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Preparation of novel bicyclic piperazines by reduction of bicyclo[4.2.2]diketopiperazines: rearrangement involving 1,2-bond migration

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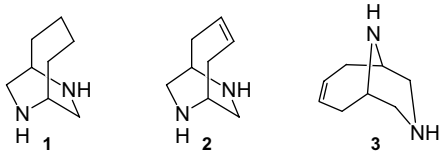
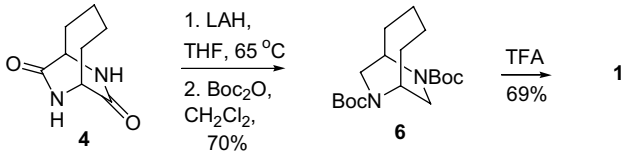
Abstract—Reduction of (1*R*,6*R*)-7,9-diazabicyclo[4.2.2]dec-3-ene-8,10-dione (**5**) with lithium aluminum hydride gave a mixture of the expected (1*R*,6*R*)-7,9-diazabicyclo[4.2.2]dec-3-ene (**2**) as well as 7,9-diazabicyclo[4.3.1]dec-3-ene (**3**), resulting from 1,2-σ (C–C) migration of the pendant *cis*-2-butenyl ring. More of the rearranged product was observed in polar solvents and upon the addition of HMPA. The relief of ring strain imparted by the olefin may promote this rearrangement, as it was not observed when the olefin was reduced prior to the reduction.

Bridged bicyclic piperazines are found in natural and synthetic biologically-active products.[1] They have attracted considerable attention in bioorganic and medicinal chemistry because the piperazine motif itself is a privileged structure that confers activity at a variety of GPCR and other protein targets.[2] Among the bicyclic piperazines that have been prepared and evaluated are those comprised of the [3.2.1]octane, [3.3.1]nonane, and [2.2.2]octane ring systems. 7,9-Diazabicyclo-[4.2.2]decane **1** has not been described although the synthesis of it has been unsuccessfully attempted;[1i] however, the benzofused variant of **2** bearing this heterocyclic ring system has been previously prepared.[1j] We herein report the preparation of useful bicyclic piperazines **1**, olefin **2**, and bis-homoazatropane **3**, resulting from an unexpected rearrangement involving 1,2-bond migration.

We have recently described the synthesis of both of the enantiomers of bicyclo[4.2.2]diketopiperazines **4** and **5** from the corresponding chiral allylglycines.[3,4] We reasoned that reduction of the amide groups of **4** and **5** would afford the corresponding chiral bicyclic piperazines, which could be converted to a variety of synthetically useful chiral intermediates.



Reduction of bicyclo[4.2.2]diketopiperazine **4** was carried out by using lithium aluminum hydride (LAH, 10 mol-equiv) under typical conditions reported for the reduction of diketopiperazines to the corresponding piperazines (Scheme 1).[5] Bis-Boc derivative **6** was formed to facilitate the workup of the reaction, followed by treatment with TFA to afford bicyclic piperazine (1*R*,6*R*)-7,9-diazabicyclo[4.2.2]decane **1** (48% overall yield). The



Scheme 1. Reduction of diketopiperazine **4** with LAH.

Keywords: Bicyclic piperazines; 1,2-Bond migration; Ring strain; LAH reduction; Sigmatropic rearrangement.
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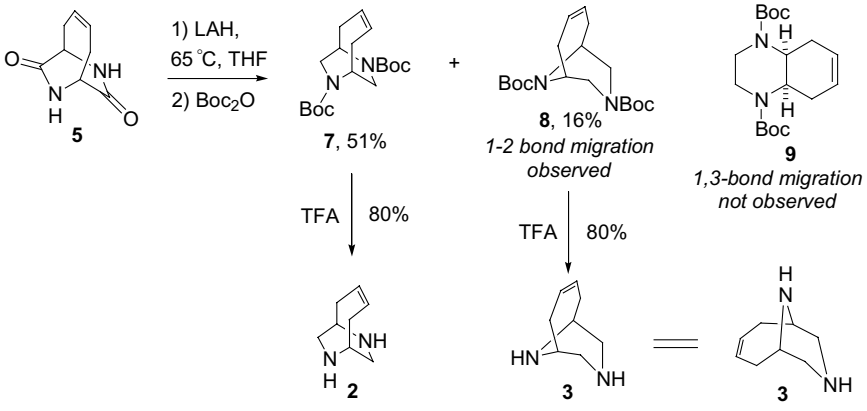
1*S*,6*S* stereoisomer was prepared in the same manner starting from the corresponding 1*S*,6*S* enantiomer of **4**.[3,6]

When the same reaction sequence to form **1** was applied to the reduction of **5**, we were surprised to find that two products (**7** and **8**) were obtained (Scheme 2). Their ^{1}H and ^{13}C NMR spectra were complicated by the presence of Boc-group rotamers, which disappeared after deprotection to **2** and **3**. As for starting diketopiperazine **5**, DEPT and ^{13}C NMR experiments revealed that **7** and **8** were symmetric and mass spectral analysis revealed the same MW for both of them. A distinctive difference in the ^{13}C NMR spectra was that the relative difference between the bridge and methylene carbons adjacent to the nitrogens was greater for **7** than for **8** ($\Delta\delta = 6.8$ ppm for **7** vs 0.8 ppm for **8**). We relied upon X-ray crystal determination for a definitive structural assignment, which revealed that major product **7** was the expected bicyclic piperazine, whereas **8** had a novel 8,10-diazabicyclo[4.3.1]dec-3-ene ring system as shown (Fig. 1). Diamine **8** is formed by 1,2-bond migration of the pendent olefin-bearing side chain. Alternative product **9** resulting from 1,3-bond migration was not observed. Piperazine **3** is a *C*2 symmetric bis-homoazatropane derivative. Both **2** and **3** are attractive scaffolds because chemical diversity can be readily incorporated by means of substitution or modification of the amine and olefin functionalities.

Tertiary amide reduction with LAH is thought to proceed by initial hydride attack at the carbonyl followed by fragmentation of the *O*-aluminate complex to an imine intermediate, and further reduction to the amine.[7] With primary and secondary amides, deprotonation of the amide hydrogens is the first step. In addition to hydride reaction with the imine, suitably disposed oxygen atoms (hydroxyl or silyl ether groups) can act as nucleophiles and add as well.[8] The rearrangement we describe appears to be the first case in which a 1,2-σ (C–C) bond migration is associated with the LAH reduction of an amide.

Initial deprotonation of both of the amides of **5** would occur upon treatment with LAH to prepare a manifold of possible intermediates. A [3,3]-aza-Cope rearrangement of the alkene with the imine is unlikely because it would require a highly unfavored non-chair transition state. Migration of the allylic group from the bridgehead to the imine carbon would then be followed by subsequent reduction to **8**. This migration may be assisted by the participation of the lone pair on the adjacent nitrogen at the hemiaminal stage, converting one imine/iminium to another prior to the addition of hydride. The driving force for the rearrangement is proposed to be the relief of ring strain of the 7,9-diazabicyclo[4.2.2]dec-3-ene-8,10-dione system. We had previously found that diketopiperazine **5** is highly strained in the solid state with atypical bond angles in which the alkenyl, allylic, and bridgehead carbons are in a planar orientation, consistent with computational analysis.[3] The bond angles for the pendant tetramethylene chain and bridgehead carbons of **4** are as expected.[3] The difference in ring strain for **5** versus **4** may be the reason that the rearrangement is only observed for **5**.[9]

Given the novelty and potential utility of bicyclic piperazines **1**–**3**, we investigated their preparation in greater detail. We sought to find conditions that would favor



Scheme 2. Reduction of diketopiperazine **5** with LAH.

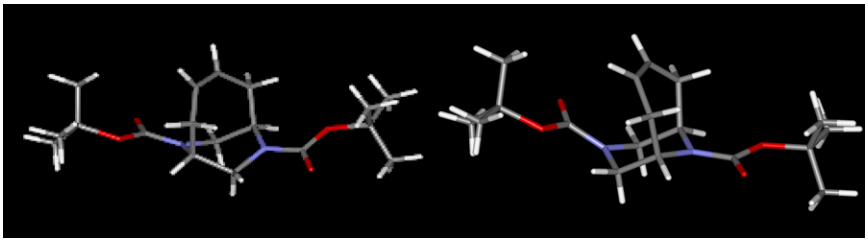


Figure 1. X-ray crystal structures of **7** (left) and **8** (right).

the production of either of the piperazine products upon reduction of **5**, as well as to provide greater insight into the mechanism of the rearrangement. Variation of both solvent and temperature influenced the ratio of products formed (Table 1). As shown, reduction of **5** using LAH in THF resulted in a 3.2:1 mixture of **7** and **8** (67%). When **5** was reduced in the less polar solvents diethyl ether or toluene, only expected product **7** was observed (entries 2 and 3). Rearranged product **8** was produced to a greater extent when the reaction was run in DME (entries 4 and 5). For example, when DME was used at 85 °C (24 h), a 79% yield of a 1.3:1 ratio of **7** and **8** was observed (entry 4). Only **7** was formed when **5** was reduced with DIBAL or AlH_3 (entries 6 and 7).

Table 1. Reduction of **5** varying solvent and reductant

Entry	Reducing agent	Solv.	Temp. (°C)	Yield (%)	Products (**7**:**8**)
1	LAH	THF	65	67	3.2:1
2	LAH	Et_2O	35	80	1:0
3	LAH	Tol	110	33	1:0
4	LAH	DME	85	79	1.3:1
5	LAH	DME	35	46	2.5:1
6	DIBAL	THF	65	59	1:0
7	AlH_3	THF	65	20	1:0

We investigated the effect of adding LiCl or agents known to coordinate with lithium (Table 2). Addition of LiCl to the reduction of **5** with LAH in THF produced **7** and **8** in a ratio of 1.9:1 (entry 1). The addition of TMEDA, 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA),[10] or 12-crown-4 (12-C-4) did not significantly alter the ratio of products observed (entries 2–4). When HMPA[11] was added, the ratio was inverted to give predominantly rearranged product **8** (entries 5 and 6). In summary, polar solvents and additives promote the rearrangement, possibly because they stabilize one or more relevant polar transition states in the formation of **8**.

Table 2. Reduction of **5** with LAH in THF in the presence of additives

Entry	Additive (mol-equiv)	Temp. (°C)	Yield (%)	Ratio (**7**:**8**)
1	LiCl (10)	65	56	1.9:1
2	TMEDA (10)	65	44	2.1:1
3	HMTETA (10)	65	40	3.8:1
4	12-C-4 (10)	65	85	1.6:1
5	HMPA (10)	65	75	1:2.7
6	HMPA (20)	65	48	1:2.9

We have prepared novel bicyclic piperazines **1**–**3** by the reduction of diketopiperazines **4** and **5**. Piperazines **1** and **2** are chiral and their opposite enantiomers can be obtained in the same manner starting with the opposite enantiomers of **4** and **5**.[3] Bicyclic amines **1**–**3** are new, constrained piperazine mimics that may find value in medicinal and bioorganic chemistry. During the course of preparing **2** upon reduction of diketopiperazine **5** with LAH we found an unexpected rearrangement to afford **3**, whose structure was confirmed by X-ray structure analysis of bis-Boc derivative **8**. The formation of **3** involves formal 1,2-σ (C–C) bond migration concomitant with trapping of an imine species during the LAH reduction of the amide. Novel bicyclic piperazine **3** is an achiral bis-homoazatropane derivative, which can serve as a useful scaffold for further derivatization.

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Supplementary data

Procedures and spectral data for all new compounds (32 pages). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 649056 and 649057. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.080.

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