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A novel and efficient method for the synthesis of 1,2-diazetidines

Wei Miao, Weiliang Xu, Zhiliu Zhang, Rujian Ma,* Shu-Hui Chen and Ge Li

WuXi PharmaTech Co. Ltd., 288 FuTe Zhong Road, No.1 Building, WaiGaoQiao Free Trade Zone, Shanghai 200131, PR China

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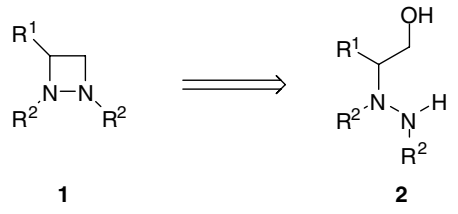
Abstract—A novel and efficient method has been developed for the preparation of racemic or optically pure 1,2-diazetidine from 1-(1-hydroxy-propan-2-yl)hydrazine-1,2-dicarboxylate under very mild conditions with excellent yield.

1. Introduction

1,2-Diazetidine is an important moiety in organic and medicinal chemistry.[1,2] So far, there have been a limited number of efficient synthetic methods developed for its synthesis. Currently, the most popular synthetic method involves the use of [2+2] cycloaddition reaction.[1] A few examples utilizing intramolecular cyclization to prepare 1,2-diazetidine have also been reported.[2,3] As one of our on-going programs, we need to develop a more efficient method to prepare 1,2-diazetidines, particularly the 3-substituted 1,2-diazetidine **1**. We envisioned the preparation of such compounds via intramolecular cyclization of 1-(1-hydroxy-3-propan-2-yl)hydrazine derivatives **2** as illustrated in Figure 1.

We firstly tested the intramolecular Mitsunobu reaction of the dibenzyl 1-(1-hydroxy-3-phenylpropan-2-yl)-hydrazine-1,2-dicarboxylate **2a**, which was in turn prepared readily from 3-phenylpropanal according to the protocol described by List.[4] To our satisfaction,



1 2

Figure 1. Retrosynthetic analysis for the synthesis of 1-substituted 1,2-diazetidine.

the desired 1,2-diazetidine derivative **1a** was obtained in 88% yield.

Despite the success achieved with Mitsunobu reaction as shown in Scheme 1, we encountered problems with the final product purification (removal of triphenyl phosphine oxide). In light of this issue, we decided to develop other milder and cleaner reaction conditions for such cyclizations. We considered activation of the hydroxyl group to a better leaving group such as mesylate, which could then be displaced by the nitrogen nucleophile (within **2a**) through an intramolecular cyclization process to give the desired 1,2-diazetidine (such as **1a**) as depicted in Scheme 2.

Treatment of dichloromethane solution of **2a** with 1.5 equiv of MsCl along with 3 equiv of Et_3N resulted in only trace amount of the desired product **1a**. The major product formed was the intermediate **3** as judged by LC–MS (entry A). No improvement was observed even under prolonged heating. When the same reaction was tried in the presence of 8 equiv of Et_3N, the desired product **1a** was obtained in 25% yield (entry B). Interestingly, replacement of Et_3N with DIEA led to only 5% of the desired product (entry C). In contrast, replacing Et_3N by DBU afforded the desired product **1a** in almost quantitative yield (entry D). Detailed experimental procedure for this intramolecular cyclization is provided in Ref. 5. When K_2CO_3 or Cs_2CO_3 was used as base in conjunction with acetonitrile as solvent, the desired diazetidine **1a** was produced in 85% or 92% yield, respectively (entries E and F) (Scheme 3).

To further probe the generality of above method, we examined the cyclizations with a series of 1-(1-hydroxy-propan-2-yl)hydrazine-1,2-dicarboxylate derivatives

* Corresponding author. Tel.: +86 21 5046 1111; fax: +86 21 50463718; e-mail: marj@pharmatechs.com

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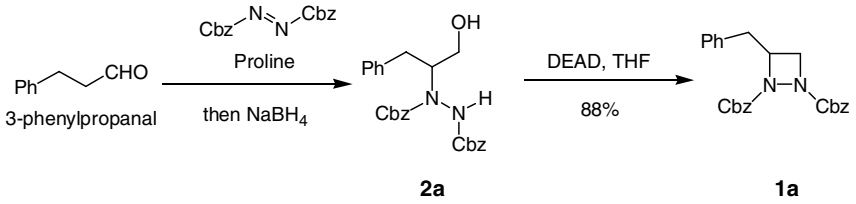
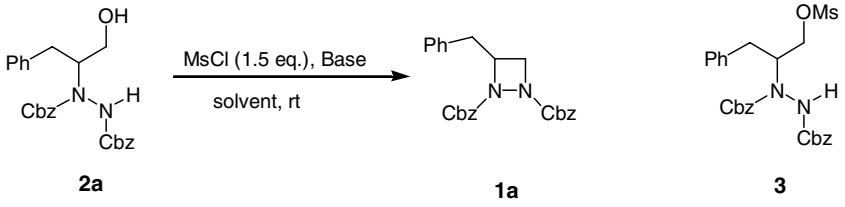
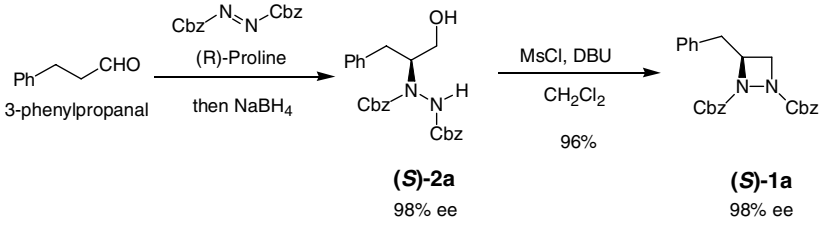


Scheme 1. Intramolecular Mitsunobu cyclization method.



Scheme 2. One-pot synthesis of 1-substituted 1,2-diazetidine.



Scheme 3. The synthesis of the optically pure 1,2-diazetidine.

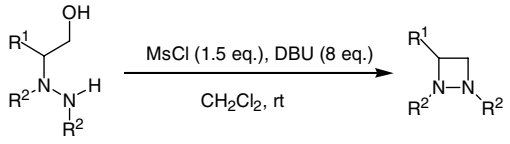
bearing different R_1 and R_2 groups under the reaction conditions described in entry D of Table 1. The results are summarized in Table 2. To our satisfaction, all of the substrates examined (entries G–N), regardless of the nature of R_1 and R_2 moieties used, gave the corresponding 1,2-diazetidines in excellent yield.

Since the acyclic intermediate **2a** can be prepared in enatiomerically pure form,[4] we envisioned that the two-step sequence discussed in this letter could be used to prepare optically pure 1,2-diazetidine derivatives. Thus, the optically pure precursor (*S*)-**2a** was prepared from proline-catalyzed amination of 3-phenylproponal with Cbz protected azodicarboxylate according to the protocol of List.[4] Further treatment of (*S*)-**2a** with MsCl in the presence of DBU led to the formation of enatiomerically pure (*S*)-1-benzyl-1,2-diazetidine **1a** in 96% yield. The ee value of **1a** was determined to be 98% on the basis of chiral HPLC analysis.[6]

Table 1. Optimization of the reaction conditions

Entry	Base	Equivalent	Solvent	Reaction time	Yield (%)
A	Et_3N	3	CH_2Cl_2	2 days	Trace
B	Et_3N	8	CH_2Cl_2	2 days	25
C	DIEA	8	CH_2Cl_2	2 days	5
D	DBU	8	CH_2Cl_2	6 h	96
E	K_2CO_3	8	CH_3CN	2 days	85
F	Cs_2CO_3	8	CH_3CN	1 day	92

Table 2. Generation of cyclizations



2 **1**

Entry	R^1	R^2	Yield (%)
G	$PhCH_2$–	Cbz	96
H	$PhCH_2$–	COOEt	90
I	$PhCH_2$–	COO*i*Pr	90
J	$PhCH_2$–	Boc	85
K	CH_3–	Cbz	96
L	$CH_3CH_2CH_2$–	Cbz	95
M	$(CH_3)_2CH_2$–	Cbz	93
N	$CH_3(CH_2)_3$–	Cbz	93

2. Conclusions

We describe herein a general and efficient method for the synthesis of 3-substituted racemic or chiral 1,2-diazetidine from 1-(1-hydroxy-propan-2-yl) hydrazine-1,2-dicarboxylate under very mild conditions in excellent yield.

References and notes

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5. *Typical cyclization procedure of* **2**: To a solution of **2a** (2.20 g, 5.1 mmol) and DBU (6.16 g, 40.6 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise MsCl (0.6 mL, 7.6 mmol) in anhydrous CH_2Cl_2 at 0 °C. After addition, the ice-bath was removed and the reaction mixture was stirred for 5–8 h (monitored by TLC) at room temperature. The reaction mixture was cooled to 0 °C and neutralized with saturated aqueous citric acid to pH 7, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (30 mL), brine, dried (Na_2SO_4), filtered, and evaporated under vacuum to afford the crude product. Purification by chromatography on silica gel (Hexane/ethyl acetate 15:1) afforded 1,2-diazetidine **1a** (2.02 g, yield 96%). ^{1}H NMR of **1a** (400 MHz, $CDCl_3$) δ: 7.50–7.10 (m, 15H), 5.30–5.10 (m, 4H), 4.45–4.54 (m, 1H), 4.18 (d, $J = 10.8$ Hz, 1H), 4.14 (d, $J = 10.8$ Hz, 1H), 2.95 (dd, $J = 12.8$ and 5.2 Hz, 1H), 2.80 (dd, $J = 12.8$ and 10.0 Hz, 1H).
6. In order to determine the ee% value of (*S*)-**1a** and (*S*)-**2a**, (*R*)-**1a** and (*R*)-**2a** were prepared following a similar procedure using (*S*)-proline for the asymmetric hydrazination step. The ee% value measured for **2a** was 98% using chiral HPLC (Daicel Chiralcel AD-H, 0.46×25 cm $\times$ 5 μm; MeOH/CO_2 (3:7), 2.35 mL/min; 100 bar; 30 °C; Rt = 6.90 min for *R*-isomer; Rt = 8.01 min for *S*-isomer). The ee% value measured for **1a** was 98% using chiral HPLC (Daicel Chiralcel AS-H, 0.46×25 cm $\times$ 5 μm; isopropanol/CO_2 (1:9) 2.35 mL/min; 100 bar; 30 °C; Rt = 7.32 min for *R*-isomer; Rt = 8.13 min for *S*-isomer).