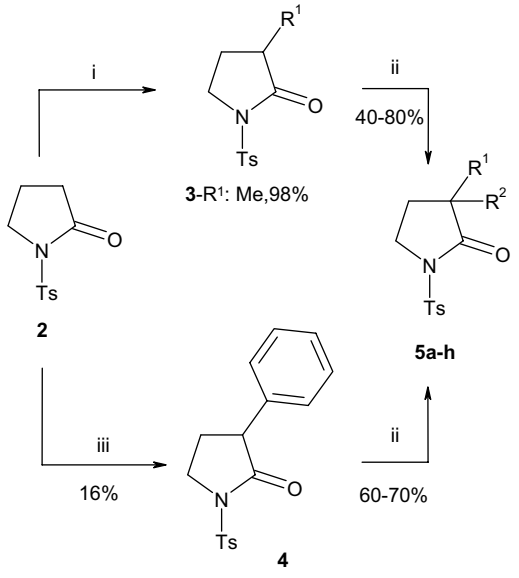
1

Figure 1.

Keywords: Azepine; Metathesis; Pyrrolidinone; Wittig.
* Corresponding author. Tel.: +34 91 623 36 65; fax: +34 91 663 34 11; e-mail: mendiola_javier@lilly.com

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.05.088

N-tosylpyrrolidinone,[9] which is easily obtained by reaction of commercially available pyrrolidinone with tosyl chloride. Substitution at C-3 was achieved in two different ways depending on the nature of the R group. Thus, to incorporate alkyl or benzyl groups a one-pot process was carried out by reaction with LiHMDS as base and R^1–Br, and subsequent reaction with one additional equivalent of base and R^2–Br. When one of the alkyl groups was a methyl, initial substitution with MeI was more convenient as it could be easily controlled to prevent disubstitution. Thus, treatment of N-tosylpyrrolidinone **2** with LiHMDS followed by slow addition of MeI provided the monoalkylated pyrrolidinone **3**[10] in 98% yield (Scheme 1).



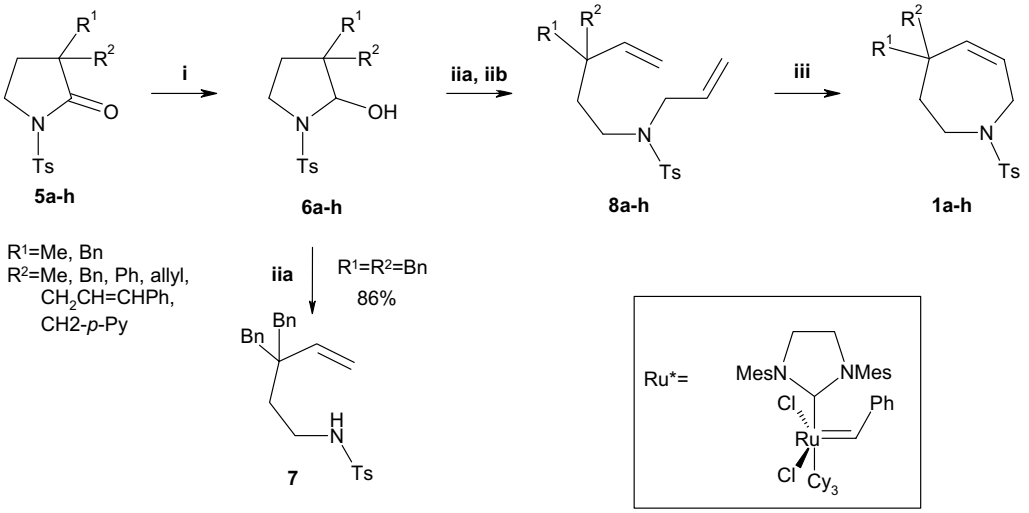
Scheme 1. Reagents and conditions: (i) LiHMDS, R^1–Br, THF, −78 °C; (ii) LiHMDS, R^2–Br, THF, −78 °C; (iii) Ph–Br, Pd_2dba_3, BINAP, LiHMDS, dioxane, 70 °C.

On the other hand, monoarylated pyrrolidinone **4** was prepared albeit in low yield, employing Hartwig conditions.[11] Unfortunately, attempts to improve the reported yield by changing the base, solvent, catalyst and temperature failed. Treatment of **4** with LiHMDS and R^2–Br provided new tosylpyrrolidin-2-ones **5g**,**h** (Scheme 2).

Reduction of pyrrolidinones **5a**–**h** to pyrrolidinols **6a**–**h** was conveniently carried out with Dibal-H, the best conditions being those employing the reagent as a 1 M toluene solution added to a THF solution of the lactam at 0 °C. When R^1 and R^2 were different, a mixture of diastereomers was isolated, showing a complex ^{1}H NMR spectrum. No attempt was made to separate these isomers, which were carried to the next step without further purification.

Olefination of pyrrolidinol[12] **6** was investigated next. When **6a** was reacted with methylene triphenylphosphorane, the Wittig product **7** was obtained in good yield. Next, a one-pot process was attempted by combining the olefination and following allylation reactions to reduce the total number of synthetic steps.[13] Thus, once olefination was complete as determined by LCMS, the amino group was captured by treatment with 3 equiv of allyl bromide. Compounds **8a**–**h** were isolated in 41–73% yield, employing this one-pot methodology. This is the first time that these two processes have been combined in a single pot to afford a tertiary amine from pyrrolidinol derivatives.

Finally, a metathesis reaction was applied as the ring closure event. Reaction of **8a**–**h** in refluxing dichloromethane in the presence of 10 mol % of 1,2-dimesitylpyrrolidin-2-yl-Ru=CHPh$(Cl)_2(PCy_3)$ catalyst afforded the corresponding 4,4-disubstituted 2,3,4,7-tetrahydroazepine[14] **1a**–**h** in moderate to excellent yields. This methodology allows the incorporation of a variety of substituent types at the 4-position of the resulting

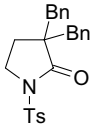
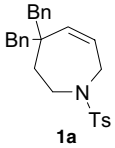
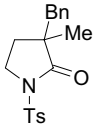
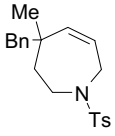
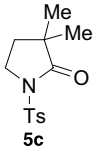
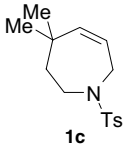
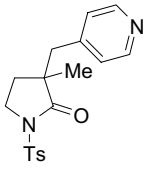
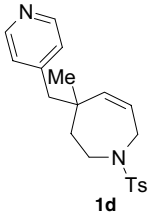
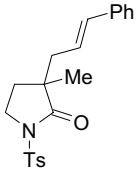
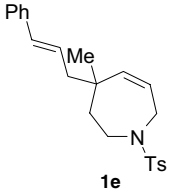
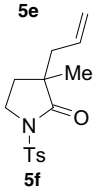
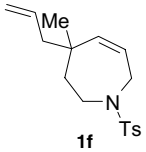
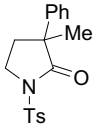
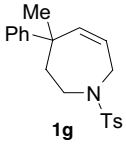
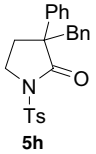
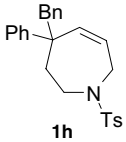


Scheme 2. Reagents and conditions: (i) Dibal-H/toluene/1 M, THF, 0 °C; (ii) (a) Ph_3PMeBr, *t*-BuOK, THF, 0 °C; (b) $BrCH_2CH{=}CH_2$, rt; (iii) 1,2-dimesitylpyrrolidin-2-yl-Ru=CHPh$(Cl)_2(PCy_3)$ (10 mol %), CH_2Cl_2, 50 °C.

azepine derivative: methyl, benzyl, 4-pyridylmethyl, cinnamyl, allyl and phenyl in combination with methyl and benzyl groups. In all these cases, the metathesis reaction worked in excellent yield (70–98%) except for **1f**, which was isolated in only moderate yield (53%). In this reaction, only the seven-membered ring metathesis product was observed (no eight-membered ring was detected) together with a secondary product formed by reaction between the terminal olefin of **1f** and the olefin contained in the ruthenium Grubbs catalyst. This product was isolated as **1e** in 10% yield (Table 1).

The methodology here described constitutes a general, versatile and straightforward route for the synthesis of

Table 1.

Entry	Pyrrolidinone	Reduction[a] (%)	Wittig[b] (%)	Metathesis[c] (%)	Azepine
1	 **5a**	92	73	79	 **1a**
2	 **5b**	99	56	82	 **1b**
3	 **5c**	70	65	70	 **1c**
4	 **5d**	90	82	73	 **1d**
5	 **5e**	71	41	97	 **1e**
6	 **5f**	99	72	53[d]	 **1f**
7	 **5g**	90	65	98	 **1g**
8	 **5h**	75	67	73	 **1h**

[a] Dibal-H/toluene/1 M, THF, 0 °C.
[b] (i) Ph_3PMeBr, *t*-BuOK, THF, 0 °C; (ii) $BrCH_2CH{=}CH_2$, rt.
[c] 1,2-Dimesitylpyrrolidin-2-yl-Ru=CHPh$(Cl)_2(PCy_3)$ (10 mol %), CH_2Cl_2, 50 °C.
[d] 10% of **1e** was isolated too.

new 4,4-disubstituted azepines as novel heterocyclic products. Substitution was achieved employing the methodology described by our research group; the next step involves a one-pot Wittig/N-allylation process followed by ring closing metathesis reaction, affording a concise and easy approach to the synthesis of 4,4-disubstituted azepine derivatives.

Acknowledgements

We wish to thank Dr. Jesús Ezquerra, Dr. Ulf Tilstam, Dr. Ioannis Houpis for their encouragement, Dr. Susana María García-Cerrada for her assistance, and we also thank Dr. Carmen Somoza, Dr. Luis Casarrubios and Dr. Ivan Collado for helpful discussions.

References and notes

1. For leading references to the synthesis and structure of natural products containing nitrogen heterocycles, see: (a) *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Cordell, G. A., Eds.; Academic: New York, 1992; (b) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1988; (c) Belen'Kii, L. J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1988; Vol. 44, Chapter 4; (d) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984.
2. *Comprehensive Heterocyclic Chemistry*; Smalley, R. K., Ed.; Pergamon: New York, 1984.
3. For examples, see: (a) Fleming, I.; Woodward, R. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1653; (b) Billett, E. H.; Fleming, I.; Hanson, S. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1661; (c) Tamura, Y.; Kita, Y.; Terashima, M. *Chem. Pharm. Bull.* **1971**, 529.
4. Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693.
5. For reviews, see: (a) Grubss, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (e) Giessert, A. J.; Diver, S. T. *Chem. Rev.* **2004**, *104*, 1317; (f) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1; (g) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176–204; (h) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
6. (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858; (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
7. For examples, see: (a) Fuerstner, A.; Guth, O.; Dueffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811; (b) Wipf, P.; Rector, S.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848; (c) Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295; (d) Cachoux, F.; Ibrahim-Ouali, M.; Santelle, M. *Syn. Lett.* **2002**, *12*, 1987; (e) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2378; (f) Frederiksen, S. M.; Grue-Sorensen, G. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 773.
8. (a) Ezquerra, J.; Pedregal, C.; Rubio, A.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665; (b) Ezquerra, J.; Pedregal, C.; Rubio, A.; Vaquero, J. J.; Matía, M. P.; Martín, J.; Díaz, A.; García-Navío, J. L.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 4327.
9. (a) Katagiri, N.; Muto, M.; Nomura, M.; Higashikawa, T.; Kaneko, C. *Chem. Pharm. Bull.* **1991**, *39*, 1112; (b) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 1904; (c) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257.
10. Padwa, A.; Kissell, W. S.; Eidell, C. K. *Can. J. Chem.* **2001**, *79*, 1981.
11. Shaughnessy, B.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.
12. (a) Shishido, K.; Sukegawa, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 993; (b) Takasuka, M.; Yamakawa, M.; Ohtani, M. *J. Med. Chem.* **1991**, *34*, 1885; (c) Shishido, K.; Sukegawa, Y.; Fukumoto, K.; Kametani, T. *Heterocycles* **1986**, *24*, 641; (d) Ihara, M.; Kirihara, T.; Kawaguchi, A.; Tsutura, M.; Keiichiro, F.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1719.
13. For the synthesis of *N*-allyl-*N*-(3,3-dimethylpent-4-enyl)-4-methylbenzenesulfonamide **8c**: A mixture of Bu^{t}OK (11.7 mmol, 4.19 g) and PPh_3PMeBr (11.74 mmol, 1.32 g) in THF (80 mL) was stirred at rt for 20 min. Compound **6c** (3.74 mmol, 1.0 g) in THF (15 mL) was added dropwise and the reaction mixture was stirred at rt for 1 h. Afterwards, allyl bromide (11.22 mmol, 1.8 mL) was added and stirred for 30 min. EtOAc was added, washed with brine and dried over Na_2SO_4. It was concentrated under reduced pressure and the brown oil was purified by flash chromatography (silica gel, ethyl acetate–hexane 5:95). Compound **8c** (741 mg, 65% yield) was isolated as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 6H), 1.60–1.49 (m, 2H), 2.41 (s, 3H), 3.06–3.00 (m, 2H), 3.77 (m, 2H), 4.93–4.85 (m, 2H), 5.19–5.11 (m, 2H), 5.72–5.59 (m, 2H), 7.29 (d, J = 7.7 Hz, 2H), 7.67 (d, J = 7.7 Hz, 2H).
14. For the synthesis of 4,4-dimethyl-1-tosyl-2,3,4,7-tetrahydro-1*H*-azepine **1c**: Grubb's catalyst (second generation, 10% mol, 41 mg) was added to a solution of **8c** (0.650 mmol, 200 mg) in CH_2Cl_2 (110 mL) and refluxed for 10 h. The solvent was removed under reduced pressure and purified by flash chromatography (silica gel column, ethyl acetate–hexane 5:95). Compound **1c** (127 mg, 70% yield) was isolated as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.68 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H), 3.32 (t, J = 6.1 Hz), 3.74 (d, J = 4.4 Hz), 5.51–5.39 (m, 2H), 7.28 (d, J = 7.7 Hz, 2H), 7.64 (d, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 29.6, 37.1, 38.7, 44.7, 45.4, 122.8, 127.6, 129.9, 135.8, 143.3, 143.5.