ORGANIC LETTERS

2006
Vol. 8, No. 14
3089−3091

A [3+3] Annelation Approach to Tetrahydropyridines

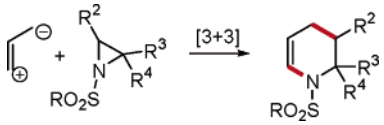
Lisa C. Pattenden,[†] Robert A. J. Wybrow,[†] Stephen A. Smith,[‡] and Joseph P. A. Harrity*,[†]

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, United Kingdom, and GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

j.harrity@sheffield.ac.uk

Received May 3, 2006

ABSTRACT



A stepwise [3+3] annelation sequence to tetrahydropyridines via addition of the BUchi Grignard to aziridines has been developed. These intermediates can be further functionalized with good regio- and stereocontrol and this methodology has been employed in the stereoselective formal synthesis of (–)-dihydropinidine.

Recent work in our labs has focused on exploiting aziridines in the stereoselective synthesis of functionalized piperidines through a [3+3] annelation strategy.[1,2] Initial studies centered on the employment of Trost's conjunctive reagent in tandem with a Pd catalyst to deliver a series of enantiopure 2-alkylpiperidines with an exomethylene moiety at C-5. Additionally, we have also discovered that an allylmagnesium based reagent can be used to deliver similar compounds, generally with greater efficiency. While TMM-based reagents **2** and **3** (Figure 1) have participated in addition to a broad range of aziridines, the exomethylene unit limited us somewhat to a single point of functionalization on the piperidine ring. Accordingly, we anticipated that synthon **4** would allow us to construct piperidines by a similar strategy, while providing the opportunity to deliver greater functionalization around the heterocycle. In this context, elegant studies by Craig and co-workers have shown that a sulfone-based three-carbon homologating agent can be used to achieve this goal.[3] We report herein that the addition of propionaldehyde homoenolate equivalent **5**[4] to aziridines represents a simple and practical alternative to these methods.[5] Furthermore, we demonstrate the employment of this methodology in target synthesis by the preparation of a representative cis 2,6-disubstituted piperidine alkaloid.

Pioneering studies by Büchi showed that 1,3-dioxolane based reagent **6** represented a competent propionaldehyde homoenolate equivalent, although it was found to decompose

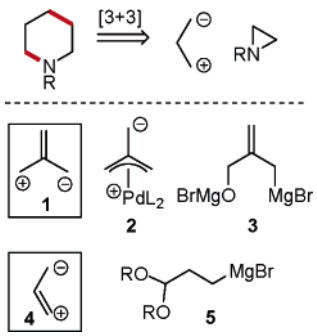


Figure 1. [3+3] cycloaddition to piperidines.

[†] University of Sheffield.
[‡] GlaxoSmithKline.

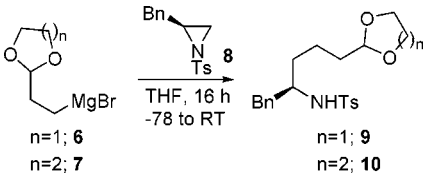
(1) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286. (c) Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5*, 3427. (d) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207. (e) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (f) Provoost, O. Y.; Hedley, S. J.; Hazelwood, A. J.; Harrity, J. P. A. *Tetrahedron Lett.* **2006**, *47*, 331.

(2) For reviews of alternative [3+3] annelations see: (a) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (b) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1333.

10.1021/ol0610789 CCC: $33.50
Published on Web 06/17/2006

at temperatures above 35 °C.[6] By way of contrast, the corresponding 1,3-dioxane **7** has been reported to be more thermally stable.[7] Given that both precursor alkylbromides are commercially available, we began our investigations by examining the efficiency of the addition of each Grignard reagent to readily available Bn-substituted aziridine **8**; our results are outlined in Table 1.

Table 1. Optimization of Aziridine Ring Opening[a]



entry	Grignard	additive	yield, %
1	**6**, 1.5 equiv	–	33
2	**6**, 5.0 equiv	–	80
3	**7**, 5.0 equiv	–	22[a]
4	**7**, 5.0 equiv	20 mol % CuBr·DMS	100
5	**6**, 2.0 equiv	20 mol % CuBr·DMS	98

[a] Reaction heated at reflux for 16 h.

Preliminary studies with the dioxolane-based reagent **6** were discouraging: a low yield of product **9** was observed which could only be improved by the use of a large excess of Grignard reagent (entries 1 and 2). Surprisingly, the dioxane-based reagent **7** proved to be inferior and a low yield of product was obtained even when a large excess of Grignard was used. Paquette and co-workers have reported that the dioxane reagent addition to enones can be promoted by Cu catalysis.[8] Indeed, the addition of 20 mol % of CuBr·DMS improved the efficiency of the Grignard addition to the aziridine and provided the desired product in quantitative yield (entry 4). Pleasingly, these conditions were also applicable to the dioxolane-based reagent, and further investigations showed that **9** could be furnished in high yield when only 2 equiv of Grignard reagent **6** were employed (entry 5).

We next turned our attention to the piperidine-forming reaction and opted to perform an in situ acid-catalyzed deprotection−cyclization protocol. This process was found to proceed efficiently with both acetal intermediates **9** and **10** to give the tetrahydropyridine **11**, without loss of enantiopurity over the two steps (Scheme 1).These studies highlighted that both Grignard reagents were suitable for the formation of tetrahydropyridines. However, the milder cyclization conditions employed in the 1,3-dioxolane system prompted us to investigate the scope of the annelation

Scheme 1

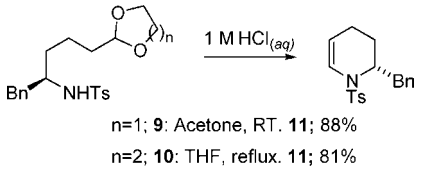
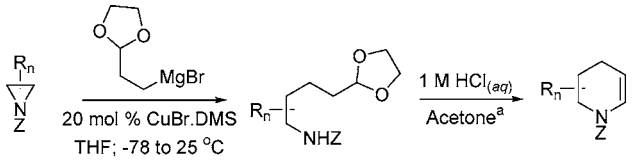
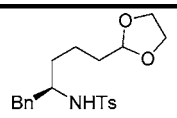
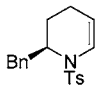
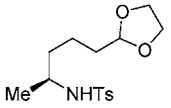
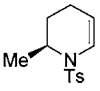
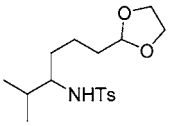
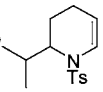
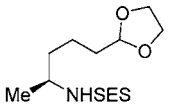
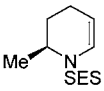
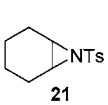
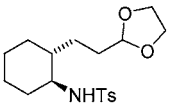
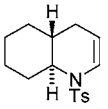
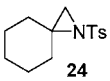
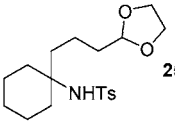
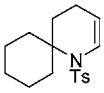
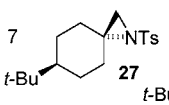
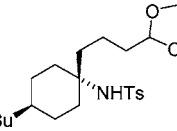
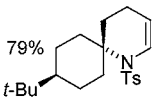


Table 2. Stepwise Annelation of Aziridines



entry	aziridine	addition product	piperidine
1		 **9**; 98%	 **11**; 88%
2		 **13**; 70%	 **14**; 84%
3		 **16**; 82%	 **17**; 98%
4		 **19**; 88%	 **20**; 62%
5		 **22**; 77%	 **23**; 63%[a]
6		 **25**; 90%	 **26**; 54%[a]
7		 **28**; 79%	 **29**; 83%

[a] Anhydrous HCl (1 M solution in ether) used in these cases.

(3) (a) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 55. (b) Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 58. (c) Adelbrecht, J.-C.; Craig, D.; Dymock, B. W.; Thorimbert, S. *Synlett* **2000**, 467. (d) Adelbrecht, J.-C.; Craig, D.; Thorimbert, S. *Tetrahedron Lett.* **2001**, *42*, 8369. (e) Adelbrecht, J.-C.; Craig, D.; Fleming, A. J.; Martin, F. M. *Synlett* **2005**, 2643.

(4) For a review of the chemistry of three-carbon homologating agents see: Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409.

(5) Büchi Grignard reagents have been added to epoxides to prepare pyrans: (a) Street, S. D. A.; Yeates, C.; Kocienski, P.; Campbell, S. F. *Chem. Commun.* **1985**, 1386. (b) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601. (c) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997.

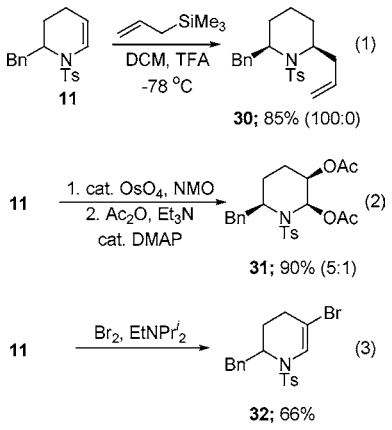
(6) (a) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122. (b) Sworin, M.; Neumann, W. L. *Tetrahedron Lett.* **1987**, *28*, 3217. (c) Ponaras, A. A. *Tetrahedron Lett.* **1976**, *7*, 3105.

(7) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.

(8) Leone-Bay, A.; Paquette, L. A. *J. Org. Chem.* **1982**, *47*, 4173.

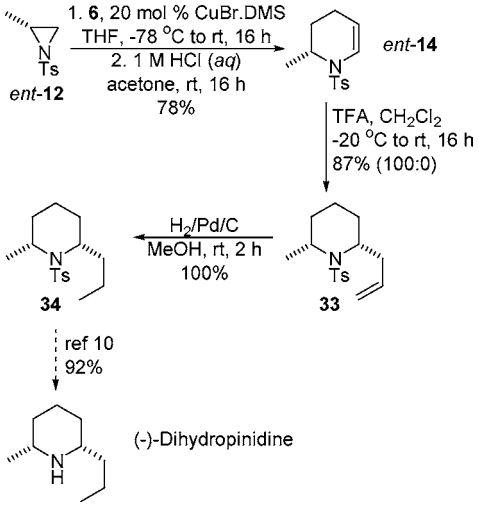
sequence with the Büchi Grignard reagent **6**, and our results are highlighted in Table 2. The Grignard addition reaction was found to proceed in good to excellent yield in all cases examined. The 2-alkyl- and 2,2′-spiroaziridines underwent regioselective addition at the methylene unit while the more hindered bicyclic aziridine participated smoothly in the addition reaction without any significant drop in yield (entry 5). In addition, we were pleased to find that this technique was compatible with a SES-protecting group (entry 4). Finally, the cyclization reactions provided the desired dihydropyridines in high yield, although they were generally found to be more sluggish in the formation of bicyclic and spirocyclic products (entries 5−7).

Having established the scope of the piperidine-forming reaction, we decided to perform some representative functionalization reactions. As outlined in eqs 1 and 2, both acid-mediated allylation and dihydroxylation processes were highly efficient and proceeded to give **30** and **31**, respectively, with good to excellent levels of diastereocontrol.[9] Moreover, regioselective substitution of the enamide moiety in **11** provided bromide **32** in good yield (eq 3).



Finally, we wished to exploit the enantiospecific piperidine-forming reaction and diastereoselective functionalization reactions in the synthesis of a piperidine alkaloid. Specifically, we envisaged that we could access the 2,6-disubstituted piperidine natural product (−)-dihydropinidine **34**[10] within a short synthetic route. Accordingly, we performed the Büchi Grignard addition−cyclization methodology on aziridine *ent*-**12** without purification and were delighted to find that piperidine *ent*-**14** was generated in excellent overall yield. The TFA-mediated allylation provided product **33** in excellent yield as a single diastereomer. Finally, hydrogenation provided compound **34**, thus completing a formal synthesis of (−)-dihydropinidine in high overall yield (Scheme 2).[11]

Scheme 2



In conclusion we report a stepwise annelation procedure to dihydropyridines that is complementary to our previously reported [3+3] strategies to functionalized piperidines. The further employment of this technique in target synthesis is currently ongoing and will be reported in due course.

Acknowledgment. We thank the EPSRC and GSK for financial support.

Supporting Information Available: Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0610789

(9) The stereochemistry of **30** was determined by X-ray crystallography; please refer to the Supporting Information for details.

(10) (a) Isolated from the Mexican Bean Beetle, *Epilachna varivestis*: Attygalle, A. B.; Xu, S.-C.; McCormick, K. D.; Meinwald, J.; Blankespoor, C. L.; Eisner, T. *Tetrahedron* **1993**, *49*, 9333. (b) For a recent asymmetric synthesis see: Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919.

(11) Lu, Z.-H.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 593.