ORGANIC LETTERS

2011
Vol. 13, No. 7
1686–1689

Synthesis and Functionalization of 3-Alkylidene-1,2-diazetidines Using Transition Metal Catalysis

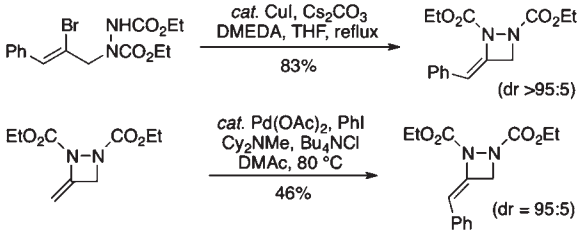
Michael J. Brown,[†] Guy J. Clarkson,[†] Graham G. Inglis,[‡] and Michael Shipman*,[†]

Department of Chemistry, University of Warwick, Coventry CV4 7AL, United Kingdom, and GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

m.shipman@warwick.ac.uk

Received January 21, 2011

ABSTRACT



An efficient two-step synthesis of a wide range of 3-methylene-1,2-diazetidines has been developed through application of a Cu(I)-catalyzed 4-*exo* ring closure. The double bond of this new class of strained heterocycle can be functionalized in a stereocontrolled manner by using palladium-catalyzed Heck reactions. Moreover, chemoselective reduction of 3-alkylidene-1,2-diazetidines gives access to saturated 1,2-diazetidines and vicinal diamines.

Four-membered heterocycles play an important role in modern medicine. For example, the highly strained β-lactam nucleus is a vital component of several essential classes of antibiotics including the penicillins, cephalosporins, carbapenems, and monobactams.[1] More recently, oxetanes[2] and azetidines[3] have emerged as important tools in medicinal chemistry primarily because of their useful physicochemical properties. Hence, the development of related four-membered heterocyclic templates for drug discovery programs seems attractive. For instance, the 1,2-diazetidine nucleus **1** (Figure 1), containing two adjacent nitrogen atoms within a four-membered ring, could have a number of potential uses. Indeed, they have been studied computationally as components of β-turn mimetics.[4] Unfortunately, systematic exploration of the practical applications of 1,2-diazetidines in medicinal chemistry has been severely hampered by a lack of high-yielding, general routes for their preparation and functionalization.[5] The best synthetic methods developed to date involve the following: $[2\pi + 2\pi]$ cycloadditions of azodicarbonyl compounds with electron-rich alkenes,[6]

[†] University of Warwick.
[‡] GlaxoSmithKline, Medicines Research Centre.

(1) (a) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 69. (b) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 93.

(2) For a recent review, see: Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052.

(3) (a) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044. (b) Ye, Y.; Wang, H.; Fan, R. *Org. Lett.* **2010**, *12*, 2802. (c) Burkett, B. A.; Ting, S. Z.; Gan, G. C. S.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 6590. (d) Hansen, C. P.; Jensen, A. A.; Christensen, J. K.; Balle, T.; Liljefors, T.; Frølund, B. *J. Med. Chem.* **2008**, *51*, 7380. (e) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988 and references cited therein.

(4) Che, Y.; Marshall, G. R. *J. Org. Chem.* **2004**, *69*, 9030.

(5) For a review, see: Lohray, B. B.; Bhushan, V. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: New York, 1996; Vol. 1B, pp 911−968.

(6) (a) Kim, D. K.; O'Shea, K. E. *J. Am. Chem. Soc.* **2004**, *126*, 700. (b) Paquette, L. A.; Webber, P.; Simpson, I. *Org. Lett.* **2003**, *5*, 177. (c) Breton, G. W.; Shugart, J. H.; Hughey, C. A.; Perala, S. M.; Hicks, A. D. *Org. Lett.* **2001**, *3*, 3185. (d) Abarca-Gonzalez, B.; Jones, R. A.; Medio-Simon, M.; Quiliz-Pardo, J.; Sepulveda-Arques, J.; Zaballos-Garcia, E. *Synth. Commun.* **1990**, *20*, 321. (e) Cheng, C. C.; Seymour, C. A.; Petti, M. A.; Greene, F. D. *J. Org. Chem.* **1984**, *49*, 2910. (f) Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376. (g) Hall, J. H.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822. (h) Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384. (i) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1972**, *13*, 4713. (j) Koerner von Gustorf, E.; White, D. V.; Kim, B.; Hess, D.; Leitich, J. *J. Org. Chem.* **1970**, *35*, 1155.

10.1021/ol200193n
Published on Web 03/02/2011

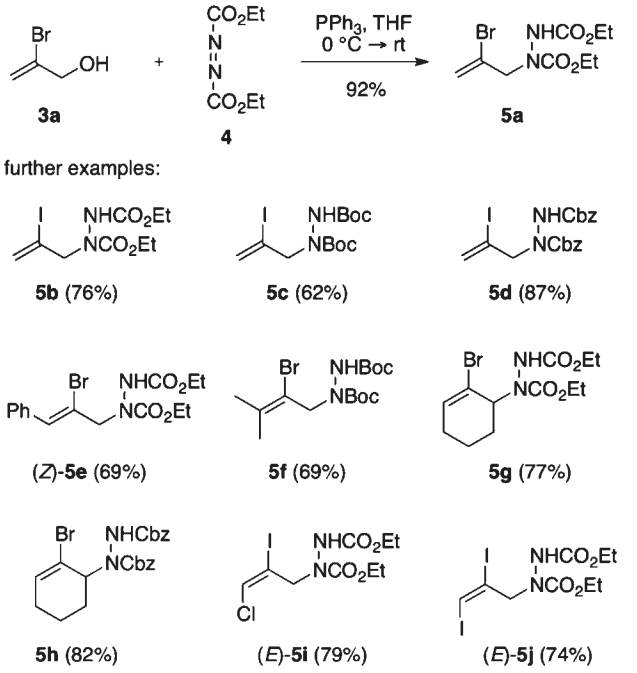
Figure 1. Structure of 1,2-diazetidine (**1**) and 3-methylene-1,2-diazetidine (**2**).

"on water" [$2\sigma + 2\sigma + 2\pi$] cycloadditions of azodicarboxylates with quadricyclane,[7] Pd-catalyzed ring closure of 2,3-allenyl hydrazines,[8] bisalkylation of 1,2-dialkylhydrazines with 1,2-dibromoethane,[9] and Hard−Soft Acids and Bases (HSAB) controlled ring closure.[10] However, significant limitations exist with all these methods in terms of efficiency and/or substrate scope.

We sought to develop a somewhat different synthetic strategy, electing to explore the preparation and reactivity of 3-methylene-1,2-diazetidine **2** and its substituted derivatives (Figure 1). Importantly, this previously unknown class of diazetidine might be expected to be readily synthesized by using copper-catalyzed ring closure of the corresponding 2-halo-2-propenyl hydrazines.[11] Moreover, the potentially rather strained double bond within **2** could provide a useful handle for conversion into a wide range of other 1,2-diazetidines by way of cycloadditions, Heck couplings, cross-metathesis, or simple addition reactions. In this Letter, we report an efficient, two-step synthesis of a wide range of 3-alkylidene-1,2-diazetidines. We further demonstrate that they can be used in diastereoselective Pd-catalyzed Heck reactions without concomitant cleavage of the diazetidine ring, and chemoselectively reduced to either saturated 1,2-diazetidines or vicinal 1,2-diamines in a stereocontrolled manner.

To prepare the hydrazine-containing cyclization precursors **5a**−**j**, a variation on the Mitsunobu reaction was employed in which the external nucleophile was omitted.[12] In this way, direct substitution of the alcohol group by the reduced azodicarboxylate takes place. For example, treatment of commercially available 2-bromoallyl alcohol (**3a**) with diethyl azodicarboxylate (DEAD, **4a**) and triphenylphosphine in THF readily provided hydrazine **5a** in 92% yield after purification by column chromatography (Scheme 1). In an identical manner, hydrazines **5b**−**j** were made by coupling of the appropriate allylic alcohols **3b**−**g** with commercially available DEAD (**4**), dibenzyl azodicarboxylate, or di-*tert*-butyl azodicarboxylate. Good to excellent yields were observed in all cases. Full details are provided in the Supporting Information.

Scheme 1. Synthesis of Hydrazines **5a**−**j**



With ready access to a wide range of suitably functionalized hydrazines, attention turned to the Cu-catalyzed ring closure. Our investigations focused on the use of the conditions developed by Li for the synthesis of other 4-membered carbocycles and heterocycles.[11] Heating bromide **5a** in THF with CuI (20 mol %) in the presence of dimethylethylenediamine (DMEDA, 40 mol %) and Cs_2CO_3 (2 equiv) induced facile ring closure to methylene-1,2-diazetidine **6a** in 98% yield (Scheme 1). This compound is produced in comparable yield (99%) by using iodide **5b** as substrate (see the Supporting Information). This cyclization tolerates variation in the nature of the *N*-substituent as illustrated by the formation of Boc (e.g., **6b** and **6e**) and Cbz (e.g., **6c** and **6g**) derivatives. Substitution of the alkene double bond is possible as established by the ring closure of *gem*-dimethyl substituted **5f** into 3-isopropylidene-1,2-diazetidine **6e**. Moreover, phenyl-substituted (*Z*)-**5e** cyclizes to (*Z*)-**6d** through retention of configuration at the sp^2-hybridized carbon. By using secondary hydrazines **5g** and **5h**, it is possible to make highly strained diazabicyclo[4.2.0]octenes **6f** and **6g**, respectively, in near-quantitative yields.

The relative propensity of competing cyclization manifolds has been explored by using dihalogenated substrates

(7) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Folkin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. See also: (b) Rieber, N.; Alberts, J.; Lipsky, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 5668.

(8) Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4581.

(9) (a) Hall, J. H.; Bigard, W. S. *J. Org. Chem.* **1978**, *43*, 2785. (b) Nelsen, S. F.; Peacock, V. E.; Weisman, G. R.; Landis, M. E.; Spencer, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 2806.

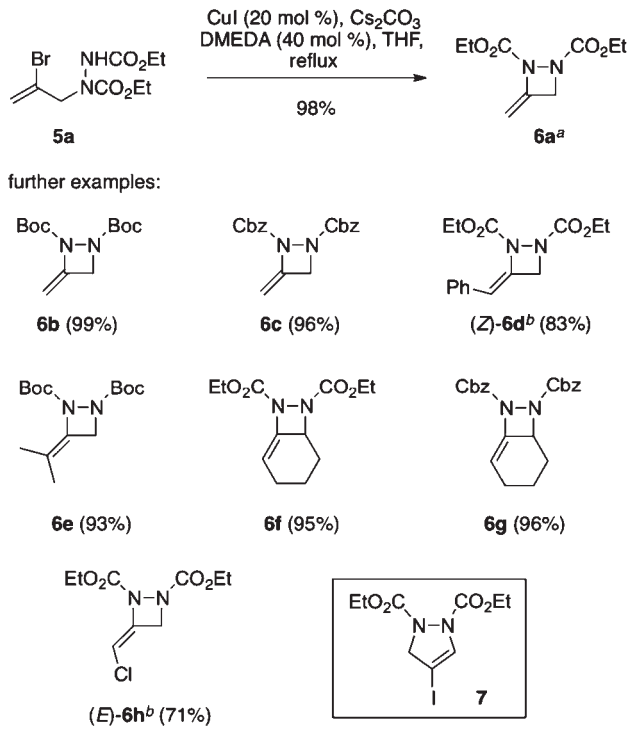
(10) Brown, M. J.; Clarkson, G. J.; Fox, D. J.; Inglis, G. G.; Shipman, M. *Tetrahedron Lett.* **2010**, *51*, 382.

(11) For the efficient synthesis of other 4-membered ring systems by Cu-catalyzed ring closure, see: (a) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (b) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, *129*, 8092. (c) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (d) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, *10*, 5285. (e) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459.

(12) Dow, R. L.; Kelly, R. C.; Schletter, I.; Wierenga, W. *Synth. Commun.* **1981**, *11*, 43. This reaction is more commonly seen as an unwanted side reaction in conventional Mitsunobu reactions, see for example: Sammes, P. G.; Smith, S. *J. Chem. Soc., Chem. Commun.* **1983**, 682.

5i and **5j**. With (*E*)-**5i**, Cu-catalyzed 4-*exo* ring closure to 1,2-diazetidine **6h** is observed, although small quantities of pyrazole **7** (15%) arising from competitive 5-*endo* ring closure were also isolated. By using diodide **5j**, this selectivity is reversed with pyrazole **7** formed in 94% yield as the only discernible product (Scheme 2). Recent reports have described four-membered ring closure as being fundamentally preferred over other modes of cyclization in Cu(I)-catalyzed C-, O-, N-, and S-vinylation.[11] To the best of our knowledge, the selective formation of pyrazole **7** from diodide **5j** represents the first demonstration of a preference for a 5-*endo* over a 4-*exo* ring closure in such cyclizations.

Scheme 2. Synthesis of 3-Methylene-1,2-diazetidines

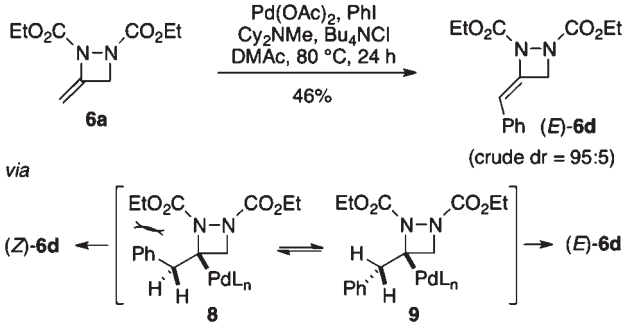


[a] Using **5b**, formed in 99% yield. [b] Configuration determined by NOE measurements. For (*Z*)-**6d**, this assignment verified by comparison with (*E*)-**6d** (Scheme 3).

With a selection of 3-alkylidene-1,2-diazetidines to hand, efforts to explore their reactivity have been initiated. For example, it is possible to functionalize the double bond of these compounds through Pd-catalyzed Heck couplings. Thus, treatment of 3-methylene-1,2-diazetidine **6a** with phenyl iodide using the phosphane-free catalyst system developed by Buchwald[13] provides (*E*)-**6d** in 46% isolated yield (Scheme 3). The structure of this product was confirmed by single-crystal X-ray diffraction (see the Supporting Information). The high degree of diastereoselectivity observed in this transformation can be rationalized through consideration of the presumed organopalladium intermediate prior to *syn*-elimination of the β-hydride.

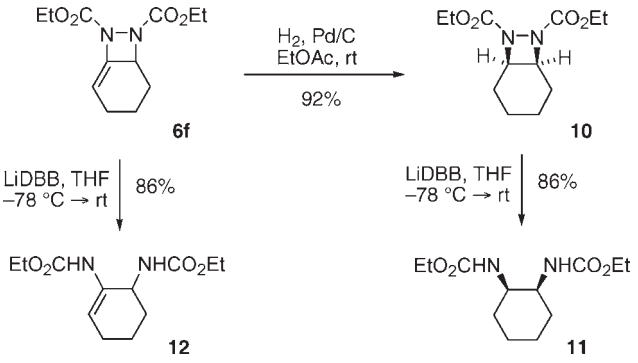
(13) Gürtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107.

Scheme 3. Stereocontrolled Heck Coupling of 3-Methylene-1,2-diazetidine **6a**



Assuming that (*Z*)- and (*E*)-**6d** are produced from **8** and **9**, respectively, which differ only in the conformation around the C−C single bond, then one can account for the preferred product observed by suggesting a lower energy for the transition state from **9** leading to (*E*)-**6d** as it does not experience the destabilizing nonbonded interactions between the Ph and CO_2Et groups (Scheme 3). An attractive feature of this chemistry is that it provides **6d** with the opposite stereochemistry to that accessed by direct Cu(I)-catalyzed ring closure (Scheme 2). Although the yield of this reaction is relatively modest, it is notable that the N−N bond of these highly strained heterocycles is stable to the reaction conditions, and does not undergo oxidative insertion by the Pd catalyst.[14]

Scheme 4. Chemoselective Reductions of 1,2-Diazetidine **6f**



Using **6f** as a representative substrate, we have examined chemoselective reductions of this new compound class. Catalytic hydrogenation under heterogeneous conditions provides 1,2-diazetidine **10** exclusively as the *cis*-stereoisomer (Scheme 4). Significantly, little N−N bond cleavage was observed under these reaction conditions, indicating that this approach may provide a useful entry point into

(14) Less strained 3-alkyl-1,2-diazetidines are known to be stable to Pd-catalyzed cross-coupling conditions, see ref 7.

saturated 1,2-diazetidines.[6−10] Further cleavage to *cis*-diamine **11** was achieved by using lithium di-*tert*-butylbiphenyl (LiDBB) as reductant.[15] At this point, the *cis*-stereochemistry of **11**, and hence **10**, was confirmed by spectroscopic comparison of **11** with authentic samples of *cis*- and *trans*-**11** prepared from the corresponding, commercially available 1,2-diaminocyclohexanes by reaction with ethyl chloroformate (see the Supporting Information). Interestingly, direct treatment of **6f** with LiDBB provides enamide **12** through chemoselective reduction of the N−N bond (Scheme 4).

In conclusion, we have developed an efficient, two-step synthesis of 3-methylene-1,2-diazetidines through application of Cu(I)-catalyzed 4-*exo* ring closure. The methodology is high yielding and has broad substrate scope. Preliminary studies indicate that this new class of N-heterocycle will serve as useful templates for the synthesis of functionalized 1,2-diazetidines, vicinal diamines, and other valued N-containing systems. Further exploration of functionalization reactions of these systems and efforts toward their enantioselective reduction are currently underway in our laboratory.

(15) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

Acknowledgment. This work was supported by GlaxoSmithKline and the Engineering and Physical Sciences Research Council. We thank Advantage West Midlands and the European Regional Development Fund for funding for the Oxford Diffraction Gemini XRD system.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for **5a−j**, **6a−h**, **7**, and **10−12**. This material is available free of charge via the Internet at http://pubs.acs.org.